

2.0



MODULE 1 OF 5 · UU LIFE PEPTIDES 2.0

FOUNDATIONS

How peptides work and how to read the science. Receptors and signaling, half-life and pharmacokinetics, routes, units, the anatomy of a study, evidence grades, safety architecture, reconstitution and storage done right.

Module 1

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Verified references

Educational and informational reference for adults. Not medical advice, not a prescription. Do not use any substance. Many compounds described are not approved for human use and several are prohibited in sport. Decisions about any compound belong to you and a licensed clinician.

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The evidence scale used in every card

GRADE	MEANING
A	Approved drug or multiple human randomized trials
B	Human trials that are small, short or single-arm, or consistent case series
C	Animal data only, or human data too weak to support the claim
D	In vitro, mechanistic or anecdotal; no reliable human or animal outcome data

Doses in this book are reported, not recommended: each one names its source, a drug label, a study with its PMID, or the explicit tag that it is commonly cited in non-clinical use and not validated in trials.

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How peptides work: receptors, signals and pharmacokinetics

A peptide's effects depend on three linked questions: what it interacts with, what that interaction changes, and how much intact compound reaches relevant tissues. Receptor pharmacology explains the signal.

Pharmacokinetics explains exposure over time. Neither, by itself, establishes a useful clinical outcome. This distinction separates an interesting laboratory finding from evidence that a treatment benefits people. (PMID: 35165272)

Peptide, protein and small molecule

Peptides consist of amino acids joined by peptide bonds. Their sequence, folding, charge and chemical modifications determine their interactions. Proteins use the same basic chemistry but generally form larger, more elaborate structures. There is no universal length boundary that reliably predicts biological behavior. A short peptide can be inactive, while a larger protein can bind a receptor with high specificity. (PMID: 35165272)

Small-molecule drugs generally have lower molecular mass and can use chemical structures unrelated to amino-acid chains. Some cross membranes readily and reach intracellular targets. Many therapeutic peptides instead act at cell-surface receptors because their size, charge and polarity limit passive membrane passage. These are tendencies, not absolute rules. NAD⁺, included in this catalog, is a nucleotide coenzyme rather than a peptide. Catalog membership does not define molecular chemistry. (PMIDs: 35165272, 33028824)

Agonist, analog and fragment describe different properties

- An agonist binds a receptor and activates signaling. An antagonist blocks agonist-mediated activation without producing the same activating response. (PMID: 21208601)
- An analog is structurally related to another molecule, with changes that can alter affinity, selectivity, stability or duration. (PMID: 35165272)
- A fragment contains part of a larger sequence. Its effects cannot be assumed to reproduce those of the parent molecule. (PMIDs: 35165272, 37171185)

The categories overlap. Semaglutide is both a GLP-1 analog and a GLP-1 receptor agonist. Its amino-acid substitutions and attached fatty-acid group help protect it from degradation and increase albumin binding. AOD-9604 is a modified growth-hormone fragment; that structural relationship does not establish equivalence to full-length GH. (PMIDs: 26308095, 25208511)

Selected catalog compounds grouped by mechanism family

This table illustrates mechanism families using a subset of the supplied catalog. It is not the complete 41-compound inventory. A shared goal, such as recovery, does not imply a shared receptor. Where targets or preparation identities remain uncertain, the table preserves that uncertainty. Findings for a parent molecule do not automatically establish effects of its fragments or modified analogs.

MECHANISM FAMILY	CATALOG COMPOUNDS	MECHANISM AND EVIDENCE BOUNDARY
Incretin receptor agonists	Semaglutide; tirzepatide	GLP-1 receptor activation; tirzepatide also activates GIP receptors. Grade A evidence supports clinical weight outcomes in studied populations. PMIDs: 32730231, 33567185, 35658024.

MECHANISM FAMILY	CATALOG COMPOUNDS	MECHANISM AND EVIDENCE BOUNDARY
GHRH receptor agonists	CJC-1295	Stimulates pituitary GH release. Short human studies support grade B hormonal effects, without establishing athletic benefits. PMID: 16352683.
IGF-related experimental constructs	PEG-MGF	Related to research on the IGF-1 splice system and MGF peptides. Endogenous MGF findings do not validate a PEG-modified preparation. PMID: 37171185.
Modified GH fragments	AOD-9604	GH-derived sequence. The cited laboratory study characterizes identity and metabolism, not clinical fat-loss efficacy or equivalence to full GH receptor pharmacology. PMID: 25208511.
Experimental tissue-response modulation	BPC-157	Multiple proposed growth and angiogenesis pathways. Grade C musculoskeletal efficacy evidence: predominantly preclinical findings and inadequate human confirmation. PMID: 40756949.
Thymosin-related tissue biology	TB-500	Associated with thymosin beta-4 research. A preparation's identity must be established before applying findings from full-length thymosin beta-4. PMID: 36709593.
Neuroactive peptides	Semax; Selank	Grade B evidence for short human functional-connectivity observations. These findings do not establish a single receptor mechanism or durable cognitive benefit. PMID: 32342318.
Melanocortin receptor agonists	PT-141, bremelanotide	Melanocortin signaling with grade A clinical evidence for a defined sexual-desire disorder population. PMIDs: 21208601, 31599840.
Mitochondrial-derived signaling	MOTS-c	Cellular effects involving folate metabolism and AMPK. Foundational intervention findings come from cells and mice, supporting grades D and C respectively. PMID: 25738459.
Coenzyme metabolism	NAD+	Redox cofactor and substrate for multiple enzymes. Neither a peptide nor a conventional peptide-receptor agonist; biochemical roles do not establish supplementation benefits. PMID: 33028824.

Under the 2026 WADA Prohibited List, AOD-9604, CJC-1295, BPC-157, TB-500 and MOTS-c are prohibited at all times. IGF-1 analogs and mechano growth factors are also prohibited at all times. These restrictions concern both competition and periods outside competition.

Worked example 1: the GLP-1 receptor

A receptor is a protein that converts molecular binding into a cellular response. GLP-1 receptors belong to the G protein-coupled receptor family. Agonist binding changes receptor conformation, engaging intracellular signaling that includes cyclic AMP, or cAMP. In pancreatic beta cells, this supports glucose-dependent insulin secretion. Other pathways influence glucagon, gastric emptying and appetite. One receptor can therefore produce different effects across tissues. (PMID: 29617641)

Affinity describes binding strength; potency describes the concentration needed for a defined response. Neither guarantees superior clinical results. Tirzepatide illustrates why: its activity spans GIP and GLP-1 receptors. Laboratory studies show a preference for cAMP signaling over beta-arrestin recruitment at GLP-1 receptors. This is biased agonism, meaning that receptor activation can favor some downstream pathways over others under the tested conditions. (PMID: 32730231)

Clinical outcomes require separate evidence. STEP 1 studied a target semaglutide dose of 2.4 mg subcutaneously once weekly, following escalation, alongside lifestyle intervention (PMID: 33567185). Participants had obesity or overweight with a weight-related condition, without diabetes. This documented trial regimen is not a recommendation for the reader. Its weight outcomes cannot be inferred from receptor binding alone.

US semaglutide labeling contraindicates treatment with personal or family medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or prior serious semaglutide hypersensitivity. Weight-loss treatment is

inappropriate during pregnancy. These boundaries remain relevant even when the receptor mechanism is well established.

Worked example 2: ghrelin and GHRH reach GH through different receptors

Ghrelin activates the growth hormone secretagogue receptor, GHS-R1a. Important signaling involves Gq proteins, phospholipase C and intracellular calcium. GHRH activates a different receptor, with prominent Gs and cAMP signaling. Both systems influence pituitary GH secretion, but they are not interchangeable. Ghrelin also participates in appetite and gastrointestinal regulation, so stimulating its receptor is not an isolated muscle-building signal. (PMIDs: 24381790, 32257855)

CJC-1295 acts through the GHRH system. A simplified sequence is receptor activation, pituitary GH release, then changes in downstream IGF-1 production. The human trials measured GH, IGF-1 and pharmacokinetics. They did not establish that the same exposure improves strength, tendon healing or longevity. A biomarker response establishes biological activity within the measured endpoint. These short trials also cannot establish long-term safety or a complete contraindication profile. (PMID: 16352683)

Worked example 3: melanocortin receptors

Melanocortin receptors form a receptor family with overlapping ligand recognition but different tissue functions. Their signaling commonly involves cAMP. Receptor subtype and tissue location therefore matter: pigment-related activity and central behavioral effects cannot be treated as the same endpoint. Designing selective melanocortin agonists is difficult because related receptors recognize overlapping structural features. (PMID: 21208601)

PT-141, or bremelanotide, demonstrates the gap between mechanism and indication. Two phase 3 trials studied bremelanotide 1.75 mg subcutaneously as needed in premenopausal women with hypoactive sexual desire disorder (PMID: 31599840). Improvements in desire and related distress apply to that studied population; they do not establish universal libido enhancement. Nausea, flushing and headache were more frequent with treatment. (PMID: 31599840)

US bremelanotide labeling contraindicates treatment in uncontrolled hypertension or known cardiovascular disease because blood pressure can increase transiently.

Half-life shapes frequency but does not determine it alone

Plasma half-life describes how long concentration takes to fall by half during a defined elimination phase. Peptides may disappear through enzymatic breakdown and clearance, while chemical modification, albumin binding and formulation can prolong exposure. Absorption can also shape the measured terminal phase. Consequently, a half-life belongs to a particular molecule, formulation, route and study population. (PMIDs: 35165272, 33969456)

Illustrative first-order elimination after absorption and distribution are complete: the remaining fraction equals one-half raised to elapsed time divided by half-life. After 1 half-life: 50%. After 2: 25%. After 4: 6.25%. After 5: 3.125%. This simplified model describes concentration decline, not effect size or a dosing instruction.

Repeated administration before complete elimination can produce accumulation. Under a simple linear model, concentrations approach steady state over roughly four to five half-lives, assuming a constant administration schedule. Plasma persistence and biological persistence differ: receptor occupancy, intracellular signaling and downstream hormone production may follow different time courses. Oral semaglutide modeling illustrates how repeated administration and prolonged persistence smooth substantial day-to-day absorption variability. (PMID: 33969456)

The albumin-binding CJC-1295 studied subcutaneously in humans had an estimated half-life of 5.8 to 8.1 days, with prolonged hormonal responses (PMID: 16352683). Those measurements cannot automatically be assigned to a different construct carrying a similar name. Dosing frequency depends on the tested exposure-response relationship, accumulation tolerability and clinical objective. It does not follow a general rule to administer every half-life.

Bioavailability and why route changes the answer

Bioavailability is the fraction of an administered dose that reaches systemic circulation intact. Intravenous administration defines complete systemic availability. Subcutaneous and intramuscular administration bypass digestion but still require absorption and can involve local degradation. Neither guarantees identical exposure. Intranasal and transdermal delivery face their own barriers. Reaching blood does not prove that a useful concentration reaches the brain. (PMIDs: 15984901, 35165272)

Most unmodified oral peptides face two major obstacles: digestive enzymes break peptide bonds, and intact molecules often cross intestinal membranes poorly. Protecting a peptide from stomach conditions solves only part of the problem. An enteric coating can change where material is released without ensuring absorption through the intestinal wall. (PMID: 15984901)

Exceptions depend on molecular design and formulation. The studied oral semaglutide formulation uses an absorption enhancer and achieves useful exposure despite low absolute bioavailability. A population analysis estimated approximately 0.8% bioavailability under its reference conditions (PMID: 33969456). Food, fasting duration and sufficiently large water volumes affected exposure. Differences between the smaller water volumes tested separately were not significant. These findings do not validate generic oral formulations of other peptides. (PMIDs: 33969456, 34080123)

Other oral peptide medicines act locally in the gastrointestinal tract, where high systemic absorption is unnecessary. This is a different pharmacological objective. Oral failure should therefore mean failure to deliver the required exposure to the intended site, rather than simply failure to enter blood. (PMID: 35165272)

Pulsatility: concentration patterns carry information

GH secretion normally occurs in pulses shaped by stimulatory signals, somatostatin inhibition and feedback. Pulse size, frequency and the concentration between pulses are separate measurements. A GH secretagogue can change one without changing all three. In a human CJC-1295 study, GH pulses persisted during prolonged stimulation, but trough concentrations increased markedly. Preserved pulsatility therefore did not mean unchanged physiology. (PMIDs: 24381790, 17018654)

This also limits conclusions from isolated blood samples. A single GH concentration cannot characterize an overnight secretion pattern. The CJC-1295 pulsatility study used repeated overnight sampling. Its findings concern hormone dynamics rather than proven recovery or performance benefits. Under this guide's scale, these short human physiological studies warrant grade B for the measured hormonal effects. (PMID: 17018654)

Tolerance, desensitization and downregulation

Desensitization means reduced signaling responsiveness. Receptor phosphorylation and beta-arrestin recruitment can reduce coupling to G proteins and promote internalization. Internalized receptors may recycle; internalization is not automatically permanent receptor loss. Downregulation refers to a reduction in receptor availability or abundance. Tolerance describes a reduced observed response and can involve mechanisms beyond the receptor itself. (PMID: 30616820)

Adaptation can be endpoint-specific. In nine healthy volunteers, continuous intravenous GLP-1 exposure produced a smaller gastric-emptying delay after a second meal than after the first. This demonstrated rapid tachyphylaxis of that response, associated with altered vagal activation. It did not show that every GLP-1 effect disappears or establish a universal cycling schedule. (PMID: 21430088)

The rule that matters: match the claim to the exact molecule, formulation, route, population and measured outcome. Receptor activity, a longer half-life or a higher biomarker does not by itself establish clinical benefit or justify a personal regimen.

Apply evidence grades to the claim being evaluated. Grade A clinical evidence does not transfer to a different indication. Short human studies support grade B within their endpoints. MOTS-c intervention findings in mice

support grade C; mechanistic pathways alone support grade D. The BPC-157 review found predominantly preclinical evidence and insufficient human evidence for confident musculoskeletal efficacy claims, consistent with grade C. A mechanism is a reason to investigate, not a guarantee. (PMIDs: 33567185, 35658024, 32342318, 25738459, 40756949)

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How to read a study and grade the evidence

A five-minute abstract review should answer a narrow question: what does this study actually support? Identify who or what was studied, the comparison, the measured outcome and the uncertainty. Save the authors' conclusion for last. This chapter provides a screening method, with deeper reading required when essential details are missing. Greenhalgh's guide explains why identifying the research question and study design comes before judging a paper's findings (PMID 9253275).

Keep every claim within the population, intervention, outcome and follow-up actually studied. Label any extrapolation. An abstract review produces a provisional assessment.

The five-minute abstract checklist

Use this sequence to create a provisional evidence note. It draws on Greenhalgh's appraisal approach and CONSORT 2010 reporting questions (PMIDs 9253275 and 20332511).

1. Minute 1: record the PMID, population or species, study type, comparison group and whether treatment assignment was randomized.
2. Minute 2: record sample size, group sizes, treatment duration and follow-up. Distinguish enrollment from completion when reported.
3. Minute 3: identify the stated primary endpoint. Classify it as a clinical outcome, biomarker or laboratory mechanism; confirm prespecification in the protocol.
4. Minute 4: extract the between-group effect, its units, confidence interval and reported harms, then inspect the P value.
5. Minute 5: check funding and disclosures. Assign a provisional A to D grade to the claim and list details requiring the full paper.

Start with study design

For treatment effectiveness, the following designs provide a useful starting point. Design determines which alternative explanations can be addressed, but execution still matters. A poorly conducted randomized trial can mislead. Observational studies remain useful for questions that trials cannot readily answer. Match the design to the question before treating a hierarchy as a verdict (PMID 9253275).

DESIGN	WHAT IT CONTRIBUTES	MAIN LIMITATION
Randomized controlled trial, RCT	Random assignment balances prognostic factors on average, although individual trials can have imbalances.	Bias can remain through poor concealment, missing outcomes or selective reporting.
Cohort study	Follows exposed and unexposed people to compare subsequent outcomes.	Differences in health, behavior or treatment selection can confound associations.
Case series	Describes outcomes in several treated people.	Without a suitable comparison, improvement cannot reliably be attributed to treatment.
Animal experiment	Tests biological effects and outcomes in a controlled organism.	Species and disease-model differences limit conclusions about people.
In vitro experiment	Tests cells, tissues or molecules under laboratory conditions.	An isolated response does not establish an effective treatment in humans.

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A review assembles evidence; it does not automatically upgrade it. Check which designs it includes, how studies were selected and whether conclusions reflect their limitations. The industry-sponsorship review below reports different certainty levels for different outcomes, illustrating why confidence should remain outcome-specific (PMID 28207928).

Count participants, time and missing outcomes

There is no universal sample-size threshold for credibility. Precision depends on variability, event frequency, design and the size of the effect being estimated. Small studies often leave wide uncertainty, while large studies can detect differences too small to matter practically. Read the confidence interval instead of judging the sample count alone (PMID 27209009).

Distinguish people enrolled, randomized, followed and analyzed. If participants leave because treatment is ineffective or poorly tolerated, analyzing only completers may distort the result. Duration also limits the question answered: an early response does not establish persistence after treatment or long-term safety. CONSORT asks authors to report participant flow, losses, analysis populations and harms so readers can examine these issues (PMID 20332511).

Find the endpoint, then separate mechanism from outcome

The primary endpoint is the prespecified outcome around which the trial's main question is organized. Some trials specify more than one. Check its definition and measurement time, then compare the paper with its protocol or registration when available. Secondary outcomes add information, but selecting impressive results from many analyses can exaggerate the apparent evidence (PMIDs 20332511 and 27209009).

A mechanism describes a possible causal pathway. A biomarker measures a biological response. A clinical outcome concerns health, symptoms or function. These questions require separate evidence. Teichman and colleagues studied CJC-1295 in two randomized trials lasting 28 and 49 days, measuring growth hormone and IGF-I responses. Those findings demonstrate endocrine activity within the experiment. They do not establish improved strength, muscle gain or longevity (PMID 16352683).

Likewise, GHK-Cu stimulated collagen synthesis in fibroblast cultures. The measured outcome was cellular collagen production, not fewer wrinkles or faster recovery in people. A plausible explanation for a benefit is a reason to test that benefit, not evidence that it has already occurred (PMID 3169264).

Read effect size before statistical significance

Effect size describes how much the groups differ. A P value measures incompatibility between the data and a specified hypothesis under the analysis assumptions. Statistical significance applies a chosen threshold to that value. Neither establishes the probability that treatment works, the probability that the null hypothesis is true, or clinical importance (PMID 27209009).

Inspect the units and comparison. Kilograms, percentage change in weight and percentage points between groups are different quantities. For binary outcomes, ask for both absolute and relative effects. A large relative change can correspond to a small absolute difference when the baseline event rate is low. CONSORT recommends reporting both for binary trial outcomes (PMID 20332511).

A confidence interval displays uncertainty under the statistical model. Ask whether its range includes effects too small to matter, substantial benefit or harm. A nonsignificant result with a wide interval may be inconclusive rather than evidence of equivalence. Conversely, a very small P value cannot repair biased measurement or an inappropriate comparison (PMID 27209009).

Check conflicts without using them as a shortcut

Check funding, employment, consulting relationships, patents and the sponsor's role in analysis and publication. An industry-funded trial can provide useful evidence, but funding deserves scrutiny. A Cochrane

review found that industry-sponsored drug and device studies more often reported favorable efficacy results and conclusions. That association does not prove that any particular paper is wrong (PMID 28207928).

If the abstract omits disclosures, mark them as unchecked. Continue to the full paper and protocol, especially when conclusions emphasize secondary results or omit important harms (PMIDs 20332511 and 28207928).

Apply the book's A to D scale

This is the book's practical classification, not a formal GRADE assessment. Apply it to a defined claim and evidence base. The examples classify the cited findings, not every possible use of each compound. A letter alone does not establish clinical relevance or treatment suitability.

GRADE	BOOK DEFINITION	EXAMPLE AND BOUNDARY
A	Approved drug or multiple human randomized trials.	Semaglutide for weight reduction in studied populations: STEP 1 and STEP 3 provide randomized human evidence (PMIDs 33567185 and 33625476).
B	Human trials that are small, short or single-arm, or consistent case series.	CJC-1295 for short-term GH and IGF-I elevation: two early randomized trials measured endocrine responses. B reflects their short duration and limited scope (PMID 16352683).
C	Animal data only or human data too weak to support the claim.	BPC-157 for muscle-crush recovery: the cited experiment reports healing and functional findings in rats, without establishing human efficacy (PMID 18668315).
D	In vitro, mechanistic or anecdotal.	GHK-Cu for collagen stimulation in the cited fibroblast experiment: cell-culture evidence cannot establish a clinical skin benefit (PMID 3169264).

The A and B definitions overlap. This chapter applies B when the available trials are small or short, even if more than one is randomized. Human biomarker trials are classified by their design and limitations; they do not become D solely because the endpoint is mechanistic. Approval for one indication does not upgrade unrelated claims. Record the population, outcome and principal limitation beside every letter.

Sport eligibility is separate. The 2026 WADA Prohibited List prohibits BPC-157 under S0 and CJC-1295 under S2 at all times, including outside competition. Source: 2026 WADA Prohibited List, https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf.

Worked example: reading STEP 1

STEP 1 randomized 1,961 adults without diabetes in a double-blind, placebo-controlled trial lasting 68 weeks. Eligibility required obesity, or overweight with at least one weight-related condition. The study reports a target semaglutide dose of 2.4 mg subcutaneously once weekly, with lifestyle intervention in both groups (PMID 33567185). Coprimary endpoints were percentage weight change and achieving at least 5% weight loss. The primary analysis targeted effects regardless of treatment discontinuation or rescue interventions.

STEP 1, PMID 33567185
Mean weight change: -14.9% with semaglutide versus -2.4% with placebo
Reported estimated difference: -12.4 percentage points
95% confidence interval for the difference: -13.4 to -11.5 percentage points
P < 0.001

Use the reported estimate, not subtraction of rounded means. Gastrointestinal events caused treatment discontinuation in 4.5% with semaglutide versus 0.8% with placebo; the abstract identifies manufacturer funding. The result supports weight reduction in the studied setting, without establishing muscle gain or lifelong safety (PMID 33567185).

Why animal doses do not translate linearly

Matching mg/kg across species assumes that body weight alone captures relevant biological differences. Metabolism and physiological functions do not scale proportionally with mass. Allometric scaling uses relationships between body size and biological properties; one common approximation converts an animal dose using body surface area. Nair and Jacob describe its use in estimating human-equivalent doses during planning for initial human trials (PMID 27057123).

Body-surface-area method, PMID 27057123
Human-equivalent dose in mg/kg = animal dose in mg/kg multiplied by animal Km divided by human Km
Km = body weight in kg divided by body surface area in square meters
The formula estimates a dose, not measured human exposure.
It does not establish a human route, frequency or treatment regimen.

This conversion is an approximation, not proof of equivalent blood concentrations or biological effects. Route, absorption, metabolism and species-specific pharmacology still matter. Estimating a first human trial dose also requires toxicology and safety considerations. A calculated human-equivalent dose is not a validated personal dose (PMID 27057123).

Find the record and preserve the evidence

Search PubMed using the title, or combine the compound with an author and year. Open the result and match its title, authors, journal and publication year. The PMID identifies the PubMed record; the DOI is a separate article identifier. For STEP 1, these are PMID 33567185 and DOI 10.1056/NEJMoa2032183. Save the identifiers with the claim and check whether the record links to corrections or retractions.

Evidence note template
Claim:
PMID and DOI:
Population, design and comparator:
Sample size and follow-up:
Primary endpoint and prespecification checked:
Effect size and confidence interval:
Harms, missing data and funding:
Provisional grade and reason:
What this paper does not establish:

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Units and math: mg, mcg, IU, mL and the syringe

A peptide calculation connects active compound mass, solution concentration, and the volume represented by a measuring device. Confusing these quantities can produce large errors. A semaglutide case series documented tenfold administration errors and confusion involving milligrams, milliliters, and syringe units. Evidence grade B applies to this descriptive human safety signal, not its frequency or proof of causation. Reference: Lambson et al., 2023, PMID 37392810.

A syringe number cannot identify peptide mass without the syringe calibration and solution concentration. An unclear instruction requires clarification from the prescribing clinician or pharmacist before use.

Mass, biological activity, and volume

Milligrams, written mg, and micrograms, written mcg, measure mass. One mg equals 1000 mcg. Conversion changes the numerical expression, not the amount of material. A milliliter, written mL, measures volume. A volume alone cannot identify how much peptide it contains. These metric relationships are definitions. Mass conversions and hypothetical vial contents below are arithmetic inputs, not administered doses.

International units, written IU, express biological activity relative to a substance-specific standard. There is no universal IU-to-mg conversion across peptides. A valid conversion requires the particular substance and its established standard. Biological unitage does not guarantee a particular clinical response. Reference: Miles and Perry, 1953, PMID 13082386, a methodological discussion rather than clinical efficacy evidence.

An insulin syringe is calibrated for insulin at a specified concentration. With matching insulin, its numbers represent insulin units. With another solution, those marks provide only a volume mapping. Calling them peptide IU is incorrect: the syringe cannot measure that peptide's biological potency. A published human case documents an insulin concentration and syringe mismatch. Reference: Barrera and Murvelashvili, 2019, PMID 31316841.

QUANTITY	EQUIVALENT	MEANING
1 mg	1000 mcg	Mass conversion, not a dose
0.1 mg	100 mcg	Mass conversion, not a dose
0.01 mg	10 mcg	Mass conversion, not a dose
1 mL	100 U-100 scale units	Volume mapping
0.1 mL	10 U-100 scale units	Volume mapping
0.01 mL	1 U-100 scale unit	Volume mapping
1 mL	40 U-40 scale units	Different calibration
IU to mg	No universal conversion	Requires a substance-specific standard

Concentration after reconstitution

Concentration is active compound mass divided by final solution volume. As a hypothetical arithmetic example, 5 mg in a final volume of 2 mL gives 2.5 mg/mL. The same hypothetical mass in 1 mL gives 5 mg/mL. Doubling concentration halves the volume representing any fixed mass. Neither example specifies an administered dose.

Final volume and added diluent are different inputs. The formulation's documented final concentration or final volume takes precedence over an assumption based on liquid added. These examples assume complete dissolution, uniform distribution, and the stated active mass. Arithmetic cannot establish identity, potency, stability, sterility, or a suitable diluent.

The four UU Life Calculator formulas

Concentration in mg/mL = active mass in mg / final volume in mL

Documented dose in mg = documented dose in mcg / 1000

Volume in mL = documented dose in mg / concentration in mg/mL

U-100 scale reading = volume in mL × 100

The second formula applies only to an input in mcg. An input already expressed in mg requires no further conversion. The final formula applies only to U-100 calibration. Units cancel through the calculation: mg divided by mg/mL leaves mL. A reverse check multiplies calculated volume by concentration to recover the original mass. Zero, negative, missing, or ambiguous inputs require an error flag.

U-100 versus U-40

U-100 means 100 insulin units per mL; U-40 means 40 insulin units per mL. One U-100 scale unit represents 0.01 mL, while one U-40 scale unit represents 0.025 mL. The same numbered mark represents 2.5 times as much volume on U-40. A case report describes recurrent hypoglycemia with U-40 syringes used for U-100 insulin. Reference: PMID 31316841. This single case illustrates the mismatch without estimating its prevalence.

SCALE READING	U-100 VOLUME	U-40 VOLUME
5	0.05 mL	0.125 mL
10	0.1 mL	0.25 mL
20	0.2 mL	0.5 mL
40	0.4 mL	1 mL

Calibration, capacity, and graduation spacing are separate properties. U-100 does not mean every syringe holds 1 mL or has one-unit graduations. Relevant device information includes calibration, maximum volume, and smallest marked interval. A calculated volume can be mathematically correct while exceeding capacity or falling between measurable marks.

Five worked examples

These exercises use semaglutide, tesamorelin, and tirzepatide. Every vial mass and final volume is a hypothetical teaching input, not a verified presentation or reconstitution instruction. Repeated compounds demonstrate how concentration changes the answer. Each example's study citation, route, and frequency apply to its complete calculation. Studied regimens are not reader recommendations or starting doses.

Semaglutide and tirzepatide contraindications include personal or family history of medullary thyroid carcinoma, MEN 2, and prior serious hypersensitivity to the respective drug or excipients. Sources: U.S. prescribing information for semaglutide and tirzepatide injections. These arithmetic examples do not establish clinical eligibility.

Example 1: semaglutide, hypothetical 5 mg vial content

Dose provenance for this calculation: SURPASS-2 studied semaglutide 1 mg subcutaneously once weekly, PMID 34170647.
Hypothetical vial mass = 5 mg
Hypothetical final volume = 2 mL
Concentration = $5 / 2 = 2.5$ mg/mL
Equivalent study dose = 1000 mcg subcutaneously once weekly, PMID 34170647
Dose conversion = $1000 / 1000 = 1$ mg
Volume = $1 / 2.5 = 0.4$ mL
U-100 scale reading = $0.4 \times 100 = 40$
Reverse check = $0.4 \times 2.5 = 1$ mg

Example 2: semaglutide, hypothetical 10 mg vial content

Dose provenance for this calculation: SURPASS-2 studied semaglutide 1 mg subcutaneously once weekly, PMID 34170647.
Hypothetical vial mass = 10 mg
Hypothetical final volume = 2 mL
Concentration = $10 / 2 = 5$ mg/mL
Volume = $1 / 5 = 0.2$ mL
U-100 scale reading = $0.2 \times 100 = 20$
Reverse check = $0.2 \times 5 = 1$ mg

The concentration doubled between these examples, so the calculated volume and scale reading halved. Copying the earlier syringe number would double the mass represented. A saved syringe number cannot substitute for the concentration.

Example 3: tesamorelin, hypothetical 2 mg vial content

Dose provenance for this calculation: a randomized trial studied tesamorelin 2 mg subcutaneously once daily in participants with HIV and abdominal fat accumulation, PMID 25038357.
Hypothetical vial mass = 2 mg
Hypothetical final volume = 1 mL
Concentration = $2 / 1 = 2$ mg/mL
Volume = $2 / 2 = 1$ mL
U-100 scale reading = $1 \times 100 = 100$
Reverse check = $1 \times 2 = 2$ mg

This theoretical result uses the entire assumed solution volume, making recoverable volume relevant. The study does not establish a regimen for healthy trainees or interchangeability with current formulations. Tesamorelin contraindications include disrupted hypothalamic-pituitary function, active malignancy, pregnancy, and known hypersensitivity to tesamorelin or excipients. Source: U.S. tesamorelin prescribing information. Tesamorelin is prohibited at all times under S2.2.4 of the 2026 WADA Prohibited List.

Example 4: tirzepatide, hypothetical 15 mg vial content

Dose provenance for this calculation: SURPASS-2 included tirzepatide 5 mg subcutaneously once weekly as a maintenance-dose arm, PMID 34170647.
Hypothetical vial mass = 15 mg
Hypothetical final volume = 1 mL
Concentration = $15 / 1 = 15$ mg/mL
Volume = $5 / 15 = 0.333333...$ mL
U-100 scale reading = $0.333333... \times 100 = 33.333333...$
Reverse check using unrounded volume = 5 mg

A repeating decimal is an arithmetic result, not an instruction to estimate a fractional graduation. The calculator should retain precision and flag the mismatch with the selected device.

Example 5: tirzepatide, hypothetical 10 mg vial content

Dose provenance for this calculation: SURPASS-2 included tirzepatide 5 mg subcutaneously once weekly as a maintenance-dose arm, PMID 34170647.

Hypothetical vial mass = 10 mg

Hypothetical final volume = 2 mL

Concentration = $10 / 2 = 5$ mg/mL

Volume = $5 / 5 = 1$ mL

U-100 scale reading = $1 \times 100 = 100$

Reverse check = $1 \times 5 = 5$ mg

Compared with Example 4, one-third the concentration requires three times the volume. A device with 0.3 mL or 0.5 mL capacity cannot contain this calculated volume. Capacity requires a separate check after conversion.

Dead space and recoverable volume

Dead space is liquid retained in the syringe tip, needle hub, or needle after expulsion. Bench measurements show that retained volume varies with device design and components. It can reduce the number of recoverable portions from a vial. Reference: Smith et al., 2021, PMID 34812330. This device study used water and provides no peptide-specific efficacy evidence.

Nominal vial mass divided by dose gives a theoretical count, not guaranteed availability. Dead space does not change solution concentration. It does not justify automatically adding extra volume: delivered-volume behavior depends on the device and its instructions. No universal dead-space correction belongs in the calculator.

Rounding and the final check

Small-volume measurements can have substantial relative error. Experimental testing of insulin devices found greater percentage error at smaller settings, particularly with syringes. These findings concern measurement precision, not a universal minimum volume for every modern device. Reference: Gnanalingham et al., 1998, PMID 9771255. This was a dispensing experiment, not a clinical outcomes trial.

1. Retain full precision through intermediate calculations; distinguish the displayed result from a measurable device setting.
2. Display a leading zero below one, such as 0.1 mL, and avoid unnecessary trailing zeros.
3. Record the actual graduation interval instead of assuming every visible line represents one scale unit.
4. Flag results between graduations or beyond capacity without silently changing the documented amount.
5. For any evaluated rounding option, display its percentage difference; clinical acceptability requires the prescriber or pharmacist.
6. Reverse-check volume against concentration and retain the compound, dose source, route, frequency, and syringe calibration with the calculation.

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UU LIFE

Reconstitution and storage depend on the formulation

Reconstitution changes a dried formulation into a solution with a different stability profile. Preserving that solution requires two separate controls: maintaining chemical and physical integrity, and preventing microbial contamination. Success with one does not establish success with the other. Formulation research addresses molecular stability. Medication-handling guidance addresses contamination prevention. Neither supports a universal storage rule for every peptide. PMID: 36986796; PMID: 27184207.

The exact formulation determines the validated diluent, preparation method, storage conditions and discard deadline. Clear appearance and refrigeration cannot establish an unknown preparation's stability or sterility.

Diluent compatibility depends on formulation

A diluent does more than dissolve powder. Its pH, preservatives and interaction with existing excipients can change solubility and degradation. A peptide's name alone does not identify a compatible diluent. Different formulations of the same molecule may require different handling because their buffers, stabilizers and concentrations differ. PMID: 36986796.

DILUENT	WHAT IT CONTAINS	DOCUMENTED CONTEXT	MAIN LIMITATION
Bacteriostatic Water for Injection	Sterile water with an antimicrobial preservative. The reviewed Bacteriostatic Water for Injection label specifies benzyl alcohol.	Drug dilution or dissolution when the exact formulation permits this preserved diluent.	Compatibility requires validation. Benzyl alcohol promoted aggregation in an experimental protein formulation. PMID: 25100180.
Sterile Water for Injection	Sterile water without an antimicrobial preservative or added buffer, according to the Sterile Water for Injection label.	Preparation of medications whose instructions specify this diluent.	The reviewed label specifies single-dose containers and disposal of unused contents. The diluent provides no preservative protection.
Acetic acid solution or acetate buffer	An acidic solvent or a defined buffering system. These are not interchangeable.	Formulation development or a validated preparation requiring controlled acidic conditions.	Dissolution does not establish suitability for administration. Acetate buffer concentration affected multimer formation in a freeze-dried peptide formulation. PMID: 10845681.

The water descriptions follow the official Sterile Water for Injection and Bacteriostatic Water for Injection labels on DailyMed. These are pharmaceutical diluents with specific labeling, not interchangeable categories of water. Both labels warn that intravenous administration without sufficient solute can cause hemolysis. The bacteriostatic label contraindicates benzyl alcohol-containing preparations in neonates and excludes their use for epidural or spinal anesthesia.

Bacteriostatic does not mean sterilizing. Preservatives do not replace aseptic preparation or justify retaining a vial after suspected contamination. They can also affect the active molecule. Benzyl alcohol increased aggregation of interferon α -2a in laboratory experiments. That finding demonstrates a compatibility concern, not instability in every preserved peptide solution. PMID: 27184207; PMID: 25100180.

Acetic acid is not a general rescue solvent for undissolved powder. Changing pH can alter both solubility and degradation. An acetate salt named on a peptide label does not establish a need for additional acetic acid.

The documented preparation sequence

The sequence below describes professional preparation principles and a labeled example. It is not a universal mixing protocol. Aseptic technique addresses contamination, while controlled transfer and movement address formulation handling. The exact product instructions remain decisive. Careful handling alone cannot establish that an unidentified powder is suitable for human administration. PMID: 27184207; PMID: 36986796.

1. Verification covers formulation identity, expiration, container integrity, specified diluent, required volume and instructions after reconstitution.
2. Professional preparation follows hand hygiene and uses a clean designated area, sterile equipment and protected connection points. PMID: 27184207.
3. Aseptic vial access includes alcohol disinfection of medication and diluent stoppers, with drying before access. PMID: 27184207.
4. The EGRIFTA SV instructions describe slow solvent transfer along the inside vial wall to limit foaming. This method belongs to that formulation.
5. The EGRIFTA SV instructions specify gentle rolling and prohibit shaking. Other formulations require their own validated mixing instructions.
6. Completion checks cover the labeled dissolution conditions and expected appearance, followed by documentation of concentration and the applicable discard deadline.

The tesamorelin EGRIFTA SV prescribing information specifies gentle rolling for 30 seconds without shaking. Its instructions describe slow solvent transfer down the vial wall. The same label requires immediate use after reconstitution and disposal if the solution is not used immediately. Refrigeration and freezing of the reconstituted solution are prohibited. These instructions cannot be transferred to a different tesamorelin formulation.

This label example addresses handling, not treatment selection. The EGRIFTA SV label lists pregnancy, active malignancy, hypothalamic-pituitary axis disruption and hypersensitivity to tesamorelin or its excipients as contraindications.

No cited study establishes a universal waiting time after diluent addition. Research on concentrated lyophilized proteins found that formulation viscosity and composition strongly influenced reconstitution time. Those results explain variability, but cannot establish timing for unrelated peptides. Persistent material outside the labeled expectation requires assessment. Stronger shaking, heating or a solvent change would introduce conditions that the instructions may not validate. PMID: 32534031.

Dry powder and dissolved peptide have different limits

Lyophilization removes water through controlled freezing and drying and can improve storage stability. It does not eliminate degradation. Freezing conditions, residual moisture and changes in the dried material can affect stability and dissolution. A manufactured lyophilized cake is therefore a formulation whose processing and physical state matter. Its handling requirements cannot be inferred from the peptide name alone. PMID: 21426937.

Direct peptide evidence illustrates the limitation. A study of a freeze-dried atrial natriuretic peptide preparation identified multimer formation that depended on processing and formulation. A separate secretin study found that storage conditions and excipients affected peptide content, particles and reconstitution time. Neither result supports assigning all dry peptide vials the same expiration date or freezer requirement. PMID: 10845681; PMID: 25636302.

After dissolution, aqueous degradation pathways and physical changes become relevant. Temperature, pH and formulation influence their rates. The unopened expiration date does not automatically define the allowable period after mixing. The applicable deadline comes from exact product instructions or, for

compounded preparations, a qualified pharmacy assessment under applicable sterile-compounding standards. PMID: 36986796; PMID: 27184207.

Refrigeration windows require evidence

The insulin storage study describes refrigerated conditions of 2 to 8 °C. That range is not a universal requirement for every dry or dissolved peptide. Cold storage cannot supply missing compatibility data or override instructions requiring immediate use. The applicable temperature range and allowable duration belong to the specific preparation. PMID: 33534816; EGRIFTA SV prescribing information.

CDC medication-vial guidance specifies disposal within 28 days after opening a multidose vial unless the manufacturer provides another interval. That deadline cannot exceed the original expiration date. This rule does not demonstrate chemical stability for an arbitrary reconstituted peptide. Adding bacteriostatic water does not establish a validated multidose preparation. Formulation stability and contamination control impose separate limits. Source: CDC, Preventing Unsafe Injection Practices; PMID: 27184207.

In a laboratory study, selected insulin formulations retained measured quality and biological activity during four weeks of temperature cycling between 25 and 37 °C. PMID: 33534816. These results apply to the tested formulations and conditions. They do not establish the same window for unrelated peptides. A defensible storage claim identifies the formulation, exposure conditions and measured outcomes.

What can damage the molecule

- Heat can accelerate degradation and aggregation. Sensitivity depends on the molecule and formulation. PMID: 36986796; PMID: 14567625.
- Light contributed to instability in the experimental insulin formulations studied. This does not establish identical light sensitivity across all peptides. PMID: 35779744.
- Agitation and exposure to interfaces can contribute to physical instability. Ordinary movement does not automatically destroy every peptide. PMID: 36986796.
- Freezing changes the local environment as ice forms. Manufacturing freeze-drying evidence does not validate repeated freezing and thawing of a reconstituted solution. PMID: 21426937.
- Moisture exposure and changes in excipient structure can undermine a lyophilized formulation during storage. PMID: 25636302.

Labeling and travel

A handling record identifies the formulation, concentration, preparation time and applicable discard deadline while preserving lot information. A clinical audit evaluated date-and-time labeling and compliance with multidose-vial policies. It did not validate a universal peptide labeling template. The record below is an organizational aid assembled from those handling principles. PMID: 36875329; PMID: 27184207.

Concentration means mass per final solution volume. Diluent volume added and final solution volume are not automatically interchangeable. The labeled formulation determines the concentration calculation. The EGRIFTA SV prescribing information provides a formulation-specific example; its relationship between diluent volume and concentration cannot be assumed for an unidentified powder.

Formulation and strength:
Lot and original expiration:
Diluent identity and lot:
Reconstitution date and time:
First puncture date and time, if different:
Final concentration in mg/mL or mcg/mL:
Required storage conditions:
Discard date and time, or immediate-use requirement:
Source of concentration and discard deadline:
Temperature excursion details:

During travel, the handling objective is to maintain the labeled conditions throughout the journey. Insulation alone does not document temperature. Monitoring records exposure, while separation from frozen packs limits direct contact with a freezing source. These are practical implications of temperature and freezing research. They do not validate a particular travel container or an untested formulation. PMID: 33534816; PMID: 21426937.

Assessment after a temperature excursion requires the observed range, duration, formulation and preparation date. Returning a vial to refrigeration does not establish that the exposure was acceptable. The secretin study demonstrates that environmental conditions can affect formulation quality. It cannot supply an excursion allowance for other peptides. Without applicable stability data, the remaining stability is uncertain. PMID: 25636302.

Clarity cannot certify quality

Unexpected cloudiness, particles or discoloration can identify a problem. Their absence cannot certify potency or sterility. Published stability experiments used chromatography, mass spectrometry, particle measurements or biological assays to detect changes beyond visible appearance. Those stability measurements do not replace microbiological controls. PMID: 35779744; PMID: 25636302; PMID: 33534816; PMID: 27184207.

The experimental stability findings cited here are laboratory evidence, grade D under this product's scale. They establish neither clinical efficacy nor human safety for an untested preparation. Regulatory handling instructions and infection-control guidance are separate evidence categories. The hospital audit evaluates clinical practice, not peptide treatment outcomes. Approval of an example drug does not upgrade an extrapolated storage claim to grade A.

Handling and storage checklist

- The exact formulation has documented diluent and preparation instructions.
- Container integrity, expiration and lot information have been checked.
- Aseptic preparation includes stopper disinfection and sterile equipment.
- Mixing method and dissolution conditions match the product instructions.
- The record identifies concentration, preparation time and the applicable discard deadline.
- Storage and travel conditions match the validated requirements.
- Temperature excursions and unexpected appearance changes trigger product-specific assessment.
- Clear appearance is never treated as proof of potency or sterility.

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Routes and technique: subcutaneous, intramuscular, intranasal, oral, topical

A route determines which barriers a peptide encounters before reaching its target. Systemic bioavailability describes the fraction of an administered dose that reaches systemic circulation intact. Local activity in the intestine or skin is a separate outcome. Neither gastric stability nor penetration into superficial skin establishes effective bloodstream exposure. Formulation, molecular properties and the delivery device all matter. There is no reliable bioavailability percentage for peptides as a class. These distinctions are supported by the absorption and delivery literature, PMIDs 25122564, 30429357 and 34936316.

Technique cannot establish the quality, efficacy or safety of an unapproved preparation. A dose documented for one formulation or route cannot be transferred to another without supporting pharmacokinetic data. Injection training belongs with a qualified clinician. PMIDs 27594187 and 42198317.

What each route changes

ROUTE	DELIVERY PRINCIPLE	MAIN LIMITATION
Subcutaneous	Absorption from tissue beneath the skin into blood and lymph.	Absorption rate and losses vary by molecule and formulation, PMID 25122564.
Intramuscular	Deposition in muscle, with exposure dependent on preparation and placement.	A needle that does not reach muscle changes the intended route, PMID 36669836.
Intranasal	Delivery onto nasal mucosa, bypassing gastrointestinal degradation for the nasally absorbed fraction.	Deposition, clearance and device performance influence exposure, PMID 23316447.
Oral	Delivery through the gastrointestinal tract.	Enzymatic degradation and poor epithelial permeability limit most peptides, PMID 30429357.
Topical	Application to skin for a potential local effect.	The stratum corneum restricts penetration; systemic delivery requires separate evidence, PMID 34936316.

Subcutaneous: site selection and rotation

Subcutaneous administration bypasses gastrointestinal digestion but does not guarantee complete absorption. Transport through interstitial tissue, uptake into blood or lymph, and degradation before systemic entry depend on the molecule. Findings from insulin or larger therapeutic proteins cannot establish the pharmacokinetics of an unrelated experimental peptide. PMID 25122564.

Insulin guidance provides a documented clinical framework for site care. Documented sites include abdominal subcutaneous tissue, thighs, buttocks and upper arms. Selection considers tissue depth, accessibility and the medicine's approved instructions. Inspection identifies inflammation, wounds and lipohypertrophy, which is thickened or lumpy tissue associated with repeated insulin administration. Such tissue can produce delayed and unpredictable insulin absorption. PMIDs 27594187 and 28670547.

A documented insulin rotation scheme divides the abdomen into quadrants or other regions into halves. It uses one section for a week before moving systematically to another, with individual puncture sites separated by 1 to 2 cm, PMID 28670547. This scheme distributes puncture sites across a defined area. The evidence

concerns insulin technique. It does not demonstrate that administration near an injured tendon directs an experimental peptide to that tendon.

Needle dimensions: diameter and depth are separate

Gauge describes needle diameter, with higher numbers indicating narrower needles. Length influences potential tissue reach, together with anatomy and placement. A pen needle and a syringe needle are different device components, so dimensions alone do not establish compatibility. Insulin guidance supports short needles to reduce accidental intramuscular delivery. That conclusion concerns the intended tissue layer and does not establish suitability for an experimental peptide preparation. PMIDs 27594187 and 28670547.

DOCUMENTED CONTEXT	GAUGE AND LENGTH	INTERPRETATION
Subcutaneous insulin pens	32 G, 4 mm; comparators included 31 G, 5 or 8 mm, PMID 20429832.	A short randomized crossover trial found comparable glycemic control across the tested needles in adults with diabetes.
Subcutaneous insulin syringes	28 to 31 G, with 6 or 8 mm lengths described, PMID 28670547.	Guidance favors shorter options when appropriate to reduce unintended muscle entry, PMIDs 28670547 and 27594187.
Adult deltoid vaccination	22 to 25 G; lengths include approximately 25 or 38 mm, PMID 36189092.	These are vaccination dimensions, not a universal specification for injectable peptides.

Hygiene and sharps handling

Documented injection practice includes clean hands, a clean preparation area, site inspection, and a new sterile needle and syringe for each administration. Pens and other injection devices are not shared. Where alcohol is used to clean skin, it is allowed to dry completely. Home insulin guidance sometimes accepts visibly clean skin without routine alcohol preparation. That context does not establish the sterility of an unapproved injectable preparation. PMIDs 27594187 and 28670547.

Documented sharps handling includes prompt placement in an appropriate puncture-resistant container, with final disposal through the applicable local collection system. Loose needles in household rubbish expose other people to injury. Recapping and manual needle handling add opportunities for needlestick injury. Device-specific removal procedures and sharps disposal therefore form part of training. PMID 28670547.

Intramuscular: placement determines the tissue reached

Intramuscular delivery depends on anatomical landmarks and sufficient needle reach without penetration into unintended structures. A systematic review found that some participants outside the underweight category required needles longer than 25 mm for adequate deltoid muscle penetration, PMID 36669836. Body mass index alone could not supply a dependable universal cutoff. These findings address anatomical placement, not dose selection or therapeutic superiority.

The deltoid is a documented vaccination site, but its needle specifications cannot simply be applied to every peptide formulation. Accidental deposition in adjacent shoulder structures can cause injury, PMID 36189092. Intramuscular administration also does not establish superior bioavailability. BPC-157 has species-dependent preclinical intramuscular absorption data, without a validated human conversion from subcutaneous or oral administration, PMID 42198317.

Intranasal: volume, deposition and device performance

Nasal absorption bypasses gastrointestinal digestion, but the nasal valve, mucus clearance and deposition pattern constrain exposure. Some deposited material can be cleared toward the throat and swallowed.

Reaching nasal tissue does not establish delivery to a particular brain region. Pump characteristics, formulation and administration technique require evaluation together. PMID 23316447.

The device review reports typical intranasal pump output of 0.1 mL per actuation, ranging from 0.025 to 0.2 mL across devices, PMID 23316447. These are device volumes, not peptide doses or administration frequencies. Nominal output describes liquid emitted by the pump, not the volume retained at a target site. Bilateral administration cannot be inferred from pump output alone.

Priming, head position and breathing instructions are device-specific. More liquid does not necessarily increase absorbed drug because retention and clearance remain limiting. Reproducible pump output also does not prove reproducible bloodstream exposure. Interpretable regimen documentation includes concentration, volume per actuation, actuations per nostril and frequency. The phrase one spray alone does not identify a peptide dose. PMID 23316447.

Nominal amount per actuation = concentration in mcg/mL x measured mL per actuation
Nominal amount per administration = amount per actuation x total actuations
These calculations describe emitted drug, not the amount deposited or absorbed.

Oral: stability, permeability and local action

Most peptides face two independent oral barriers: enzymatic breakdown and limited movement across gastrointestinal epithelium. Surviving digestion solves only the first. Oral semaglutide illustrates a formulation-specific exception. Coformulation with the absorption enhancer SNAC supports local protection from degradation and transcellular stomach absorption. Its success cannot be generalized to an ordinary capsule containing another peptide. PMID 30429357.

PIONEER 1 studied oral semaglutide target doses of 3 mg, 7 mg or 14 mg once daily versus placebo, PMID 31186300. The trial enrolled adults with type 2 diabetes and lasted 26 weeks. These are trial regimens, not reader recommendations or conversion factors for other formulations. Oral semaglutide qualifies as evidence A because it is an approved medicine. That grade does not transfer to other oral peptides or establish benefit for every training goal.

The Rybelsus US prescribing information contraindicates semaglutide with personal or family history of medullary thyroid carcinoma, or multiple endocrine neoplasia syndrome type 2. Prior serious hypersensitivity to semaglutide or formulation ingredients is also a contraindication. The label additionally warns about pancreatitis, severe gastrointestinal reactions and gallbladder disease.

BPC-157 is reported to remain stable in gastric juice, but human pharmacokinetics, formulation characterization and validated dosing remain insufficiently established, PMID 42198317. Gastric stability is grade D laboratory evidence. Proposed oral therapeutic effects remain predominantly preclinical, grade C. Chemical persistence does not demonstrate human benefit. BPC-157 is prohibited at all times under WADA category S0. Sport Integrity Canada's April 27, 2026 advisory confirms its inclusion on the 2026 Prohibited List.

KPV offers a different hypothesis: local intestinal activity involving the dipeptide and tripeptide transporter PepT1. Researchers demonstrated cellular uptake and anti-inflammatory effects, then reduced inflammation in mouse colitis models using KPV in drinking water, PMID 18061177. This supports grade C animal efficacy and grade D cellular mechanisms. It does not establish human oral bioavailability, clinical efficacy or a validated human dosing regimen.

Topical: reaching skin is not reaching every target

Topical delivery aims at local skin effects; transdermal delivery implies passage through skin toward systemic circulation. The stratum corneum restricts many peptides because molecular size, charge and hydrophilicity impede passive transport. Results obtained with penetration enhancers or barrier-disrupting devices describe those specific systems. They cannot establish the performance of every cream containing the ingredient. PMID 34936316.

For GHK-Cu, a laboratory study found almost no peptide or copper passage through intact excised human skin under its test conditions. Microneedle pretreatment increased passage, PMID 25690343. This is grade D laboratory delivery evidence, not proof of clinical rejuvenation or a validated home procedure. It also does not establish that all topical GHK-Cu formulations are inactive. Deposition within skin and complete passage through skin are different measurements.

Argireline, acetyl hexapeptide-8, shows poor passive permeation associated with its molecular properties. Chemical modification improved transport for certain analogues in laboratory experiments, PMID 29371611. Separately, a randomized study involving 60 participants reported cosmetic improvement with topical application twice daily for four weeks, PMID 23417317. That small, short human trial supports grade B cosmetic evidence, while the penetration experiments remain grade D. Neither establishes systemic exposure or reliable delivery to deep muscular targets.

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UU LIFE

Safety architecture: contraindications, interactions, red flags and drug testing

Safety assessment begins before protocol selection: identify the compound, establish its regulatory status, review medical history and medications, and define discontinuation criteria. Evidence belongs to a particular molecule, formulation, population and indication. Findings from prescribed growth hormone replacement do not establish the safety of experimental secretagogues in healthy adults. Limited human observations cannot establish the long-term safety of a research peptide. References: PMID 21602453; PMID 35319491; PMID 40756949.

A serious new symptom overrides the protocol and the next planned administration. Stop the suspected compound and seek care at the urgency described below.

Contraindications: distinguish formal exclusions from precautions

An absolute contraindication means a specific medicine should not be used in that setting. A precaution requires assessment of competing risks and alternatives. Neither term should be applied indiscriminately to an entire family. This book also uses editorial exclusions for elective physique, recovery and longevity protocols. These are broader than some prescribing labels and are identified explicitly below. The table presents selected concerns, not every contraindication.

FAMILY OR SETTING	EXCLUSION OR CONCERN	INTERPRETATION
GH axis: growth hormone and GH-stimulating compounds	Active malignancy	Active malignancy contraindicates prescribed GH replacement. Extending this exclusion to experimental GH stimulation is this book's precautionary policy, not an approved label for every secretagogue. PMID 21602453; PMID 35319491.
IGF-1 and analogues	Active malignancy or malignancy history	The Increlex US prescribing information contraindicates mecasermin in pediatric patients with malignancy or a history of malignancy. This does not establish eligibility for experimental adult IGF-1 analogues. PMID 19707272.
All elective protocols in this book	Pregnancy and breastfeeding	Excluded from this book's elective protocols because adequate safety evidence is unavailable. This is not a universal contraindication to medically necessary peptide medicines. Incretin pregnancy and lactation evidence remains limited. PMID 41885132.
Incretins with applicable thyroid warnings	Personal or family history of medullary thyroid carcinoma, or MEN2	Formal contraindications appear in the Wegovy and Zepbound US prescribing information. Ordinary hypothyroidism is different. These warnings do not establish that semaglutide or tirzepatide causes human thyroid cancer.
Bremelanotide	Known cardiovascular disease or uncontrolled hypertension	Formal contraindications in the Vyleesi US prescribing information. Bremelanotide transiently raises blood pressure. Its labeling cannot automatically be assigned to every melanocortin compound. PMID 31429064.
Incretin therapies	Previous pancreatitis	A history requiring clinical assessment, not a universal absolute contraindication. Suspected acute pancreatitis requires discontinuation and evaluation. PMID 34305810.

FAMILY OR SETTING	EXCLUSION OR CONCERN	INTERPRETATION
Semaglutide and tirzepatide	Severe gastroparesis	The Wegovy and Zepbound US prescribing information state that treatment is not recommended in severe gastroparesis. This is distinct from a formal contraindication.
Any specific medicine	Previous serious hypersensitivity to that medicine or an ingredient	Check the exact label for formal contraindications. A different formulation or repeat exposure cannot be assumed tolerable without specialist assessment. PMID 33204386.

A remote cancer history is not equivalent to active cancer. A consensus supports considering GH replacement in selected GH-deficient cancer survivors in remission after individualized assessment. This does not establish suitability for bodybuilding exposure or IGF-1 analogues. Limited observational reassurance after inadvertent early incretin exposure does not establish safety throughout pregnancy or breastfeeding. References: PMID 35319491; PMID 41885132.

Formal exclusions depend on the exact medicine and jurisdiction. The label statements above were checked against the [Wegovy US prescribing information](<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ee06186f-2aa3-4990-a760-757579d8f77b>), [Zepbound US prescribing information](<https://www.dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=487cd7e7-434c-4925-99fa-aa80b1cc776b>), [Increlex US prescribing information](<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a8b27a1b-a611-4f91-ad22-76d4b390c3ae>), and [Vyleesi US prescribing information](<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f1d0c1b5-2f39-4bad-a6a4-0066e3ad5dcf>).

Interactions: review the complete medication list

Record prescriptions, nonprescription medicines, supplements and intermittent treatments. Include the actual formulation and route. Interaction evidence for an approved molecule does not automatically cover an experimental analogue. An empty interaction database entry means insufficient information rather than demonstrated compatibility. This distinction matters especially when clinical safety evidence is inadequate, as illustrated by the BPC-157 review. Reference: PMID 40756949.

EXPOSURE	COMMON MEDICATION INVOLVED	DOCUMENTED ISSUE
GLP-1 receptor agonists	Insulin or sulfonylureas	Hypoglycemia risk increases with these background medicines. The prescriber may need to reassess treatment and glucose monitoring. PMID 34305810.
GH replacement	Diabetes medicines	GH can reduce insulin sensitivity and change glucose-lowering treatment requirements. PMID 21602453.
GH replacement	Levothyroxine or glucocorticoid replacement	GH can change thyroid and cortisol physiology, revealing inadequate replacement or previously masked pituitary deficits. PMID 21602453.
Injectable GLP-1 receptor agonists studied in the review	Oral drugs, including warfarin and digoxin	Delayed gastric emptying can change absorption timing. Reviewed studies generally found no clinically important overall exposure change. Narrow therapeutic index medicines and kidney dysfunction warrant individualized review. PMID 38273155.
Bremelanotide	Oral naltrexone	Reduced naltrexone exposure can compromise treatment. The Vyleesi US prescribing information advises avoiding this combination when oral naltrexone treats alcohol or opioid addiction.

Tirzepatide has a specific oral hormonal contraception warning. Its US label calls for nonoral contraception or an added barrier method for four weeks after initiation and four weeks after each dose escalation. This is not a blanket rule for every incretin. Reference: [Zepbound US prescribing information, sections 7.2 and 8.3]

For bremelanotide, reduced oral naltrexone exposure creates a risk of treatment failure. This is a potential clinical consequence, not an inevitable outcome. Reference: [Vyleesi US prescribing information, section 7.2] (<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f1d0c1b5-2f39-4bad-a6a4-0066e3ad5dcf>).

Planned anesthesia or deep sedation also belongs in the medication review. GLP-1 therapies delay gastric emptying, and pulmonary aspiration has been reported during procedures. The anesthesia team needs the exact exposure history; this chapter provides no universal interruption schedule. Reference: [Wegovy US prescribing information, section 5.10] (<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ee06186f-2aa3-4990-a760-757579d8f77b>).

Red flags: symptoms determine urgency

The following are triage signals, not diagnoses. Suspend further exposure to the suspected compound while arranging assessment. Emergency symptoms require emergency services rather than waiting for routine laboratory results.

SYMPTOM	POSSIBLE CONCERN	REQUIRED RESPONSE
Tongue or throat swelling, wheezing, breathing difficulty or collapse	Anaphylaxis, which can occur without a rash	Emergency services immediately; follow an existing prescribed allergy emergency plan. PMID 33204386.
Chest pain, collapse, or severe headache with neurological symptoms	Possible cardiovascular or neurological emergency	Emergency assessment immediately. These symptoms warrant assessment regardless of the suspected cause; bremelanotide additionally has a documented blood pressure warning. Vyleesi US prescribing information.
Confusion, seizure or loss of consciousness, especially with sweating or tremor	Severe hypoglycemia or another emergency	Emergency assistance; do not give food or drink to someone unable to swallow safely. Mecasermin-associated hypoglycemia is discussed in PMID 19707272.
Persistent severe upper abdominal pain, sometimes extending to the back	Possible acute pancreatitis	Urgent hospital assessment, especially with repeated vomiting. PMID 34305810.
Right upper abdominal pain with fever or jaundice	Possible gallbladder or biliary complication	Urgent same-day assessment; severe illness warrants emergency care. PMID 34305810.
Repeated vomiting, inability to retain fluids, faintness or markedly reduced urination	Dehydration and possible acute kidney injury	Urgent same-day assessment; collapse or confusion warrants emergency services. PMID 34305810.
Severe new headache with visual changes or vomiting during GH or IGF-1 exposure	Possible intracranial hypertension	Urgent assessment rather than treating this as an expected adjustment effect. PMID 19707272; PMID 21602453.
Expanding redness, severe localized pain, pus or fever after skin penetration	Possible skin or deeper tissue infection	Same-day assessment; rapidly progressive pain, confusion or systemic illness warrants emergency care. PMID 24947530.

Provide the treating team with the compound name, packaging details, route, exposure timing, other medicines and symptom chronology. These details help distinguish an adverse drug effect from infection, an interaction or an unrelated illness. Keep the record factual; a presumed explanation should not delay assessment.

When laboratory testing is warranted

Testing should answer a clinical question. In medically indicated GH treatment, assessment includes IGF-1, glucose status and relevant thyroid and adrenal function. Results are interpreted alongside symptoms and the

underlying pituitary diagnosis. Monitoring during prescribed replacement cannot establish a validated safety schedule for experimental secretagogues. Reference: PMID 21602453.

For incretin treatment, glucose monitoring is particularly relevant with insulin or sulfonylureas. Significant vomiting or diarrhea can warrant renal function and electrolyte assessment. Compatible abdominal symptoms can warrant pancreatic enzymes and imaging selected by the clinician. Isolated enzyme elevations do not establish pancreatitis. Repeated testing in an asymptomatic person does not provide clearance for continued exposure. Reference: PMID 34305810.

Routine calcitonin testing or thyroid ultrasound has uncertain value for screening asymptomatic semaglutide users. A thyroid nodule or relevant history requires its own assessment. Reference: [Wegovy US prescribing information, section 5.1](https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ee06186f-2aa3-4990-a760-757579d8f77b).

Normal bloodwork cannot validate an unstudied exposure. Grade A denotes an approved drug or multiple human randomized trials, not established safety for every use. Grade B covers small, short or single-arm human trials, or consistent case series. Grade C covers animal evidence or human data too weak for the claim. Grade D covers in vitro, mechanistic or anecdotal evidence. The BPC-157 review found predominantly preclinical evidence, one weak human study and no clinical safety data within its search through June 3, 2024. Its musculoskeletal application evidence remains grade C on this scale. Reference: PMID 40756949.

Drug testing and athlete responsibility

These examples follow the WADA 2026 Prohibited List, effective January 1, 2026. The listed S0, S2 and S4 substances are prohibited in and out of competition. Reference: [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

CATEGORY	RELEVANT EXAMPLES	INTERPRETATION
S0: Non-approved substances	BPC-157	Covers pharmacological substances without governmental approval for human therapeutic use when not addressed elsewhere on the List.
S2: Peptide hormones, growth factors, related substances and mimetics	GH, AOD-9604, CJC-1295, tesamorelin, ipamorelin, GHRPs, IGF-1 and TB-500	Medicinal approval does not remove the sporting prohibition.
S4: Hormone and metabolic modulators	MOTS-c, insulins, insulin mimetics and follistatin	Follistatin appears among myostatin-binding proteins; MOTS-c appears among AMPK activators.

A prescription is not itself a Therapeutic Use Exemption. TUE requirements and recognition depend on the athlete's status and responsible organization. Strict liability means intent is not required to establish a prohibited-substance presence violation; fault can still affect consequences. Reference: [World Anti-Doping Code, articles 2.1 and 4.4](https://www.wada-ama.org/sites/default/files/resources/files/2021_wada_code.pdf).

Verify the exact substance against the current List and applicable sport rules. Absence from this example table does not establish eligibility. Analytical methods continue to develop, and a previous negative test does not establish permission. The cited review discusses analytical research and the 2025 List; it does not establish the 2026 classifications. Reference: PMID 41702393.

Legal status: separate three different questions

An approved drug has authorization for a defined product and use. That authorization does not transfer automatically to another formulation or research analogue. A research compound may have published biological findings without approval for human treatment. The BPC-157 review describes this distinction and reports the compound's lack of FDA approval. Reference: PMID 40756949.

A cosmetic ingredient belongs to a different regulatory context. In the United States, intended use and claims help determine whether a product is a cosmetic, a drug or both. Cosmetic marketing does not establish

Jurisdiction matters: prescribing, compounding, importation, possession and supply can be governed differently. Regulatory authorization, clinical suitability and sporting eligibility are separate checks. Current local requirements must be confirmed for the exact product and intended activity with the relevant regulator or qualified professional. This chapter provides no universal legal clearance.

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The hierarchy of systems: why protocols can fail before the first dose

A protocol can fail before exposure begins because its target does not match the problem. The Protocol Room uses five assessment steps: inflammation and immunity, mitochondrial energy, nervous system and sleep, metabolism and insulin sensitivity, then tissue and anabolic stimulus. This is an editorial planning framework, not a clinically validated treatment sequence. The systems interact, and several problems may require attention together.

The rationale for this order is to examine constraints before considering additional biological stimulation. Low energy availability can compromise health and performance across multiple systems. Experimental sleep restriction reduced muscle protein synthesis in the group without added exercise (PMIDs: 37752011, 32078168). A hypertrophy assessment therefore includes food and sleep before attributing a plateau to growth signaling. These findings support checking foundations, but do not validate five sequential treatment stages.

Planning principle: identify unresolved constraints relevant to the goal before considering escalation. Their priority depends on clinical importance, not their position in this framework.

Evidence belongs to a specific claim. A means an approved drug or multiple human randomized trials. B means small, short or single-arm human trials, or consistent case series. C means animal evidence or human findings too weak to support the claim. D means in vitro, mechanistic or anecdotal evidence. Approval for one indication does not validate another goal, route or combination. Study quality and whether results support efficacy remain separate questions.

Step 1: inflammation and immunity

The intake questions concern persistent gastrointestinal symptoms, repeated illness, unresolved injury and deteriorating recovery. These observations belong in the assessment record; they are not diagnoses of systemic inflammation. The IOC consensus describes immune, gastrointestinal and performance consequences associated with problematic low energy availability. Food intake and training demand are therefore relevant assessment factors (PMID: 37752011).

BPC-157 is a catalog cross-reference for proposed inflammatory and repair pathways. Its musculoskeletal review included 35 preclinical studies and one small retrospective clinical study (PMID: 40756949). This supports Grade C for human tendon or ligament repair. Reported knee-pain relief does not establish restored tissue strength, and the review found no clinical safety data. KPV reduced inflammation in mouse colitis models, also Grade C for clinical gut-repair claims (PMID: 18061177).

Assessment first establishes the problem, nutritional adequacy and compatibility of training with injury and recovery capacity. Symptoms alone do not identify a nutritional deficiency or justify an immune intervention. Tendon & Ligament Repair, Post-Injury Recovery Accelerator and Gut Repair map here, with tissue function reassessed at step 5. Persistent or worsening unexplained symptoms warrant clinical assessment (PMIDs: 37752011, 40756949).

Step 2: mitochondrial energy

The record captures falling exercise tolerance, fatigue between sessions and difficulty sustaining previously manageable work. These are assessment prompts, not evidence of mitochondrial disease. Initial review concerns fueling, carbohydrate availability, recovery time and potentially relevant deficiencies. Low energy availability can impair performance, so fatigue alone does not establish a mitochondrial peptide target (PMID: 37752011).

MOTS-c connects this step with step 4. Its foundational study reported metabolic signaling effects and improved insulin sensitivity in mice, Grade C for therapeutic metabolic improvement in humans (PMID: 25738459). Elamipretide, cataloged as SS-31, illustrates the limits of target-based reasoning. MMPOWER-3 studied 40 mg subcutaneously once daily for 24 weeks in primary mitochondrial myopathy (PMID: 37268435). It did not improve the primary walking-distance or fatigue outcomes. This documented dose is not a reader recommendation or a regimen for unexplained fatigue.

Metabolic and Mitochondrial Reset and Longevity Maintenance therefore require a defined baseline and measurable outcome. Reset is a protocol title, not a demonstrated physiological event.

Step 3: nervous system and sleep

The screening record captures sleep opportunity, prolonged sleep onset, repeated awakenings, daytime fatigue and inconsistent concentration. Sleep assessment precedes attributing these observations to a need for cognitive enhancement. Cognitive behavioral therapy for insomnia has randomized-trial support (PMID: 26054060). A controlled study found reduced muscle protein synthesis during restricted sleep without added exercise (PMID: 32078168). Sleep therefore matters to both cognitive and tissue goals.

Catalog cross-references include Semax and Selank. The cited Semax study concerns protective signaling in rat cerebral ischemia; the Selank study concerns brain monoamines in mice (PMIDs: 34201112, 19093364). These provide Grade C support for proposed human applications, without demonstrating cognitive enhancement or neuro-regeneration in healthy trainees. DSIP has Grade B study-level evidence from a small insomnia trial. Its weak findings did not establish meaningful therapeutic benefit (PMID: 1299794).

Deep Sleep, Cognitive Focus and Neuro-Regeneration map here, but require different endpoints. Libido and Sexual Response also intersects this step. PT-141, or bremelanotide, has Grade A evidence from two randomized trials in premenopausal women with hypoactive sexual desire disorder. Those trials studied 1.75 mg subcutaneously as needed (PMID: 31599840). Desire and related distress improved, while nausea, flushing and headache were more frequent. These findings do not establish universal sexual enhancement. Uncontrolled hypertension and known cardiovascular disease are contraindications because bremelanotide can transiently raise blood pressure. Source: [U.S. bremelanotide prescribing information, contraindications and warnings](<https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f1d0c1b5-2f39-4bad-a6a4-0066e3ad5dcf>).

Step 4: metabolism and insulin sensitivity

The record includes weight and waist trends, eating patterns, training performance and clinically indicated glucose measurements. Subjective energy and appetite do not establish insulin sensitivity. Nutrition planning considers the goal, protein adequacy and the risk of problematic underfueling (PMIDs: 37752011, 28698222).

Semaglutide is the catalog example with established clinical weight-management evidence. STEP 1 studied a target dose of 2.4 mg subcutaneously once weekly, after escalation, alongside lifestyle intervention (PMID: 33567185). Participants had overweight or obesity without diabetes; gastrointestinal adverse effects were common. Grade A weight-management evidence does not establish muscle preservation. Contraindications include personal or family medullary thyroid carcinoma, multiple endocrine neoplasia type 2, and prior serious hypersensitivity to semaglutide or formulation ingredients. Source: [U.S. semaglutide weight-management prescribing information, contraindications](<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee06186f-2aa3-4990-a760-757579d8f77b>). MOTS-c remains Grade C for the human metabolic treatment claim based on the cited mouse experiment (PMID: 25738459).

Fat Loss with Muscle Preservation, Non-Incretin Recomposition and Metabolic and Mitochondrial Reset meet here. Non-incretin describes a category, not an equivalent evidence base. Clean Bulk and Advanced Hypertrophy also revisit this checkpoint. In an older-adult trial, the nonpeptide ghrelin mimetic MK-677 increased fat-free mass and reduced insulin sensitivity. Strength and function did not demonstrably improve; statistical power for functional endpoints was limited (PMID: 18981485).

Step 5: tissue and anabolic stimulus

Assessment now concerns training progression, tissue tolerance and nutritional support for adaptation. A plateau alone does not establish insufficient anabolic signaling. A meta-analysis found that protein supplementation augmented resistance-training gains (PMID: 28698222). Its modeled plateau was approximately 1.6 g/kg/day of total dietary protein consumed orally each day, with no further average fat-free-mass benefit above that level (PMID: 28698222). This is a population estimate, not an individual prescription or evidence for a specific meal schedule.

CJC-1295 is the catalog cross-reference for growth-hormone signaling. Short randomized studies of the long-acting form documented increased GH and IGF-I, Grade B for those hormonal endpoints (PMID: 16352683). They did not establish athletic hypertrophy, tendon recovery or long-term safety. BPC-157 remains Grade C for human musculoskeletal repair (PMID: 40756949). GHK-Cu literature includes mechanistic and preclinical tissue-remodeling findings. Extrapolation to a systemic Skin Hair and Connective Tissue regimen or human longevity benefit remains Grade D, without clinical validation (PMID: 29986520).

Mapping the 14 Protocol Room entries

This table assigns assessment priorities, not treatment sequences. Every entry still receives the full five-step review. The names describe intended goals; the cited studies do not validate these complete protocols or their combinations.

PROTOCOL	PRIMARY STEPS	FIRST PLANNING CHECKPOINT	OUTCOME TO DOCUMENT
Tendon & Ligament Repair	1 and 5	Injury assessment and workload	Function and load tolerance
Post-Injury Recovery Accelerator	1, 2 and 5	Diagnosis and rehabilitation plan	Rehabilitation milestones
Gut Repair	1	Cause of persistent symptoms	Symptoms and nutritional adequacy
Clean Bulk	4 and 5	Energy intake and progressive training	Strength, weight and waist
Advanced Hypertrophy	3, 4 and 5	Sleep, protein and recoverable workload	Strength and muscle measurements
Fat Loss with Muscle Preservation	4 and 5	Energy deficit and protein adequacy	Weight trend and strength
Non-Incretin Recomposition	2, 4 and 5	Evidence for the exact intervention	Waist and performance
Metabolic and Mitochondrial Reset	2 and 4	Fatigue assessment and metabolic baseline	Function and relevant laboratory results
Deep Sleep	3	Sleep opportunity and insomnia assessment	Sleep continuity and daytime function
Cognitive Focus	3	Sleep and baseline cognitive complaint	Repeatable task performance
Neuro-Regeneration	1 and 3	Neurological diagnosis and rehabilitation	Condition-specific function
Longevity Maintenance	1 through 5	Established risks and functional baseline	Function and risk-factor trends
Libido and Sexual Response	3 and 4	Nature and context of sexual symptoms	Desire, distress and response
Skin Hair and Connective Tissue	1 and 5	Diagnosis and nutritional assessment	Standardized photographs and function

Turning the hierarchy into a decision record

The decision record starts with the goal, unresolved constraint and evidence gap before any dose field. For example, a hypertrophy plateau with shortened sleep and inconsistent food intake generates a recovery and nutrition review. It does not establish growth-hormone deficiency. Reassessment distinguishes changes in symptoms, biomarkers and actual function.

Goal:
Primary hierarchy step:
Unresolved constraint:
Baseline measure:
Nonpeptide factors to address:
Compound evidence grade for this exact outcome:
Study population, route and frequency:
Documented dose source, if applicable:
Relevant contraindications and evidence gaps:
Review date and reassessment criteria:

Under the WADA 2026 Prohibited List, BPC-157, MOTS-c, CJC-1295, MK-677, IGF-1 and thymosin-beta-4 derivatives including TB-500 are prohibited at all times. BPC-157 appears in S0, MOTS-c in S4, and the other listed substances in S2. Sporting eligibility is a separate constraint from biological plausibility or evidence grade. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

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Your first 30 days: from reading to a documented plan

Your first month has a concrete deliverable: one defined goal, an evidence file, completed pre-checks, and a record another person can understand. Understand. Plan. Apply with judgment. This calendar organizes your work with UU LIFE PEPTIDES 2.0. It is an educational schedule, not a clinically validated treatment timeline. A documented decision to defer treatment is a completed outcome.

The calendar never authorizes treatment. Any treatment start requires a clinician-reviewed plan documenting the indication, contraindications, interactions, source, monitoring schedule, and stopping criteria.

Week 1: understand the system and define the question

Read Foundations before opening the Protocol Room. Use the glossary whenever a term changes your interpretation, especially mechanism, route, half-life, and evidence grade. Create one folder for references, calculator checks, clinical questions, sourcing documentation, and tracker exports. Keep unanswered questions visible.

DAY	ACTION	SAVED OUTPUT
1	Read Foundations and note unfamiliar terms in the glossary.	A short glossary and a list of unresolved questions.
2	Use the Master Map to identify one goal and its relevant module.	One goal sentence and one primary outcome to track.
3	Read the two or three cards most relevant to that goal.	A comparison of evidence, study population, outcomes, and uncertainties.
4	Open the cards' references and compare the studies with their claims.	A source file with PMIDs and notes on applicability.
5	Run the calculator as a documented arithmetic rehearsal using a sourced card example.	Inputs, units, source, result, and questions requiring verification.
6	Collect your health history, medication list, and existing measurements for clinical review.	A pre-check packet with missing information clearly marked.
7	Review the packet and open the progress tracker.	A baseline record and a decision to investigate, defer, or seek clinical review.

Choose a goal you can describe without naming a peptide. For example: document waist measurements under consistent conditions while maintaining the planned training schedule. Define the measurement method, timing, and what change would matter before collecting results. Keep secondary observations separate from the primary outcome.

Apply the system's evidence scale to each relevant claim. A means an approved drug or multiple human randomized trials. B means small, short, or single-arm human trials, or consistent case series. C means animal data only or human evidence too weak to support the claim. D means in vitro, mechanistic, or anecdotal evidence. Record the indication beside the grade. Approval or evidence for one purpose does not establish benefit for another.

On days 8 through 10, take the shortlisted cards and questions to a qualified clinician. Include medicines and supplements, allergies, relevant diagnoses, previous adverse reactions, and pregnancy or breastfeeding status where applicable. Document the intervention-specific contraindication and interaction review. Ask which examination, measurements, or laboratory tests are relevant. Record the answer; this chapter does not assign a universal peptide laboratory panel.

On days 11 through 14, use the Smart Buyer scorecard as a documentation audit. Record supplier identity and authorization, product classification, traceability, and the connection between the product lot and its certificate of analysis. Record the laboratory, report date, methods, and results. Keep identity, purity, and any required sterility or endotoxin documentation as separate fields. Mark absent evidence as missing.

The scorecard documents sourcing questions; it does not establish suitability for human use or provide medical clearance. For prescribed treatment, record dispensing details reviewed with the clinician or pharmacist. If competitive sport applies, record current WADA status from the official list, including applicable restrictions, the date checked, and any required review.

Revisit the calculator after the source review. Every dose figure needs route, frequency, and provenance in the same field. Use a study PMID, a named regulatory label, or the exact tag: commonly cited in non-clinical use; not validated in trials. That tag describes reported use, not a validated regimen. Use mcg, mg, IU, and mL consistently. Leave unsupported inputs blank.

Calculator verification record

Card and version:

Source PMID, named regulatory label, or non-clinical provenance tag:

Reported amount, unit, route, frequency, and provenance together:

Other required inputs and their sources:

Calculator output and unit, with provenance if a dose:

Independent arithmetic check:

Clinician or pharmacist questions:

Status: arithmetic verified, unresolved, or not applicable

Arithmetic verification does not establish clinical suitability.

Week 3: open the protocol record and log consistently

On day 15, identify the relevant Protocol Room entry and compare it with the reviewed plan. Record discrepancies for resolution. If treatment has been prescribed and pre-checks are complete, document the clinician-set start date and instructions. Otherwise, open a baseline-only record. The onboarding schedule continues without forcing a treatment start.

Written monitoring has evidence as a general behavior-change tool. A meta-analysis found that interventions promoting progress monitoring improved goal attainment, with larger effects when progress was physically recorded. This supports the logging habit, not peptide effectiveness or this calendar. Harkin B, 2016, Psychological bulletin, PMID 26479070.

- Log the date, primary outcome, measurement conditions, and whether the scheduled entry was completed.
- Record training, nutrition, sleep, illness, and medication changes as context.
- For prescribed treatment, record actual administration details and deviations. Each dose entry includes units, route, frequency, provenance, and the associated clinical instructions.
- Record new symptoms with onset, duration, severity, and the action taken. Symptoms requiring prompt assessment should not wait for day 30.
- Mark missing observations as missing instead of reconstructing them from memory.

Week 4: check completeness and prepare the review

On days 22 through 29, check the tracker for missing entries, inconsistent measurements, unrecorded changes, and unresolved symptoms. Summarize baseline and follow-up observations using the method

chosen in week one. Separate treatment exposure from adherence to logging. An empty tracker cannot establish that either treatment or monitoring occurred as planned.

CENT guidance addresses reporting formal N-of-1 trials, which use clinical-trial methods to evaluate individual treatment effects. This chapter adapts its emphasis on explicit methods and transparent reporting as an educational workflow. An ordinary before-and-after tracker does not establish causation or become a trial. Vohra S, 2016, *Journal of clinical epidemiology*, PMID 26272792. Interpret observed improvement alongside other changes.

Day 30: answer the review questions

1. What was the original goal, and did I measure the outcome I selected?
2. How complete is the baseline, and how many scheduled observations are missing?
3. Were measurement methods and conditions consistent enough to compare?
4. What changed, and did it meet the meaningful-change criterion recorded beforehand?
5. What training, nutrition, sleep, illness, or medication changes complicate interpretation?
6. What symptoms or adverse events occurred, and were the planned responses followed?
7. Do unresolved evidence, calculator, clinical, or sourcing questions remain?
8. What does the clinician recommend next, and when will the next review occur?

Finish with a dated record: continued observation, further assessment requested, or the clinician's documented treatment decision. Save the reasoning beside the tracker export and source file. Day 30 closes the onboarding review. It does not automatically end treatment, justify escalation, or establish long-term safety.

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Understand first.

Every card in the next three modules assumes these eight chapters.

UU.LIFE

2.0



MODULE 2 OF 5 · UU LIFE PEPTIDES 2.0

RECOMPOSITION

Fat loss and hypertrophy. Incretin analogs, GH fragments, GHRH and GHRP secretagogues, IGF-1 variants and myostatin pathway compounds: what each does, what the literature actually shows, and how they are sequenced.

Module 2

UU LIFE PEPTIDES 2.0

Verified references

Educational and informational reference for adults. Not medical advice, not a prescription. Do not use any substance. Many compounds described are not approved for human use and several are prohibited in sport. Decisions about any compound belong to you and a licensed clinician.

A UU LIFE PRODUCT · UU.LIFE

Cards in this module

01	Tirzepatide Dual GIP/GLP-1 receptor agonist	Evidence A
02	Semaglutide GLP-1 receptor agonist	Evidence A
03	Retatrutide Triple GIP/GLP-1/glucagon receptor agonist	Evidence A
04	Cagrilintide Long-acting amylin analog	Evidence A
05	Liraglutide GLP-1 receptor agonist	Evidence A
06	AOD-9604 Modified GH C-terminal fragment	Evidence C
07	HGH Fragment 176-191 GH C-terminal fragment	Evidence C
08	CJC-1295 GHRH analog	Evidence B
09	Ipamorelin Selective ghrelin receptor agonist (GHRP)	Evidence C
10	GHRP-2 Ghrelin receptor agonist	Evidence A
11	GHRP-6 Ghrelin receptor agonist	Evidence C
12	Hexarelin Ghrelin receptor agonist	Evidence C
13	Sermorelin GHRH analog	Evidence B
14	Tesamorelin GHRH analog	Evidence A
15	IGF-1 LR3 IGF-1 analog with reduced binding-protein affinity	Evidence C
16	PEG-MGF IGF-1 splice variant, pegylated	Evidence D
17	Follistatin-344 Activin and myostatin binding protein	Evidence C

Each card: what it is, mechanism, evidence grade, regulatory and sport status, reported doses with provenance, stacking, safety, reconstitution with a worked calculation, buying notes, common mistakes and the references you can verify.

Tirzepatide

Mounjaro, Zepbound

Dual GIP/GLP-1 receptor agonist

Module 2 · Recomposition

Goals: Fat loss

Route: SC weekly

Approved once-weekly GIP/GLP-1 receptor agonist with substantial weight-loss evidence. A body-composition substudy found roughly one quarter of lost mass was lean tissue.

WHAT IT IS

A synthetic 39-amino-acid peptide based on GIP, with aminoisobutyric acid at positions 2 and 13. A C20 fatty diacid attached through a linker at lysine 20 promotes albumin binding and prolonged exposure. Molecular weight is 4813.53 Da, according to the Zepbound US prescribing information. Its place in Recomposition rests on documented weight and fat-mass reduction in clinical populations. Relevant trade-offs include gastrointestinal intolerance, accompanying lean-mass loss and weight regain after withdrawal. These findings do not establish benefits for lean, trained adults.

MECHANISM

Tirzepatide activates GIPR and GLP-1R, incretin receptors that stimulate cAMP signaling and glucose-dependent insulin secretion. Laboratory receptor-binding affinities were 0.135 nM at GIPR and 4.23 nM at GLP-1R. These assay results describe receptor pharmacology, not the relative contribution of each receptor in an individual patient. Experiments using receptor-deficient mouse islets demonstrated activity through either remaining receptor (PMID 30473097).

Human effects include reduced food intake, improved glycemic control and delayed gastric emptying. Gastric-emptying delay was strongest after initial exposure and diminished with repeated treatment. Residual delay remained in participants with diabetes during escalation, so attenuation does not mean complete disappearance (PMID 32519795).

Animal experiments help explain possible contributions from GIPR. In obese mice, treatment reduced food intake and fat mass, with a small increase in energy expenditure (PMID 30473097). In obese mice lacking GLP-1R, tirzepatide improved insulin sensitivity through increased glucose disposal in white adipose tissue (PMID 34003802). These findings do not establish increased energy expenditure or muscle preservation in humans. Clinical trials establish treatment effects, but do not isolate each receptor's contribution to weight loss (PMIDs 34170647 and 40353578).

EVIDENCE · GRADE A

Approved drug supported by multiple large randomized trials for type 2 diabetes and weight management. Obesity trials generally enrolled adults with BMI at least 30, or at least 27 with a weight-related condition. Grade A does not extend to athletic performance, cosmetic use in lean adults or preservation of skeletal muscle.

Human data. SURMOUNT-1 randomized 2539 adults without diabetes to tirzepatide 5, 10 or 15 mg SC once weekly, or placebo, for 72 weeks (PMID 35658024). Mean weight changes were -15.0, -19.5 and -20.9 percent, respectively, versus -3.1 percent. Adverse-event discontinuation occurred in 4.3, 7.1 and 6.2 percent, versus 2.6 percent. SURPASS-2 studied 1879 adults with diabetes for 40 weeks.

Tirzepatide 5, 10 or 15 mg SC once weekly was

Animal and mechanistic data. Obese-mouse studies demonstrated reduced food intake and predominantly fat-mass loss (PMID 30473097). Receptor-deficient mice provided evidence for weight-independent insulin sensitization through GIPR (PMID 34003802). An ovariectomized, obese-diabetic mouse model also showed weight reduction during treatment (PMID 39113264). Rodent thyroid C-

compared with semaglutide 1 mg SC once weekly (PMID 34170647). HbA1c decreased by 2.01 to 2.30 percentage points versus 1.86; additional weight reduction ranged from 1.9 to 5.5 kg. SURMOUNT-5 randomized 751 adults with obesity without diabetes. At 72 weeks, mean weight change was -20.2 percent with tirzepatide versus -13.7 percent with semaglutide under maximum-tolerated-dose regimens (PMID 40353578). SURMOUNT-4 randomized 670 participants after a 36-week treatment lead-in. Over the next 52 weeks, continued treatment produced another 5.5 percent reduction; switching to placebo produced a 14.0 percent increase from randomization weight (PMID 38078870). The SURMOUNT-1 DXA analysis included 160 participants with baseline and follow-up scans. Approximately 74 percent of lost mass was fat and 26 percent was lean mass, versus 75 and 25 percent with placebo (PMID 39996356). DXA lean mass includes water and nonmuscle tissues; these proportions do not quantify skeletal-muscle loss or predict individual outcomes. A SURMOUNT-1 extension followed 1032 participants with obesity and prediabetes through 176 treatment weeks (PMID 39536238). The LEAN-PREP publication describes a planned resistance-exercise and protein trial, not completed results (PMID 42020128). The cited evidence does not establish performance benefits in lean athletes.

cell tumors support the US boxed warning; their relevance to humans remains unknown.

REGULATORY STATUS AND SPORT

STATUS	As of September 2026, the US Mounjaro label covers type 2 diabetes from age 10 and cardiovascular-event risk reduction in high-risk adults with type 2 diabetes. Zepbound is approved for adult weight reduction and long-term maintenance, and moderate to severe obstructive sleep apnea in adults with obesity. Weight-management eligibility includes obesity, or overweight with a weight-related condition. The EMA Mounjaro authorization includes type 2 diabetes and adult weight management. Sources: current US prescribing information and EMA Mounjaro EPAR. These authorizations do not establish an indication for athletic enhancement.
WADA	Not prohibited under the 2026 WADA Prohibited List. Markers of tirzepatide are included in section 6 of the 2026 WADA Monitoring Program, both in and out of competition. Monitoring does not itself constitute prohibition. The 2026 narrative review supports the non-prohibited classification, but does not justify excluding tirzepatide from monitoring (PMID 42511463). Status is specific to the current annual documents.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Approved route: subcutaneous administration in the abdomen, thigh or upper arm, with site rotation, according to the US prescribing information. The trials summarized here used SC administration. Neither oral nor intramuscular administration is an approved route in these labels.
HALF-LIFE	Approximately 5 days in phase 1 and a population model pooling 19 studies (PMIDs 30473097 and 38356317). The current Zepbound label reports approximately 5 to 6 days in obesity populations. Its median time to peak concentration is 24 hours, with an 8 to 72 hour range. Steady state occurs after approximately 4 weeks of weekly administration.
TIMING	US labels describe weekly administration at any time, independent of meals. They specify at least 72 hours between doses when changing the administration day. Missed-dose guidance uses a 96-hour window, followed by omission if that window has passed. Labels also specify non-oral contraception or additional barrier contraception for 4 weeks after initiation and each escalation.
CYCLE LENGTH	Continuous treatment has been studied through 176 weeks in adults with obesity and prediabetes (PMID 39536238). The labels do not define short treatment cycles. SURMOUNT-4 documented

substantial regain after withdrawal, measured relative to weight at week 36 (PMID 38078870). It did not compare abrupt discontinuation with tapering, so it cannot establish that tapering prevents regain. Neither study establishes an optimal treatment duration for lean, trained adults.

TITRATION

Approved escalation schedules reflect indication, response and tolerability, as described in the dose records. Early phase 1 schedules established dose-dependent gastrointestinal limitations; they do not validate accelerated routine escalation (PMID 30473097). The Zepbound label allows consideration of a lower maintenance dose when the current maintenance dose is not tolerated. No validated microdosing or split-week regimen is established by the evidence reviewed here.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved adult type 2 diabetes regimen	The Mounjaro US prescribing information starts at 2.5 mg SC once weekly. It permits 2.5 mg increases after at least 4 weeks at the current dose when additional glycemic control is needed. The adult maximum is 15 mg SC once weekly.	SC	Once weekly	Mounjaro US prescribing information, section 2.1, current label checked September 2026.
Approved adult weight-management and obstructive sleep apnea regimens	The Zepbound US prescribing information reports 2.5 mg SC once weekly for 4 weeks, followed by 5 mg SC once weekly. Subsequent increases are 2.5 mg after at least 4 weeks. Maintenance is 5, 10 or 15 mg SC once weekly for weight management, and 10 or 15 mg SC once weekly for sleep apnea. Maximum: 15 mg SC once weekly.	SC	Once weekly	Zepbound US prescribing information, sections 2.1 and 2.2. Initiation is not a maintenance regimen.
SURMOUNT-1, adults without diabetes, 72 weeks	Target doses were 5, 10 or 15 mg SC once weekly, reached through gradual escalation; the trial included an escalation period of up to 20 weeks (PMID 35658024).	SC	Once weekly	Randomized, placebo-controlled phase 3 trial, PMID 35658024. · PMID 35658024
SURMOUNT-5, obesity without diabetes, 72 weeks	Maximum tolerated tirzepatide doses were 10 or 15 mg SC once weekly. Comparator semaglutide doses were 1.7 or 2.4 mg SC once weekly (PMID 40353578).	SC	Once weekly	Open-label randomized phase 3b trial, PMID 40353578. · PMID 40353578
Phase 1 single-ascending-dose study	Single SC doses ranged from 0.25 to 8 mg. Vomiting was dose-limiting in the 8 mg group; 5 mg was considered the single-dose maximum tolerated dose in that study (PMID 30473097).	SC	One administration per single-dose cohort participant	Early experimental dose-finding study, PMID 30473097; not an approved initiation schedule. · PMID 30473097
Phase 1 repeated-dose studies over 4 weeks	Healthy participants received fixed doses from 0.5 to 4.5 mg SC once weekly or escalation to 10 mg SC once weekly. Diabetes cohorts included fixed 0.5 or 5 mg SC once weekly and escalation to 10 or 15 mg SC once weekly (PMID 30473097).	SC	Once weekly for 4 administrations	Separate healthy-volunteer and diabetes cohorts in PMID 30473097; their accelerated schedules are historical research methods. · PMID 30473097
Obese-diabetic, ovariectomized female mouse model	The study administered 10 nmol/kg SC once daily for 4 weeks, approximately 48.1 mcg/kg using the labeled molecular weight of 4813.53 Da (PMID 39113264). This conversion describes mouse exposure, not a human-equivalent dose.	SC	Once daily for 4 weeks	Animal study, PMID 39113264; mass conversion uses the Zepbound US label molecular weight. · PMID 39113264

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– Semaglutide

The Zepbound label does not recommend coadministration with another GLP-1 receptor agonist. Additional clinical benefit and a tolerable combined regimen have not been established.

– Liraglutide

Another GLP-1 receptor agonist, covered by the same Zepbound label limitation. Overlapping activity does not establish additive benefit.

– Retatrutide

Overlapping incretin-receptor activity. The verified studies do not establish combination efficacy, tolerability or dosing.

– Cagrilintide

A separate satiety pathway is insufficient evidence of clinical synergy. The reviewed tirzepatide studies do not establish this combination's benefit or gastrointestinal tolerability.

– Tesamorelin

The cited studies do not establish that adding this agent preserves skeletal muscle during tirzepatide treatment. Combination benefits and risks remain unquantified.

– Ipamorelin

The proposed lean-mass rationale lacks supporting human combination results in the verified evidence. A mechanistic hypothesis is not evidence of muscle preservation.

SAFETY

COMMON EFFECTS

Gastrointestinal effects predominate. SURPASS-2 reported nausea in 17 to 22 percent, diarrhea in 13 to 16 percent and vomiting in 6 to 10 percent (PMID 34170647). Most were mild to moderate. Labels also describe constipation, dyspepsia, abdominal symptoms, injection-site reactions and indication-specific reports of fatigue and hair loss. Hypoglycemia risk rises with insulin or sulfonylureas. Lean-mass reduction occurred in the DXA substudy, but its approximate one-quarter proportion is a group result, not an individual forecast (PMID 39996356).

SERIOUS SIGNALS

US label warnings include rodent thyroid C-cell tumors, pancreatitis, gallbladder disease, severe gastrointestinal reactions, dehydration-associated kidney injury, serious hypersensitivity and peri-anesthetic pulmonary aspiration. Rapid glycemic improvement can temporarily worsen diabetic retinopathy. A meta-analysis found increased gastrointestinal events, without statistically significant pancreatic or biliary increases for tirzepatide; uncommon harms remain possible (PMID 40189856).

CONTRAINDICATIONS

Formal US contraindications are personal or family history of medullary thyroid carcinoma, MEN 2, and previous serious hypersensitivity to tirzepatide or formulation ingredients. Severe gastroparesis is a condition in which use is not recommended. Pregnancy, lactation, pancreatitis history and coadministration restrictions are not interchangeable with formal contraindications. Zepbound is discontinued when pregnancy is recognized. Lactation data show low milk transfer, but infant outcomes remain insufficiently characterized. Type 1 diabetes and athletic enhancement are not labeled indications. Sources: current US prescribing information.

STOP RULES

Suspected pancreatitis or serious hypersensitivity requires discontinuation and urgent assessment under the US labels. Severe persistent abdominal pain, facial or throat swelling, breathing difficulty or fainting warrants urgent care. Persistent vomiting, dehydration, jaundice, visual deterioration or neck symptoms require prompt clinical review. An arbitrary 24-hour waiting period is inappropriate for severe symptoms. Pregnancy recognition or planning requires medication review. The

anesthesia team needs advance notice because delayed gastric emptying can persist despite fasting.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

Approved presentations are ready-to-use solutions. Current US labels list single-dose pens and vials containing 2.5, 5, 7.5, 10, 12.5 or 15 mg per 0.5 mL. Multidose vials and KwikPens provide the corresponding SC once-weekly dose amounts per 0.6 mL. These are distinct concentrations and presentations. Neither US label describes an approved lyophilized product requiring reconstitution.

SOLVENT

Approved solutions require no added solvent. Phase 1 used sterile saline or sterile water under investigational formulation controls (PMID 30473097). That study does not establish compatibility, sterility, preservative effectiveness or stability for arbitrary research vials. Bacteriostatic water cannot be assumed to reproduce the studied formulation.

STORAGE

Current US labels specify refrigeration at 2 to 8 C and protection from freezing, heat and light. Single-dose presentations allow a total of 21 days at no more than 30 C. Unopened multidose presentations allow 30 days at room temperature. Opened multidose presentations have limits of 30 days after first use, 30 cumulative room-temperature days, or four weekly doses, whichever applies first. These limits are presentation-specific and cannot establish a beyond-use date for reconstituted research material.

The Zepbound US label includes 5 mg SC once weekly as a weight-management maintenance dose. Its single-dose presentation contains 5 mg in 0.5 mL, equivalent to 10 mg/mL. The arithmetic is 5 mg divided by 10 mg/mL equals 0.5 mL. The same label lists a multidose presentation containing 20 mg in 2.4 mL, providing four 5 mg SC once-weekly doses of 0.6 mL each. This illustrates why total container mass, concentration and per-dose volume must be distinguished. It is a labeled-presentation calculation, not a recipe for preparing a research product. Insulin-syringe markings describe volume; they are not tirzepatide IU.

BUYING NOTES

Regulatory approval provides review of manufacturing quality, identity, strength and product-specific stability. Compounded and research preparations do not inherit that approval or the approved product's storage instructions. A certificate of analysis describes a tested sample; it does not establish that a supplied container matches that sample. Chromatographic purity, molecular identity, quantitative potency, sterility and endotoxin testing address different questions. A high purity percentage alone does not establish the amount of active drug or suitability for administration. Batch traceability and validated methods matter more than a generic certificate. Price alone cannot establish authenticity or prove adulteration.

COMMON MISTAKES

- Treating escalation intervals as optional or transferring accelerated phase 1 research schedules into routine use. The approved schedules address gastrointestinal tolerability.
- Confusing total container mass with the administered amount, or assuming all approved presentations use the same concentration and volume.
- Equating DXA lean mass with skeletal muscle or treating the approximately one-quarter lean-loss fraction as an individual prediction (PMID 39996356).
- Interpreting SURMOUNT-4's 14 percent regain as 14 percent of previously lost weight. It was an increase from randomization weight (PMID 38078870).
- Assuming a second appetite or growth-hormone pathway establishes a useful combination. The verified studies do not support the proposed peptide stacks.
- Treating the absence of a statistically significant rare-event signal as proof that pancreatitis, gallbladder disease or other serious events cannot occur.
- Assuming obesity approval establishes benefits for lean athletes, or confusing WADA monitoring with prohibition.

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Semaglutide

Ozempic, Wegovy, Rybelsus

GLP-1 receptor agonist

Module 2 · Recomposition

Goals: Fat loss

Route: SC weekly or oral daily

A GLP-1 receptor agonist with Grade A evidence for weight management and specific cardiometabolic indications. Trade-offs include gastrointestinal effects, loss of some lean mass, and substantial weight regain after withdrawal.

WHAT IT IS

Semaglutide is a modified analog of human glucagon-like peptide-1, or GLP-1. This intestinal hormone participates in glucose regulation, appetite signaling and gastric emptying. Semaglutide belongs in Module 2, Recomposition, because controlled trials demonstrate substantial weight reduction in populations with overweight or obesity.

Its molecular design prolongs exposure compared with native GLP-1. An amino-acid substitution at position 8 increases resistance to enzymatic degradation by DPP-4. A fatty diacid attached through a linker at lysine 26 promotes albumin binding. Substitution at position 34 directs attachment to the intended site. These modifications support an elimination half-life of approximately one week (Knudsen 2019, PMID 31031702).

Approved formulations include weekly subcutaneous injections and daily oral tablets. Oral formulations contain the absorption enhancer SNAC. The route, formulation and indication determine the dosing schedule. Oral and injectable milligram amounts are not interchangeable.

The clinical evidence concerns specified pharmaceutical formulations, eligibility criteria, follow-up and accompanying lifestyle interventions. It does not establish equivalent quality or outcomes for products sold as research material. The strongest weight-management trials enrolled adults with obesity, or overweight plus a related condition. They do not establish the benefit-risk balance for already-lean athletes seeking additional definition.

MECHANISM

Established receptor mechanism: semaglutide activates the GLP-1 receptor. This receptor signals principally through cyclic AMP and downstream pathways involved in hormone secretion and neuronal activity. In pancreatic beta cells, semaglutide enhances glucose-dependent insulin secretion. It also reduces inappropriate glucagon secretion. These effects explain improved glucose control and the relatively low hypoglycemia risk when semaglutide is used without insulin or insulin secretagogues (PMID 31031702).

Established appetite mechanism: reduced energy intake is a major driver of weight loss. In a crossover study of 30 adults with obesity, subcutaneous semaglutide was escalated to 1 mg once weekly over 12 weeks. Total intake across the measured freely available meals was 24 percent lower than with placebo. Participants reported less hunger, fewer cravings and better control of eating. Resting metabolic rate adjusted for lean mass did not differ between treatments. Mean weight declined by 5.0 kg, predominantly from fat mass (Blundell 2017, PMID 28266779). This finding does not demonstrate an increase in resting metabolism or guarantee the same appetite response in another population.

Animal studies help identify the relevant neural pathways. Semaglutide accessed selected brainstem and hypothalamic regions through circumventricular organs and sites adjacent to the ventricles. Broad passage across the blood-brain barrier was not demonstrated in that experiment. Direct and indirect neuronal activation involved circuits regulating eating, reward and meal termination. Rodents ate less and lost weight without reduced energy expenditure in the reported experiments (Gabery 2020, PMID 32213703). These findings describe that experimental model, not a complete map of human brain exposure.

Gastric emptying can also be delayed. Its contribution varies with treatment duration, formulation, meal characteristics and measurement method. A universal claim that this effect either disappears or persists

unchanged is unsupported. Delayed gastric emptying also matters for gastrointestinal tolerability and procedures involving anesthesia.

Established clinical outcomes extend beyond weight loss. Cardiovascular event reductions were demonstrated in SUSTAIN-6 and SELECT. Kidney outcomes improved in FLOW, and liver histology improved in the interim ESSENCE analysis (PMIDs 27633186, 37952131, 38785209, 40305708). These outcomes do not establish how much benefit comes from weight loss versus other physiological effects.

Semaglutide is not established as a muscle-preserving treatment. However, lean mass measurements are not interchangeable with skeletal muscle mass or strength. Lean tissue includes water and organs, and definitions vary by measurement method. A review reported substantial variation across GLP-1-based therapies, with lean mass representing approximately 15 percent or less to 40 to 60 percent of weight lost. That range is not a semaglutide-specific prediction for an individual (Neeland 2024, PMID 38937282).

EVIDENCE · GRADE A

Grade A applies to approved indications and outcomes supported by large randomized trials. It does not transfer automatically to athletic performance, cosmetic weight loss in lean adults, longevity or untested combinations.

STEP 1 enrolled 1961 adults without diabetes and found mean weight changes of minus 14.9 percent with semaglutide and minus 2.4 percent with placebo. Both groups received lifestyle intervention. At week 68, 86.4 percent of semaglutide participants with the relevant assessment had lost at least 5 percent of baseline weight. About half had lost at least 15 percent (PMID 33567185).

SELECT demonstrated fewer major cardiovascular events in adults with established cardiovascular disease and overweight or obesity without diabetes. Event proportions were 6.5 percent versus 8.0 percent, with a hazard ratio of 0.80 (PMID 37952131). This supports secondary cardiovascular prevention in the studied population. It does not establish the same absolute benefit in young, low-risk adults.

Trial averages describe groups, not guaranteed individual outcomes. Diabetes status, baseline risk, treatment persistence, formulation and statistical estimand affect comparisons. Results measured regardless of treatment discontinuation can differ from estimates assuming continued treatment.

Human data. STEP 1: subcutaneous semaglutide, escalated to 2.4 mg once weekly, was studied for 68 weeks with lifestyle intervention. Mean weight loss was 14.9 percent versus 2.4 percent with placebo. Gastrointestinal events caused discontinuation in 4.5 percent versus 0.8 percent (Wilding 2021, PMID 33567185). STEP 1 extension: 327 participants entered the exploratory extension analysis. Semaglutide participants had lost 17.3 percent at treatment completion and remained 5.6 percent below baseline one year later. Approximately two thirds of the previous loss had returned after both medication and structured lifestyle intervention ended. This was substantial regain, not near-complete regain in every participant (Wilding 2022, PMID 35441470). STEP 8: subcutaneous semaglutide targeted 2.4 mg once weekly, with 1.7 mg once weekly permitted for intolerance. Mean weight loss was 15.8 percent at 68 weeks. Gastrointestinal adverse events occurred in 84.1 percent of the semaglutide group (Rubino 2022, PMID 35015037). SURMOUNT-5: the semaglutide arm used the maximum tolerated subcutaneous dose of 1.7 mg or 2.4 mg once weekly. Mean weight loss was 13.7 percent at 72 weeks. This active-comparator trial does not establish results for other semaglutide

Animal and mechanistic data. Rodent experiments support appetite-related neural mechanisms. Semaglutide reduced food intake and body weight while accessing selected brain regions involved in feeding control (Gabery 2020, PMID 32213703). Animal exposure and clearance differ from human pharmacokinetics, so these experiments do not define human schedules. A mouse study investigating an experimental GLP-1 analog included semaglutide as a comparator. It reported weight changes of minus 10.9 percent with semaglutide and minus 23.0 percent with semaglutide plus cagrilintide. The study primarily concerned another experimental molecule. Its abstract did not sufficiently establish the semaglutide comparator's route and chronic dosing frequency for reproducing a complete dose entry here (Sun 2024, PMID 38582303). Class-level thyroid research demonstrated GLP-1 receptor-mediated calcitonin release and C-cell proliferation in rodents, with important species differences. This was not a dedicated semaglutide carcinogenicity study and does not establish the absence of human risk (Bjerre Knudsen 2010, PMID 20203154). Semaglutide-specific rodent tumor findings are described separately in regulatory labeling

doses or concurrent use of the compared agents (Aronne 2025, PMID 40353578). SUSTAIN-6: subcutaneous semaglutide at 0.5 mg or 1 mg once weekly reduced the cardiovascular composite, with a hazard ratio of 0.74. Retinopathy complications increased, with a hazard ratio of 1.76. Participants had type 2 diabetes and high cardiovascular risk (Marso 2016, PMID 27633186). SELECT: subcutaneous semaglutide targeted 2.4 mg once weekly in 17,604 adults without diabetes who had established cardiovascular disease. Mean follow-up was 39.8 months. Adverse events led to permanent discontinuation in 16.6 percent versus 8.2 percent with placebo (Lincoff 2023, PMID 37952131). PIONEER 1: oral semaglutide at 3 mg, 7 mg or 14 mg once daily improved HbA1c over 26 weeks. At 14 mg orally once daily, the treatment-policy estimate for weight change was 2.3 kg more loss than placebo. That number is a between-group difference, not the total weight loss in the treatment group (Aroda 2019, PMID 31186300). OASIS 1: oral semaglutide was escalated to 50 mg once daily during a 68-week trial. Mean weight loss was 15.1 percent versus 2.4 percent with placebo. This placebo-controlled study did not directly establish equivalence to an injectable formulation (Knop 2023, PMID 37385278). FLOW: subcutaneous semaglutide at 1 mg once weekly was studied in 3533 adults with type 2 diabetes and chronic kidney disease. The primary kidney-related composite had a hazard ratio of 0.76 over a median 3.4 years of follow-up (Perkovic 2024, PMID 38785209). ESSENCE: subcutaneous semaglutide at 2.4 mg once weekly improved liver histology in adults with MASH and stage F2 or F3 fibrosis. The interim analysis included the first 800 participants assessed at 72 weeks. MASH resolution without fibrosis worsening occurred in 62.9 percent versus 34.3 percent with placebo. Fibrosis improvement without MASH worsening occurred in 36.8 percent versus 22.4 percent. These histological endpoints do not yet establish reduced liver-related mortality (Sanyal 2025, PMID 40305708).

REGULATORY STATUS AND SPORT

STATUS

United States status checked against current prescribing information on September 5, 2026. Approved semaglutide formulations cover type 2 diabetes, weight management and specified cardiovascular indications. Injectable semaglutide also has an indication for kidney risk reduction in adults with type 2 diabetes and chronic kidney disease. [Ozempic prescribing information] (<https://www.novo-pi.com/ozempic.pdf>). The current weight-management label includes tablets and an additional higher-dose injectable presentation. Injectable semaglutide also has accelerated approval for noncirrhotic MASH with F2 to F3 fibrosis. Confirmation of clinical benefit remains required. [Wegovy prescribing information] (<https://www.novo-pi.com/wegovy.pdf>). FDA determined that the injectable semaglutide shortage was resolved on February 21, 2025. Restrictions on compounding essentially copies apply, subject to statutory conditions and applicable enforcement policies. Compounding is not categorically lawful only during a shortage, and compounded preparations are not FDA-approved. [FDA compounding policy] (<https://www.fda.gov/drugs/drug-alerts-and-statements/fda-clarifies-policies-compounders-national-glp-1-supply-begins-stabilize>).

Research-labeled material has no approval for human administration. A label claiming semaglutide does not establish molecular identity or pharmaceutical equivalence.

WADA

Not prohibited under the 2026 WADA rules. Markers of semaglutide are explicitly included in the 2026 Monitoring Program, both in and out of competition. Monitoring concerns substances outside the Prohibited List and does not itself prohibit use. Status is specific to the current rules and does not establish medical suitability. [WADA 2026 Monitoring Program](https://www.wada-ama.org/sites/default/files/2025-09/2026_list_monitoring_program_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

The established clinical routes are subcutaneous injection and oral administration using specifically formulated tablets. Weekly subcutaneous administration is supported by the major injectable trials. Daily oral administration is supported by PIONEER 1 and OASIS 1 (PMIDs 33567185, 31186300, 37385278). Oral exposure depends on formulation and administration conditions. Earlier clinical pharmacology studies estimated approximately 0.8 percent bioavailability under recommended conditions. This estimate is not universal across all newer oral formulations. Water volume, fasting and the interval before food or other medication influence exposure (Overgaard 2021, PMID 33969456). The oral prescribing information describes morning fasting administration with no more than approximately 120 mL water, followed by at least 30 minutes before food, other drinks or oral medication. These are label conditions, not a conversion method for injectable material. [Semaglutide tablet prescribing information](https://www.novo-pi.com/rybelsus.pdf). The reviewed evidence does not support treating intramuscular, intranasal, sublingual or research-powder preparations as equivalent alternatives.

HALF-LIFE

Approximately one week after subcutaneous or oral administration. Dedicated pharmacokinetic studies support prolonged exposure across the studied populations (Ikushima 2018, PMID 29536338; Granhall 2019, PMID 30565096). Steady state generally develops over several weeks of repeated administration. A weekly elimination half-life does not mean the drug disappears after one week. After five half-lives, approximately 3 percent remains under a simple first-order model. This calculation is an approximation, not a guarantee of an individual symptom timeline or complete elimination. Semaglutide undergoes proteolytic cleavage and metabolism of its fatty-acid side chain. Drug-related material is eliminated through urine and feces. The disposition study does not support describing clearance as dependent on a single organ (Jensen 2017, PMID 28323117).

TIMING

Weekly injectable trials used scheduled administration without a demonstrated need to coordinate treatment with workouts. No reviewed trial establishes that administration before a rest day improves outcomes or reliably prevents nausea. The Ozempic injection label describes a missed-dose allowance of five days, followed by omission if that interval has passed. It also specifies minimum spacing when changing the scheduled weekday. This is product-specific labeling, not a general early-or-late window for every formulation. Oral timing differs because absorption depends on administration conditions. The prescribed fasting interval and limited water volume are part of the studied delivery system (PMID 33969456). The evidence does not justify saying that any deviation invariably reduces absorption to zero. A prolonged interruption changes tolerability considerations. Re-escalation may be necessary under the relevant prescribing information. A maintenance dose previously tolerated is not automatically an appropriate restart dose.

CYCLE LENGTH

Semaglutide was developed and studied as ongoing treatment for chronic disease. The cited trials do not validate short physique cycles, scheduled drug holidays or repeated stop-start programs. Treatment lasted 68 weeks in STEP 1, 72 weeks in the semaglutide comparator arm of SURMOUNT-5 and 104 weeks in SUSTAIN-6. SELECT followed participants for a mean 39.8 months, while FLOW reported median follow-up of 3.4 years (PMIDs 33567185, 40353578, 27633186, 37952131, 38785209). The STEP 1 extension documented substantial regain after withdrawal, but also discontinued structured lifestyle intervention. It therefore cannot isolate every contribution to regain or prove that everyone will recover all lost weight. The extension also did not test a taper against abrupt cessation (PMID 35441470). There is no established taper that reliably prevents weight regain. Appetite may return as exposure declines, but a fixed deadline for its return is unsupported. Maintenance planning concerns nutrition, physical activity, disease control and clinical follow-up, not simply the date of the final administration.

TITRATION

Escalation schedules primarily address gastrointestinal tolerability while progressing toward a dose with evidence for the intended indication. They are not evidence that the highest available dose is appropriate for every person. STEP 8 permitted a reduction from the target of 2.4 mg to 1.7 mg subcutaneously once weekly for intolerance (PMID 35015037). The appetite crossover study used escalation to 1 mg subcutaneously once weekly (PMID 28266779). These studies answer different questions and do not establish interchangeable maintenance regimens. Lower appetite, slower weight loss or the absence of nausea cannot independently determine whether treatment is

adequate. Conversely, persistent vomiting or nutritional compromise should not be treated as evidence that a dose is working especially well. The reviewed trials do not establish microdosing, split weekly administration or indefinite low-dose plateaus as validated weight-management strategies.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
STEP 1 adult obesity trial and established injectable weight-management escalation	0.25 mg during weeks 1 to 4, 0.5 mg during weeks 5 to 8, 1 mg during weeks 9 to 12, then 1.7 mg during weeks 13 to 16. The target was 2.4 mg thereafter, all subcutaneous once weekly, as reported in STEP 1, PMID 33567185.	Subcutaneous	Once weekly	STEP 1, PMID 33567185; the extension confirms the 16-week escalation, PMID 35441470. These are study exposures, not individualized dosing instructions. · PMID 33567185
Type 2 diabetes injectable labeling and cardiovascular outcomes evidence	The Ozempic prescribing information reports 0.25 mg subcutaneously once weekly for four weeks, then 0.5 mg once weekly. Further increases to 1 mg and 2 mg once weekly require at least four weeks at the preceding dose when additional glycemic control is needed.	Subcutaneous	Once weekly	Ozempic prescribing information. The initiation dose is not considered effective for glycemic control, which does not mean it has no biological activity. SUSTAIN-6 studied maintenance doses of 0.5 mg or 1 mg subcutaneously once weekly, PMID 27633186. · PMID 27633186
Original oral formulation for type 2 diabetes	The Rybelsus prescribing information reports 3 mg orally once daily for 30 days, then 7 mg once daily. From day 61, 14 mg once daily is an option when further glycemic control is needed.	Oral	Once daily	Rybelsus prescribing information. PIONEER 1 studied 3 mg, 7 mg and 14 mg orally once daily, PMID 31186300. Tablet formulation and fasting conditions matter. · PMID 31186300
Newer oral formulation for type 2 diabetes	The current Ozempic tablet prescribing information reports 1.5 mg orally once daily for 30 days, then 4 mg once daily. From day 61, 9 mg once daily is an option when further glycemic control is needed.	Oral	Once daily	Current combined Rybelsus and Ozempic tablet prescribing information. These formulations are explicitly not substitutable milligram for milligram.
Current oral weight-management and cardiovascular-risk-reduction label	Wegovy prescribing information: 1.5 mg orally once daily for days 1 to 30, 4 mg for days 31 to 60, 9 mg for days 61 to 90, then 25 mg once daily.	Oral	Once daily	Wegovy prescribing information, revised June 2026. This approved schedule is distinct from the OASIS 1 investigational schedule.
Additional injectable adult weight-management maintenance option	Wegovy prescribing information permits 7.2 mg subcutaneously once weekly after at least four weeks tolerating 2.4 mg subcutaneously once weekly, when additional weight reduction is clinically indicated.	Subcutaneous	Once weekly	Wegovy prescribing information, revised June 2026. This option is indication-specific and was not the regimen evaluated in STEP 1 or SELECT.
OASIS 1 investigational oral obesity regimen	Escalation to 50 mg orally once daily during a 68-week treatment period, as reported in OASIS 1, PMID 37385278. The escalation itself did not last 68 weeks.	Oral	Once daily	OASIS 1, a randomized trial of 667 adults without type 2 diabetes. The trial dose should not be confused with current labeled oral strengths. · PMID 37385278

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
FLOW kidney outcomes trial	1 mg subcutaneously once weekly, as reported in FLOW, PMID 38785209, in adults with type 2 diabetes and chronic kidney disease.	Subcutaneous	Once weekly	FLOW randomized 3533 participants and reported median follow-up of 3.4 years. This dose has a disease-specific evidence base. · PMID 38785209
ESSENCE liver histology trial	2.4 mg subcutaneously once weekly, as reported in ESSENCE, PMID 40305708, in adults with MASH and F2 or F3 fibrosis.	Subcutaneous	Once weekly	ESSENCE planned interim analysis at 72 weeks. Histological improvement is distinct from established prevention of liver failure or liver-related death. · PMID 40305708

STACKING

+ Cagrilintide

Controlled human combination evidence exists. A phase 2 trial escalated both components to 2.4 mg each, subcutaneously once weekly, over a 32-week treatment period. Mean weight loss was 15.6 percent with the combination versus 5.1 percent with semaglutide alone (Frias 2023, PMID 37364590). REDEFINE 1 studied the same target amounts, each 2.4 mg subcutaneously once weekly, for 68 weeks. Mean weight loss was 20.4 percent versus 3.0 percent with placebo, using the treatment-policy estimand. Gastrointestinal events occurred in 79.6 percent versus 39.9 percent (Garvey 2025, PMID 40544433). Trial evidence does not establish compatibility, stability or equivalent exposure for independently sourced materials mixed together.

– Tirzepatide

Both agents activate GLP-1 receptors. Their concurrent use has no established efficacy or safety advantage in the cited trials. SURMOUNT-5 evaluated separate treatment groups, not combination treatment (PMID 40353578). Overlapping gastrointestinal effects and medication complexity are concerns.

– Liraglutide

Both are GLP-1 receptor agonists. STEP 8 evaluated separate treatment groups and provides no evidence for using them together (PMID 35015037). Concurrent GLP-1 agonist use is not recommended in the weight-management prescribing information.

– Retatrutide

GLP-1 receptor activity overlaps. Additional receptor activity does not establish a rationale for combining treatments. No controlled combination evidence was identified in this review, and additive adverse effects remain a concern.

– Tesamorelin

No controlled evidence identified here establishes additive benefit or muscle preservation with semaglutide. Independent activity on another hormonal pathway is insufficient to classify this pair as a demonstrated synergy.

– Ipamorelin

No controlled evidence identified here establishes prevention of semaglutide-associated lean tissue loss. Adding a secretagogue introduces another exposure without demonstrated benefit for this purpose.

SAFETY

COMMON EFFECTS

Common adverse effects include nausea, vomiting, diarrhea, constipation and abdominal discomfort. Gastrointestinal events affected 84.1 percent of semaglutide participants in STEP 8. In STEP 1, gastrointestinal events caused discontinuation in 4.5 percent versus 0.8 percent with placebo (PMIDs 35015037, 33567185). Many events occur during escalation and are transient, but persistence and severity vary. Frequency of gastrointestinal symptoms is different from frequency of serious complications. Trial discontinuation rates also depend on follow-up duration and management procedures. Reduced intake can compromise hydration and nutritional adequacy. Fatigue or declining training performance may reflect several causes and cannot automatically be attributed to calorie restriction. Hair loss and altered skin sensation appear in current weight-management labeling. Claims that mood changes or hair shedding simply track the size of the deficit are not established. Body-composition changes warrant interpretation alongside strength, function and nutritional status. A decrease in measured lean mass does not quantify muscle loss by itself (PMID 38937282).

SERIOUS SIGNALS

Clinically important concerns include pancreatitis, gallbladder disease, severe gastrointestinal reactions, hypersensitivity and acute kidney injury associated with volume depletion. Hypoglycemia risk increases with insulin or insulin secretagogues. Kidney injury should not be described as invariably caused by dehydration. SUSTAIN-6 found more diabetic retinopathy complications with semaglutide, with a hazard ratio of 1.76. Rapid improvement in glucose is a relevant clinical consideration, particularly with pre-existing retinopathy (PMID 27633186). Pulmonary aspiration has been reported during general anesthesia or deep sedation. Current multisociety guidance allows continuation for many patients and calls for individualized assessment of higher-risk circumstances. A universal one-week interruption is outdated. [Multisociety perioperative guidance] (<https://pmc.ncbi.nlm.nih.gov/articles/PMC11666732/>). EMA concluded in June 2025 that non-arteritic anterior ischemic optic neuropathy, or NAION, is a very rare adverse effect of semaglutide. Sudden visual loss requires urgent assessment. [EMA safety review] (<https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-2-5-june-2025>). Rodent thyroid C-cell tumors remain the basis for the United States boxed warning. Human relevance remains uncertain. Class-level species differences do not eliminate this uncertainty (PMID 20203154). In January 2026, FDA requested removal of the suicidal behavior and ideation warning after finding no increased risk in its comprehensive review. New suicidal thoughts still require urgent care regardless of suspected cause. [FDA safety communication](<https://www.fda.gov/drugs/drug-safety-communications/fda-requests-removal-suicidal-behavior-and-ideation-warning-glucagon-peptide-1-receptor-agonist-glp>).

CONTRAINDICATIONS

United States labeling contraindicates semaglutide in people with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Prior serious hypersensitivity to semaglutide or formulation ingredients is also a contraindication. Weight-loss treatment is inappropriate during pregnancy. The prescribing information specifies discontinuation at least two months before planned pregnancy because of prolonged exposure. Severe gastroparesis is a labeled reason that treatment is not recommended. History of pancreatitis, active gallbladder symptoms, diabetic retinopathy, eating disorders and nutritional vulnerability require individualized assessment. These concerns should not all be mislabeled as formal contraindications. Semaglutide is not an insulin replacement or treatment for diabetic ketoacidosis. Lean athletes lack an established cosmetic weight-loss evidence base. That evidence gap does not quantify their individual muscle loss or establish that adverse effects are proportionally greater.

STOP RULES

Severe persistent abdominal pain, especially with vomiting or radiation to the back, warrants prompt assessment for pancreatitis. Labeling calls for discontinuation when pancreatitis is suspected. Right upper abdominal pain with fever or jaundice warrants urgent gallbladder assessment. Inability to retain fluids, markedly reduced urination, fainting or confusion warrants urgent evaluation. There is no requirement to wait a full day when dehydration or systemic illness is developing. Facial or throat swelling, breathing difficulty or collapse requires emergency care. Sudden visual loss or rapidly worsening vision requires urgent ophthalmic assessment, whether or not diabetes is present. EMA recommends discontinuation if NAION is confirmed. A neck mass, persistent hoarseness or swallowing difficulty warrants medical evaluation. Pregnancy recognition requires prompt review of treatment for weight management. New suicidal thoughts require immediate support even though a causal drug association has not been established. Before anesthesia or deep sedation, medication history and gastrointestinal symptoms belong in the procedural assessment. The anesthesia team determines whether continuation, dietary modification, postponement or interruption is appropriate. Sustained deterioration in intake, function or training performance warrants reassessment rather than an automatic dose or calorie adjustment.

TYPICAL VIAL

Approved injectable semaglutide is supplied as a prepared solution in specified delivery devices. Oral formulations are finished tablets. Neither presentation requires home reconstitution. There is no clinically standardized typical research vial. Advertised fill weight does not establish identity, active peptide content, sterility or uniformity. Powder may include water, counter-ions or other material. A gross powder weight cannot automatically be treated as the same amount of active semaglutide. The clinical trial evidence belongs to the formulations actually studied. An analytical match on one property does not establish pharmaceutical equivalence.

SOLVENT

No validated universal home-reconstitution solvent or procedure was established by the reviewed semaglutide studies. Bacteriostatic water does not sterilize contaminated powder, remove endotoxin or demonstrate peptide stability. The presence of a preservative does not establish that an arbitrary formulation remains suitable for repeated access. Compatibility depends on formulation composition, concentration, container, handling and validated storage conditions.

STORAGE

Storage conditions are formulation-specific. Approved injection labels describe refrigeration before use and presentation-specific limits after removal from refrigeration or first use. For example, the Ozempic injection label specifies a 56-day in-use period under its stated conditions. That period does not apply to arbitrary reconstituted material. No validated shelf life for a generic research-market semaglutide solution was established in this review. A general multidose-container convention does not demonstrate the stability of its active ingredient. Temperature excursions, visible particles or discoloration require product-specific assessment. A clear appearance cannot establish sterility or potency.

Dimensional-analysis illustration only, not a preparation specification: a hypothetical solution containing 5 mg in a final volume of 2 mL has a concentration of 2.5 mg/mL. This arithmetic assumes that the stated active mass and final volume are accurate.

STEP 1 began with 0.25 mg subcutaneously once weekly before escalation, as reported in its protocol, PMID 33567185. That study amount equals 250 mcg. At the hypothetical concentration above, the corresponding mathematical volume would be 0.10 mL. This does not validate the hypothetical preparation or authorize its administration.

The general relationship is volume in mL equals mass in mg divided by concentration in mg/mL. Syringe markings represent a volume calibration; they are not universal semaglutide dose units. IU should not be substituted for mg or mcg.

A correct conversion cannot correct inaccurate vial content, degradation, contamination or the wrong formulation. Container yield calculations also assume no residual volume or handling loss. Approved device dosing and product-specific instructions cannot be replaced by a generic vial calculator.

BUYING NOTES

Quality assessment begins with the distinction between an approved finished medicine, a compounded preparation and research-labeled material. Approval involves review of manufacturing controls and clinical evidence. It does not justify an absolute guarantee that every distributed package is authentic or defect-free.

Compounded preparations are not FDA-approved. Identity, concentration, formulation and traceability still require assessment. Semaglutide sodium and semaglutide acetate are different active ingredients from the semaglutide used in approved products, as FDA explains. Their presence should not be dismissed as a naming detail. [FDA concerns about unapproved GLP-1 products](<https://www.fda.gov/drugs/drug-alerts-and-statements/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss?os=av>).

A certificate of analysis is evidence about the tested sample and listed methods. Its relevance depends on authentic laboratory attribution, a matching batch identifier, sampling records and traceability. A certificate for bulk material does not establish the condition of each finished container.

Mass spectrometry can support molecular identity, while chromatography can describe separation from detectable impurities. Chromatographic area purity is not the same measurement as active peptide mass per container. A high reported purity percentage does not demonstrate sterility, acceptable endotoxin levels or stability throughout storage.

Useful documentation distinguishes identity, assay or content, impurity testing, microbiological testing and stability evidence. Each answers a different question. A single purity threshold cannot substitute for the whole assessment.

Price, packaging and a research-only statement do not resolve these uncertainties. No supplier names or purchasing directions are needed to explain the distinction.

COMMON MISTAKES

- Treating the evidence grade as universal. Grade A supports specified clinical indications, while lean-athlete physique use and performance claims remain extrapolations.
- Equating all lost weight with fat, or equating all measured lean tissue loss with muscle. Measurement method, hydration, strength and function affect interpretation (PMID 38937282).
- Describing withdrawal as inevitable complete regain. The STEP 1 extension found approximately two thirds regained on average after medication and lifestyle support ended (PMID 35441470).
- Presenting an initiation dose as biologically inactive. The Ozempic label describes its initiation step as not effective for glycemic control, not as having no physiological effect.
- Treating dose escalation as a competition. Trial schedules balance tolerability and indication-specific evidence; they do not validate a highest-dose goal for every person.
- Assuming oral and injectable milligram amounts are interchangeable. Exposure depends on route, tablet formulation and administration conditions.
- Reporting a placebo-adjusted difference as total weight loss. PIONEER 1's quoted weight differences compare groups rather than describing the entire change from baseline (PMID 31186300).
- Calling similar results from different trials proof of equivalence. OASIS 1 did not directly compare oral and injectable semaglutide (PMID 37385278).
- Classifying speculative hormonal combinations as established synergies. A plausible pathway does not demonstrate clinical benefit, compatibility or protection against lean tissue loss.
- Using one missed-dose rule or storage interval for every formulation. Product-specific labeling governs these details.
- Applying an automatic one-week medication hold before every procedure. Contemporary perioperative assessment considers symptoms, escalation status and procedural risk.
- Treating a correct calculator result or high chromatographic purity as proof that a preparation is suitable for human administration. Neither establishes identity, finished-product sterility or stability.

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Retatrutide (LY3437943)

LY3437943

Triple GIP/GLP-1/glucagon receptor agonist

Module 2 · Recomposition

Goals: Fat loss

Route: SC weekly

Investigational once-weekly triple GIP, GLP-1 and glucagon receptor agonist with substantial randomized-trial weight and glucose reductions. Long-term clinical outcomes and maintenance after withdrawal remain unresolved.

WHAT IT IS

A single synthetic peptide that activates the GIP receptor, GLP-1 receptor and glucagon receptor. Its pharmacokinetics support once-weekly subcutaneous administration, with an approximately six-day half-life (PMID 36354040). Developed as LY3437943, it remains investigational despite published phase 3 diabetes results (PMID 42250575).

Module 2, Recomposition, goal Fat loss: human trials document reductions in body weight, body fat and liver fat in selected metabolic disease populations. These findings do not establish benefits for lean, healthy athletes or prove preservation of muscle strength during weight loss.

MECHANISM

Cell assays show approximately balanced glucagon and GLP-1 receptor activity, with greater GIP receptor activity (PMID 35985340). Incretin receptor activation supports glucose-dependent insulin secretion and appetite regulation. A separate report documents delayed gastric emptying with retatrutide (PMID 37311727). The relative contribution of each receptor to human satiety and gastrointestinal symptoms has not been isolated.

In obese mice, GIP and GLP-1 receptor activity reduced calorie intake, while glucagon receptor activity increased energy expenditure (PMID 35985340). This animal result supports the triple-agonist rationale. It does not quantify increased energy expenditure in humans. Claims that GIP activity reliably prevents nausea remain mechanistic hypotheses.

The liver substudy documented substantial reductions in liver fat, correlated with weight loss and metabolic changes (PMID 38858523). It did not establish that direct glucagon-driven fat oxidation independently caused those reductions. Human diabetes trials demonstrate net glucose lowering despite the glucose-raising potential of glucagon receptor activation (PMID 37385280, PMID 42250575).

Body composition measurements show reduced fat mass alongside some lean mass loss (PMID 40609566). Heart rate increased dose-dependently in the obesity trial, peaked at 24 weeks and subsequently declined (PMID 37366315). The individual receptor contributions to this heart rate response remain uncertain.

EVIDENCE · GRADE A

Grade A applies to body weight and glycaemic outcomes because multiple randomized human trials exist. It does not indicate regulatory approval or established long-term safety. Evidence includes phase 2 obesity and diabetes trials and a published phase 3 diabetes trial. Liver fat and body composition findings warrant grade B interpretation because they come from smaller substudies. Animal kidney findings are grade C. Cardiovascular event prevention, longevity and athletic performance are not established indications.

Human data. Phase 2 obesity enrolled 338 adults for 48 weeks. Subcutaneous retatrutide 1, 4, 8 or 12 mg once weekly produced mean weight reductions of 8.7, 17.1, 22.8 and 24.2 percent, respectively (PMID 37366315). Placebo produced a 2.1 percent reduction. These are group averages, not expected

Animal and mechanistic data. Obese mice showed reduced intake and increased energy expenditure, supporting complementary receptor mechanisms (PMID 35985340). In db/db mice, retatrutide improved renal biochemical measures and reduced inflammatory and fibrosis markers over 10 weeks

individual outcomes. Phase 2 diabetes randomized 281 adults for 36 weeks. Subcutaneous retatrutide 4 mg with escalation, 8 mg with slow escalation and 12 mg once weekly reduced HbA1c by 1.39, 1.99 and 2.02 percentage points at week 24 (PMID 37385280). Placebo reduced HbA1c by 0.01 percentage points. Weight fell 16.94 percent at week 36 with subcutaneous retatrutide 12 mg once weekly (PMID 37385280). The liver substudy included 98 participants. Subcutaneous retatrutide 12 mg once weekly reduced liver fat by 82.4 percent relative to baseline at week 24 (PMID 38858523). Normal liver fat, below 5 percent, occurred in 86 percent of that group. This does not demonstrate reversal of fibrosis or prevention of cirrhosis. TRANSCEND-T2D-1 randomized 537 adults for 40 weeks. Subcutaneous retatrutide 4, 9 or 12 mg once weekly reduced HbA1c by 1.69, 1.86 and 1.94 percentage points, respectively (PMID 42250575). Corresponding weight reductions were 11.5, 13.9 and 15.3 percent. Placebo changes were 0.81 percentage points and 2.6 percent. Adverse-event discontinuations were 2 to 5 percent with retatrutide; no severe hypoglycaemia was reported.

(PMID 39212900). Glucose lowering was not superior to both comparators. These results do not establish human kidney protection. The animal dosing interval was absent from the retrieved abstract, so an incomplete animal regimen is not reproduced.

REGULATORY STATUS AND SPORT

STATUS

Reviewed September 5, 2026. Retatrutide remains investigational and is not FDA-approved. FDA states that retatrutide cannot be used in compounding under US federal law. [FDA regulatory statement](<https://www.fda.gov/drugs/drug-alerts-and-statements/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss>). Published phase 3 diabetes efficacy does not constitute marketing authorization (PMID 42250575). A 2026 news report describes US compassionate access, which is distinct from approval or routine prescribing (PMID 42567543). Trial design reports and preliminary announcements do not establish clinical outcome benefits.

WADA

Official sources reviewed do not support an unqualified permitted-status statement. Sport Integrity Australia explicitly states that retatrutide is not listed under the 2026 Prohibited List. [Sport Integrity Australia retatrutide guidance](<https://www.sportintegrity.gov.au/what-we-do/anti-doping/substance-education/retatrutide>). However, WADA section S0 prohibits unapproved pharmacological substances not addressed by subsequent sections, including drugs in clinical development. Its wording appears applicable to retatrutide, creating an unresolved conflict with that guidance. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Absence by name does not establish permission. Athlete-specific status requires clarification from the responsible anti-doping authority.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

The human efficacy trials summarized here used subcutaneous administration once weekly (PMID 36354040, PMID 37366315, PMID 37385280, PMID 42250575). No validated oral, intranasal or intramuscular regimen was identified in the reviewed records. Animal intraperitoneal administration is not evidence for a human route.

HALF-LIFE

Approximately six days in the phase 1b study; systemic exposure was dose proportional (PMID 36354040). Dose proportionality describes exposure, not a progressively longer half-life. Under standard accumulation assumptions, concentrations approach steady state over roughly four to five half-lives. This is a pharmacokinetic estimate, not a measured stopping interval. Drug concentrations decline gradually after discontinuation, and symptom duration cannot be predicted precisely from half-life alone.

TIMING

The cited trials evaluated weekly administration. Their retrieved abstracts do not establish an optimal clock time, meal relationship or training-day schedule. Claims that fasting administration improves fat loss are unsupported by these records. Dose escalation, gastrointestinal tolerance and treatment interruption were managed within trial protocols.

CYCLE LENGTH

No evidence-based cycling schedule was identified. The summarized completed trials lasted 12, 36, 40 or 48 weeks. The 48-week obesity result is a study duration, not a maximum acceptable exposure or an established treatment endpoint (PMID 37366315). A single-dose observation extending to day 43 does not establish maintenance after prolonged treatment withdrawal (PMID 35985340). Controlled retatrutide withdrawal data were not identified in this review.

TITRATION

Higher-dose study arms often used escalation, but fixed-dose arms also existed. In phase 2 obesity, starting at 2 mg rather than 4 mg subcutaneously once weekly partially reduced gastrointestinal events (PMID 37366315). The phase 2 diabetes trial also demonstrated tolerability differences between escalation groups (PMID 37385280). Complete schedules require the relevant protocol; they cannot be reconstructed reliably from maintenance targets alone. The highest maintenance dose in these cited trials was 12 mg subcutaneously once weekly (PMID 37366315, PMID 37385280, PMID 42250575). It is not an approved ceiling or a personal target.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Phase 1b type 2 diabetes, 12 weeks	Study regimens included 0.5, 1.5 or 3 mg subcutaneously once weekly, and escalating cohorts reaching 6 or 12 mg subcutaneously once weekly (PMID 36354040).	Subcutaneous	Once weekly	PMID 36354040, randomized multiple-ascending-dose study. Fixed-dose and escalating cohorts were both included. These are research exposures, not an approved treatment schedule. · PMID 36354040
Phase 2 obesity, 48 weeks	Maintenance doses were 1, 4, 8 or 12 mg subcutaneously once weekly; selected higher-dose arms began at 2 or 4 mg subcutaneously once weekly (PMID 37366315).	Subcutaneous	Once weekly	PMID 37366315. The highest maintenance arm began at the lower starting dose. Lower initiation partially mitigated gastrointestinal adverse events. Not every arm required escalation. · PMID 37366315
Phase 2 type 2 diabetes, 36 weeks	Maintenance doses were 0.5, 4, 8 or 12 mg subcutaneously once weekly; escalating arms began at 2 or 4 mg subcutaneously once weekly (PMID 37385280).	Subcutaneous	Once weekly	PMID 37385280. The study included fixed-dose, slow-escalation and fast-escalation groups. Gastrointestinal events occurred in 35 percent overall and 50 percent in the fast-escalation group. · PMID 37385280
Phase 3 TRANSCEND-T2D-1, 40 weeks	Assigned maintenance doses were 4, 9 or 12 mg subcutaneously once weekly (PMID 42250575).	Subcutaneous	Once weekly	PMID 42250575, randomized placebo-controlled monotherapy trial. The retrieved abstract establishes maintenance targets but does not provide the complete escalation schedule. · PMID 42250575

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– Tirzepatide

Overlapping GIP and GLP-1 receptor activity creates a pharmacological duplication concern. Added benefit and combination safety were not established in the reviewed retatrutide trials. Additive gastrointestinal effects are plausible.

– Semaglutide

Overlapping GLP-1 receptor activity creates potential for additive gastrointestinal intolerance and delayed gastric emptying. The reviewed evidence does not establish a beneficial retatrutide combination.

– **Liraglutide**

Additional GLP-1 receptor agonism has no established retatrutide combination benefit. Different dosing intervals do not eliminate overlapping exposure or adverse-effect concerns.

– **Cagrilintide**

A separate satiety pathway is a hypothesis, not demonstrated synergy with retatrutide. No pairing trial was identified. Added gastrointestinal intolerance is plausible; efficacy and interaction risks remain unquantified.

– **Tesamorelin**

No retatrutide combination trial was identified. Evidence from a separate disease population does not establish protection against retatrutide-associated lean mass loss. The proposed muscle-preservation rationale remains unsupported.

SAFETY

COMMON EFFECTS

Nausea, diarrhoea, vomiting and constipation were the dominant adverse events, generally mild to moderate and related to dose or escalation. In phase 2 diabetes, gastrointestinal events affected 35 percent of retatrutide participants versus 13 percent receiving placebo (PMID 37385280). Heart rate increased dose-dependently in the obesity trial, peaking at week 24 before declining (PMID 37366315). Phase 3 diabetes participants also predominantly reported gastrointestinal events that diminished over time (PMID 42250575).

SERIOUS SIGNALS

The available trials cannot reliably quantify rare or long-latency harms. Pancreatic and biliary disorders, severe gastrointestinal intolerance and retained gastric contents during anaesthesia are relevant GLP-1-family concerns (PMID 38843460). These require distinction from proven retatrutide-specific causal effects. A case report describes vomiting, dehydration, ketonaemia and acute kidney injury after exposure to an online-labelled retatrutide product (PMID 42669023). Concurrent *Shigella* infection and insulin omission confounded attribution; diabetic ketoacidosis did not develop. No severe hypoglycaemia in selected trial populations does not establish compatibility with insulin or sulfonylureas. The body composition substudy found lean mass loss proportional to overall weight loss, broadly similar to other obesity treatments (PMID 40609566). It does not support a universal claim that users lose one tenth of their lean tissue. DXA lean mass is not equivalent to measured muscle strength.

CONTRAINDICATIONS

No approved retatrutide label defines formal contraindications. Relevant screening concerns include prior serious hypersensitivity, personal or family medullary thyroid carcinoma, and MEN2. Related GLP-1 prescribing information treats the thyroid history and MEN2 as contraindications; application to retatrutide is precautionary extrapolation. [Related GLP-1 prescribing information] (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee06186f-2aa3-4990-a760-757579d8f77b>). Pregnancy, breastfeeding and insulin-deficient diabetes lack an established retatrutide treatment role. Pancreatitis history, active gallbladder symptoms, severe gastroparesis, tachyarrhythmia, poor nutritional intake and concurrent glucose-lowering therapy require individual assessment. Planned anaesthesia is a management issue, not an automatic contraindication or a fixed stopping interval.

STOP RULES

Severe persistent abdominal pain, jaundice, fainting, chest pain, persistent palpitations or inability to retain fluids warrant urgent medical assessment. Breathing difficulty or facial or throat swelling warrants emergency care. Low urine output, confusion or ketosis symptoms are especially concerning during vomiting or insulin deficiency. These symptoms warrant assessment without waiting for a preset duration. Pregnancy, progressive nutritional compromise or sustained functional decline requires clinician review. There is no validated self-directed pause, escalation or restart rule for retatrutide.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved commercial retatrutide vial strength or public patient reconstitution standard exists. The cited clinical publications establish administered doses, not equivalence between trial material

and powders sold outside regulated research. Advertised vial content is not proof of peptide identity, delivered mass or formulation suitability.

SOLVENT

The reviewed clinical evidence does not validate bacteriostatic water as a universal solvent for independently sourced retatrutide. Compatibility depends on the peptide formulation, excipients, concentration, container and stability testing. Preservative content does not establish sterility. Visual clarity cannot establish identity, potency, endotoxin control or microbiological quality.

STORAGE

No validated storage temperature, freezing rule or beyond-use period for independently sourced retatrutide was established by the reviewed publications. Chemical stability, microbial control and container compatibility are separate requirements. A general multidose-vial convention does not establish retatrutide potency after reconstitution. Refrigeration cannot correct an unidentified, contaminated or degraded preparation.

Dimensional analysis only: concentration equals verified peptide mass divided by final solution volume. A documented study dose divided by that concentration gives a theoretical volume. These calculations assume correct identity, measured content, complete dissolution and known final volume. They cannot establish that an unknown preparation matches trial material. The unit conversion is 1 mg equals 1000 mcg. Syringe scale units measure volume and are not international units of retatrutide activity. A calculator must distinguish mass, concentration and volume explicitly.

BUYING NOTES

A certificate of analysis is evidence about the submitted sample, not proof that every delivered container has the same contents. Meaningful documentation distinguishes peptide identity, quantitative content, chromatographic purity, related impurities, sterility and bacterial endotoxins. These are different measurements and cannot substitute for one another. A reported purity percentage does not establish the mass of active peptide. Water, counter-ions, residual solvents and assay methodology affect interpretation. Molecular mass alone cannot establish sequence, correct modification or biological activity. Batch linkage, sample traceability, test dates, analytical methods and laboratory accountability determine what a certificate can support. Neither a certificate nor research-only wording establishes approval, suitability for human administration or equivalence to clinical trial material.

COMMON MISTAKES

- Treating group-average weight loss as an individual forecast or proof of superiority across unrelated trials.
- Confusing maintenance targets with starting doses, or assuming that every study participant followed the same escalation schedule.
- Reporting HbA1c changes as relative percentages when the trial reports absolute percentage-point changes.
- Calling reduced liver fat evidence of reversed fibrosis, or interpreting mouse kidney findings as demonstrated human kidney protection.
- Assuming that additional incretin or satiety-pathway drugs produce proven synergy with retatrutide.
- Equating DXA lean mass with skeletal muscle alone, or assuming that large weight loss preserves strength automatically.
- Treating a general vial-storage convention, clear appearance or high chromatographic purity as proof of stability and sterility.
- Attributing a confounded case report entirely to retatrutide, or treating the absence of severe events in a trial as absence of risk.
- Assuming that not being named on the WADA list settles the status of an investigational drug.
- Treating a long half-life as a validated withdrawal, cycling or restart protocol.

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Cagrilintide

CagriSema (with semaglutide)

Long-acting amylin analog

Module 2 · Recomposition

Goals: Fat loss

Route: SC weekly

A long-acting, lipidated amylin analogue studied for weight management, alone and with semaglutide. Multiple randomized trials support weight reduction; it remains investigational.

WHAT IT IS

Cagrilintide, development code NNC0174-0833, is an analogue of human amylin, a pancreatic hormone released with insulin that contributes to satiation. Its development addressed the aggregation tendency and short duration of native amylin. Stabilizing modifications and lipidation produced a longer-acting molecule suitable for investigation with weekly administration (Kruse 2021, PMID 34288673).

Cagrilintide activates amylin receptors and the calcitonin receptor. It is therefore described as a dual amylin and calcitonin receptor agonist, abbreviated DACRA. Its measured human half-life is approximately one week (Enebo 2021, PMID 33894838).

CagriSema denotes the combination of cagrilintide and semaglutide. It is not an alias for cagrilintide or a separate peptide. Results for that combination cannot be attributed entirely to cagrilintide. Trial formulations also cannot establish equivalence with independently prepared mixtures.

Within this curriculum, cagrilintide belongs in Module 2, Recomposition, under weight management. The strongest clinical evidence concerns body-weight reduction in adults with overweight or obesity. It does not establish muscle preservation, improved athletic performance or a suitable regimen for normal-weight trainees.

MECHANISM

Receptor pharmacology. Amylin receptors comprise the calcitonin receptor, encoded by CALCR, associated with a receptor activity-modifying protein. RAMP1, RAMP2 and RAMP3 form AMY1R, AMY2R and AMY3R, respectively. Cagrilintide activates these receptors and the calcitonin receptor, including Gs-mediated signaling.

Cao 2025 resolved structures involving all three amylin receptors and the calcitonin receptor. Cagrilintide displayed an amylin-like binding mode with distinct receptor-complex dynamics (PMID 40204768). Gu 2026 examined AMY1R and calcitonin receptor complexes. Phenylalanine 23, an internal E14-R17 salt bridge and the terminal proline contributed to the observed binding architecture (PMID 40847076). These experiments establish molecular interactions. They do not quantify how much each receptor contributes to human weight loss.

Brainstem pathways. In mice lacking RAMP1 and RAMP3, cagrilintide's weight and feeding effects were attenuated. Area postrema neuronal activation also decreased, supporting involvement of AMY1R and AMY3R (Carvas 2025, PMID 40609154). Because the genetic deletion was not confined to one brain region, this experiment does not independently localize every relevant action.

Ludwig 2026 identified two conserved populations of CALCR-expressing brainstem neurons. Acute treatment altered gene expression in area postrema Calcr/Ramp3 cells. Longer treatment increased Prlh expression in nucleus of the solitary tract Calcr/Prlh cells. Reducing dorsal vagal complex Prlh expression abolished cagrilintide responses in rats while preserving semaglutide responses (PMID 42260119). This supports partly distinct mechanisms for the two agents. It does not establish completely separate circuits or prove a particular degree of clinical synergy.

Downstream physiology. Amylin signaling engages brain systems involved in satiation and food reward (D'Ascanio 2024, PMID 36883831). Reduced food intake is directly documented in cagrilintide animal

experiments. Human randomized trials establish weight reduction, but the cited efficacy abstracts do not isolate gastric emptying, glucagon suppression or energy expenditure as its principal mechanism.

In the phase 2 diabetes trial, cagrilintide monotherapy reduced HbA1c by 0.9 percentage points over 32 weeks. The combination reduced it by 2.2 points (Frias 2023, PMID 37364590). These results describe clinical outcomes, not a direct measurement of pancreatic receptor action.

Preclinical uncertainty. Receptor-balance experiments suggest that relative amylin and calcitonin receptor activity can influence metabolic effects in rats (Larsen 2022, PMID 36242844). The contribution of calcitonin receptor activation to human efficacy remains unresolved. Bone, cartilage, longevity and direct muscle-building benefits are not established indications.

EVIDENCE · GRADE A

Grade A under this product's definition because multiple human randomized trials exist. This grade reflects clinical evidence for weight management, not regulatory approval or comprehensive long-term safety. Monotherapy has randomized evidence, including a dedicated phase 2 dose-finding trial and smaller arms within phase 3 studies. The largest evidence base concerns the combination with semaglutide. Trial populations, background treatments, duration and statistical estimands differ. Their percentages are not interchangeable forecasts for an individual. The cited studies do not establish cardiovascular event reduction from cagrilintide or benefits for healthy, normal-weight athletes.

Human data. Monotherapy. Lau 2021 randomized 706 adults without diabetes across cagrilintide, liraglutide and placebo groups. Cagrilintide targets were 0.3, 0.6, 1.2, 2.4 or 4.5 mg subcutaneously once weekly for 26 weeks (PMID 34798060). Mean weight reduction ranged from 6.0 to 10.8 percent, versus 3.0 percent with placebo, using the trial product estimand. That analysis estimated effects assuming treatment adherence. The highest cagrilintide target exceeded the active comparator's weight reduction, 10.8 versus 9.0 percent. Frias 2023 randomized 92 adults with type 2 diabetes receiving metformin, with or without an SGLT2 inhibitor. Cagrilintide and semaglutide targets were each 2.4 mg subcutaneously once weekly, alone or together, for 32 weeks (PMID 37364590). Weight reductions were 8.1 percent with cagrilintide, 5.1 percent with semaglutide and 15.6 percent with the combination. The combination's HbA1c advantage over semaglutide was not statistically significant in this small trial. Early combination evidence. Enebo 2021 randomized 96 participants, with 95 exposed to treatment. Cagrilintide targets ranged from 0.16 to 4.5 mg subcutaneously once weekly, alongside semaglutide 2.4 mg subcutaneously once weekly (PMID 33894838). At the cagrilintide 2.4 mg subcutaneous weekly target, mean weight reduction was 17.1 percent at 20 weeks. The relevant semaglutide-plus-placebo comparison was 9.8 percent. These were small cohorts with exploratory weight endpoints. Phase 3. REDEFINE 1 randomized 3417 adults without diabetes, including 302 assigned to cagrilintide alone. At 68 weeks, combination treatment produced 20.4 percent mean weight reduction versus 3.0 percent with placebo (Garvey 2025, PMID 40544433). REDEFINE 2 randomized 1206 adults with type 2 diabetes and reported 13.7

Animal and mechanistic data. Carvas 2025 administered cagrilintide 3 nmol/kg subcutaneously once daily for three weeks in high-fat-fed mice (PMID 40609154). Wild-type mice lost approximately 3.4 g, while the absence of RAMP1 and RAMP3 attenuated its effect. This is a species-specific experimental exposure, not a human dose conversion. Ludwig 2026 combined transcriptomic mapping and neuronal interventions across species. Functional experiments in rats supported a role for brainstem PrLh signaling in sustained cagrilintide responses (PMID 42260119). Conserved cell populations were identified, but human therapeutic circuit dependence was not experimentally established. Gabery 2025 directly compared cagrilintide with a related research tool compound. Both reduced food intake and weight in diet-induced obese rats, mainly through fat-mass reduction, and enhanced semaglutide responses. Effects in diet-induced obese mice were smaller and transient (PMID 40628316). The paper contains cagrilintide experiments, but the related compound is not interchangeable with it. Larsen 2022 demonstrated dose-dependent weight and glucose effects in obese and diabetic rat models (PMID 36242844). Together, these studies support receptor and feeding mechanisms. They do not establish human lean-mass preservation or justify scaling rodent doses by body weight.

versus 3.4 percent (Davies 2025, PMID 40544432). Both estimates used a treatment-policy approach, reflecting outcomes regardless of treatment adherence. REDEFINE 5 randomized 331 adults in Japan and Taiwan. Weight reduction was 18.4 percent with the combination versus 11.9 percent with semaglutide at 68 weeks. Its primary trial product estimand assumed treatment was taken as intended (Yamauchi 2026, PMID 42009015). REIMAGINE 2 randomized 2713 adults with type 2 diabetes, including 152 in a cagrilintide monotherapy arm. The combination's HbA1c reduction exceeded semaglutide's by 0.16 percentage points at 68 weeks under the efficacy estimand (Buse 2026, PMID 42251859). Pooled evidence. Ahmed 2026 included three trials and 3545 participants. Combination treatment produced about 7.5 percentage points more weight reduction than semaglutide. The pooled monotherapy comparison did not establish superiority over semaglutide (PMID 41834765). Dutta 2024 reported less vomiting with cagrilintide alone than with GLP-1 comparators (PMID 39676787). These analyses overlap with primary trials and do not represent additional independent participants.

REGULATORY STATUS AND SPORT

STATUS

Investigational as of this September 2026 review. FDA states that cagrilintide is not a component of an FDA-approved drug and cannot be used in compounding under US federal law. No approved cagrilintide prescribing label was identified. Source: [FDA statement on unapproved weight-loss drugs](<https://www.fda.gov/drugs/drug-alerts-and-statements/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss>). Published phase 3 trials establish advanced clinical development, not authorization to market the drug. Regulatory submission, acceptance for review and marketing approval are different events. A worldwide absence of approval was not independently established jurisdiction by jurisdiction in this review. The cited clinical literature covers both cagrilintide monotherapy arms and combination development. The combination's clinical results cannot create an approved indication, dose or contraindication list for cagrilintide alone. Trial identifiers and completion projections are omitted where their current registry status was not verified. There is no approved preparation, storage or missed-dose instruction established by these papers for independently sourced material.

WADA

Prohibited at all times under S0 while cagrilintide remains an unapproved investigational pharmacological substance. This classification applies the S0 rule to its investigational status; it does not depend on cagrilintide appearing by name. S0 covers substances lacking governmental approval for human therapeutic use when they are not addressed by another section. Source: [WADA 2026 Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Combining it with another substance does not remove this prohibition.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Subcutaneous administration is documented in the cited human efficacy and pharmacokinetic studies. Repeated-treatment trials generally used weekly administration; organ-impairment studies used single administrations. Thus, not every human study was a weekly treatment course. The reviewed records do not establish effective oral or intranasal formulations. Rodent administration schedules reflect individual experimental designs and cannot establish human timing. The reviewed abstracts do not support a universal injection-site rotation protocol specific to cagrilintide.

HALF-LIFE

Enebo 2021 reported a terminal half-life of 159 to 195 hours, approximately 6.6 to 8.1 days, and median peak concentrations after 24 to 72 hours (PMID 33894838). Exposure increased with cagrilintide dose. Adding cagrilintide did not materially affect semaglutide exposure or elimination in that study. This does not prove the absence of every possible bidirectional interaction. Under a simple linear pharmacokinetic model, approximately five half-lives correspond to near steady state

after about five to six weeks at an unchanged dose. This is a calculation, not a trial-defined waiting period or explanation for all continuing weight loss. Escalation changes the accumulation pattern. Small single-dose studies found no consistent clinically relevant exposure differences across renal or hepatic impairment categories (Nielsen 2026, PMID 42228334). They do not establish unrestricted long-term use in severe organ disease.

TIMING

Weekly administration was the schedule in the cited repeated-treatment human trials. A fixed weekday can describe a trial schedule, but the reviewed abstracts do not establish an optimal morning or evening time. Peak concentration after one to three days does not by itself prove when nausea will occur. No validated relationship to training sessions or fasting was identified. Missed-dose and restart rules cannot be borrowed from semaglutide simply because both agents were studied weekly. No independent cagrilintide label establishes those rules.

CYCLE LENGTH

Published treatment periods include 20 weeks in Enebo 2021, 26 weeks in Lau 2021 and 32 weeks in Frias 2023. REDEFINE 1 and REDEFINE 2 lasted 68 weeks (PMIDs 33894838, 34798060, 37364590, 40544433 and 40544432). These are study durations, not recommended cycles. The phase 2 monotherapy study included six weeks of follow-up without treatment, but its abstract does not quantify subsequent weight regain. These records do not establish intermittent cycling, a short course that permanently resets appetite, or a maintenance strategy for normal-weight athletes.

TITRATION

Dose escalation was documented in the principal repeated-treatment trials. Lau 2021 used escalation over up to six weeks (PMID 34798060). Enebo 2021 co-escalated treatment at four-week intervals over 16 weeks, followed by four weeks at target (PMID 33894838). Single-dose pharmacokinetic studies are an exception, so the statement that every human trial escalated was inaccurate. Gastrointestinal tolerability is relevant to escalation, but the published abstracts do not support one universal cagrilintide schedule. Separate randomized maintenance targets are not interchangeable with sequential steps for an individual.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human phase 2 monotherapy dose-finding trial. There were 706 participants across all treatment groups, with 26 weeks of treatment and escalation over up to six weeks.	0.3, 0.6, 1.2, 2.4 or 4.5 mg target doses, as reported by Lau 2021, PMID 34798060.	Subcutaneous	Once weekly	Randomized controlled trial, Lau 2021, PMID 34798060. These were assigned trial targets, not recommended starting doses. · PMID 34798060
Human phase 1b study with semaglutide. Target treatment followed co-escalation at four-week intervals, with 20 weeks of treatment overall.	Cagrilintide 0.16, 0.30, 0.60, 1.2, 2.4 or 4.5 mg with semaglutide 2.4 mg, both subcutaneous once weekly, Enebo 2021, PMID 33894838.	Subcutaneous for both agents	Once weekly for both agents	Randomized phase 1b trial, Enebo 2021, PMID 33894838. Small ascending-dose cohorts supplied the pharmacokinetic findings. · PMID 33894838
Human phase 2 trial in type 2 diabetes. Treatment lasted 32 weeks, with cagrilintide and semaglutide studied separately and together.	Cagrilintide 2.4 mg alone or with semaglutide 2.4 mg, both subcutaneous once weekly after escalation, Frias 2023, PMID 37364590.	Subcutaneous	Once weekly	Randomized controlled trial, Frias 2023, PMID 37364590. Background treatment was metformin with or without an SGLT2 inhibitor. · PMID 37364590
Human phase 3 REDEFINE 1 trial in adults without diabetes. Treatment lasted 68 weeks and included individual-component comparison arms.	Cagrilintide 2.4 mg with semaglutide 2.4 mg, or cagrilintide 2.4 mg alone, subcutaneous once weekly targets, Garvey 2025, PMID 40544433.	Subcutaneous	Once weekly	Randomized controlled trial, Garvey 2025, PMID 40544433. Published maintenance targets do not specify a self-directed escalation schedule. · PMID 40544433

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human phase 3 REIMAGINE 2 trial in type 2 diabetes, lasting 68 weeks. Different maintenance-dose groups were randomized separately.	Cagrilintide plus semaglutide at 2.4 mg each or 1.0 mg each, and cagrilintide 2.4 mg alone, subcutaneous once weekly, Buse 2026, PMID 42251859.	Subcutaneous	Once weekly	Randomized controlled trial, Buse 2026, PMID 42251859. The lower maintenance arm is not evidence for a universal titration step. · PMID 42251859
Human phase 1 pharmacokinetic studies comparing normal organ function with renal or hepatic impairment.	Cagrilintide 0.6 mg in the renal study and 0.9 mg in the hepatic study, each as one subcutaneous administration, Nielsen 2026, PMID 42228334.	Subcutaneous	Single administration in each study	Two small clinical pharmacokinetic studies, Nielsen 2026, PMID 42228334. These exposures do not establish maintenance regimens. · PMID 42228334

STACKING

+ Semaglutide

The documented pairing has randomized human evidence. The combination exceeded either component's weight reduction in the small phase 2 diabetes trial (Frias 2023, PMID 37364590). Larger phase 3 trials confirmed substantial weight reduction (Garvey 2025, PMID 40544433; Davies 2025, PMID 40544432). Preclinical work supports partly distinct mechanisms, not a guarantee of pharmacological synergy. Pooled data found more nausea and administration-site conditions than with semaglutide alone (Ahmed 2026, PMID 41834765). These findings describe manufactured trial products and supervised protocols; they do not validate independently mixed formulations.

– Liraglutide

No human cagrilintide-plus-liraglutide trial was identified in the reviewed evidence. Liraglutide was an active comparator in Lau 2021, not a combination partner (PMID 34798060). Shared GLP-1 rationale does not establish a regimen, added benefit or tolerability. It is therefore excluded from documented synergies.

– Tirzepatide

No randomized human combination evidence was identified in this review. Cagrilintide is an amylin and calcitonin receptor agonist, not a second incretin. Overlapping effects on appetite and gastrointestinal tolerability create plausible concerns, but the combination's actual benefit and adverse-event rates remain unestablished.

– Retatrutide

No human evidence for this pairing was identified in the reviewed records. Multiple receptor targets do not imply additive benefit, predictable appetite suppression or acceptable tolerability. Established cagrilintide-semaglutide findings cannot be transferred to this combination.

SAFETY

COMMON EFFECTS

Gastrointestinal and administration-site events predominate. In Lau 2021, gastrointestinal events affected 41 to 63 percent of cagrilintide participants across dose groups, versus 32 percent with placebo. Nausea affected 20 to 47 percent versus 18 percent; constipation and diarrhea also occurred (PMID 34798060). Approximately 4 percent of all randomized participants discontinued treatment because of adverse events, not necessarily because of cagrilintide. Combination trials reported gastrointestinal events in 79.6 percent versus 39.9 percent with placebo in REDEFINE 1. REDEFINE 2 reported 72.5 percent versus 34.4 percent. Most were transient and mild or moderate (PMIDs 40544433 and 40544432). Ahmed 2026 found higher nausea and administration-site event

rates with the combination than with semaglutide (PMID 41834765). Dutta 2024 found less vomiting with cagrilintide alone than with GLP-1 comparators (PMID 39676787). These comparisons do not predict an individual's symptoms.

SERIOUS SIGNALS

Ahmed 2026 reported a higher pooled serious-adverse-event risk with cagrilintide monotherapy than with semaglutide: risk ratio 1.83, 95 percent confidence interval 1.03 to 3.24 (PMID 41834765). This requires attention, but the abstract does not establish a particular mechanism or explain which events drove the difference. Overall serious events were comparable between the combination and semaglutide. A modest LDL cholesterol difference also favored semaglutide in that analysis; its clinical importance remains uncertain. A randomized study in 105 healthy participants found no clinically relevant QTc prolongation after escalation to cagrilintide 4.5 mg subcutaneously once weekly (Gabe 2024, PMID 39279639). This addresses cardiac repolarization under study conditions, not cardiovascular outcomes generally. Frias 2023 reported no level 2 or 3 hypoglycemia on metformin with or without an SGLT2 inhibitor (PMID 37364590). REIMAGINE 3 included 274 participants receiving basal insulin and reported no severe hypoglycemia under supervised trial conditions (Rosenstock 2026, PMID 42251856). Neither finding establishes zero risk with insulin, sulfonylureas, reduced food intake or unsupervised dose changes.

CONTRAINDICATIONS

No approved cagrilintide label supplies an official contraindication list. Pregnancy, breastfeeding, severe gastrointestinal motility disease, recurrent hypoglycemia and previous serious hypersensitivity require particular clinical scrutiny because evidence is limited or related-drug concerns apply. The pramlintide label contraindicates confirmed gastroparesis, hypoglycemia unawareness and serious hypersensitivity. It also carries a boxed warning about severe hypoglycemia with insulin. These establish amylin-family concerns, not automatically proven cagrilintide contraindications or equivalent risk magnitude. Source: [Pramlintide US prescribing information](<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=4aea30ff-eb0d-45c1-b114-3127966328ff>). Semaglutide-related contraindications and precautions remain relevant when semaglutide is present, but cannot be assigned wholesale to cagrilintide monotherapy. Small single-dose organ-impairment studies do not resolve chronic treatment safety in advanced renal or hepatic disease (Nielsen 2026, PMID 42228334). Adult trial findings do not establish pediatric suitability.

STOP RULES

General clinical warning signs include persistent severe abdominal pain, repeated vomiting with inability to retain fluids, markedly reduced urination, fainting, confusion or suspected hypoglycemia. Facial swelling, breathing difficulty or a systemic allergic reaction warrants emergency assessment. Persistent vomiting should not be observed for an arbitrary full day before seeking help. These are clinical escalation signals, not a verified list of cagrilintide trial withdrawal criteria. Persistent symptoms, pregnancy or a newly recognized contraindication warrant prompt prescriber or trial-team review before further exposure. The reviewed abstracts do not establish a universal dose-hold or restart algorithm.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No standard consumer vial size or approved home-reconstitution presentation is established by the verified clinical literature. The human evidence concerns investigational medicinal products prepared for defined protocols. A research powder's labeled mass does not establish its identity, recoverable peptide content, sterility or equivalence to those products.

SOLVENT

No universally validated solvent for independently sourced cagrilintide powder was identified in the reviewed sources. Bacteriostatic water is not automatically compatible with a peptide or its container. Its preservative does not sterilize contaminated powder. Compatibility depends on formulation, pH, excipients, concentration and handling. Cagrilintide's engineering to reduce aggregation does not validate arbitrary reconstitution conditions (Kruse 2021, PMID 34288673). Visible particles or discoloration can indicate a quality problem; a clear solution cannot establish acceptable identity, potency or microbiological quality.

STORAGE

No validated shelf life, freezing condition or post-reconstitution expiry for independently sourced powder was established by the reviewed studies. A generic refrigeration range cannot substitute for formulation-specific stability testing. The familiar 28-day multidose convention concerns contamination control and does not establish cagrilintide's chemical stability, potency or sterility. Applicable storage limits must come from validated documentation for the exact investigational formulation and container, including any in-use stability assessment.

Calculator illustration only, using an assumed concentration rather than a preparation recipe. Lau 2021 studied a cagrilintide target of 0.6 mg subcutaneously once weekly, among other targets (PMID 34798060). That amount equals 600 mcg. If an independently established concentration were 2.5 mg/mL, dimensional arithmetic gives 0.6 mg divided by 2.5 mg/mL, or 0.24 mL. The concentration is hypothetical and was not a validated preparation reported by that trial.

The calculation relates mass to volume only. It does not establish an appropriate dose, solvent, device, injection volume or formulation. A syringe marking measures volume according to the device scale; it is not an IU of cagrilintide activity. The same volume contains a different peptide mass when concentration changes. Labeled powder mass alone is insufficient to establish final concentration if identity, content or recovery is uncertain.

BUYING NOTES

A certificate of analysis documents particular tests on an identified sample. It is not regulatory approval or proof that a material is suitable for human administration. Relevant documentation includes traceable sample and batch identifiers, the testing laboratory, methods, dates, specifications and actual results.

Identity testing and purity testing answer different questions. Mass spectrometry can support molecular identity; chromatography can describe resolved impurities under the specified method. A high chromatographic area percentage does not establish net peptide content, biological potency, sterility or absence of endotoxin. Neither does an arbitrary purity cutoff establish suitability.

Net content testing matters because gross powder mass can include water, counterions and excipients. For a lipidated peptide, adequate characterization must address the intended molecular structure and relevant impurities. Sterility, endotoxin, particulate matter, residual solvents and stability require their own appropriate assessments.

A laboratory report also needs a documented connection to the material represented by it. A matching lot number improves traceability but cannot alone prove representative sampling or custody. The related tool compound described by Gabery 2025 is chemically distinct from cagrilintide despite comparable effects in selected rodent experiments (PMID 40628316). Neither that paper nor a research-use label validates commercial preparations or independent co-formulation with semaglutide.

COMMON MISTAKES

- Treating CagriSema as another name for cagrilintide. It contains both cagrilintide and semaglutide, so its weight-loss results cannot be assigned to either component alone.
- Reading a published maintenance target as a starting dose. The principal repeated-treatment studies used escalation, and their assigned targets are not universal self-administration instructions.
- Comparing weight percentages without checking diabetes status, duration, background treatment and estimand. REDEFINE 1 and REDEFINE 5 used different primary estimand approaches.
- Interpreting Grade A as approval or comprehensive safety. Here it means multiple randomized human trials support the studied clinical claim.
- Equating body-weight reduction with fat-only loss or muscle preservation. Rat body-composition findings do not establish that outcome in humans who train.
- Treating the absence of a detected pharmacokinetic interaction as proof of an uncomplicated combination. Gastrointestinal effects can overlap without changing drug exposure.
- Using volume markings as peptide dose units. Concentration determines peptide mass per mL, and cagrilintide has no established IU-based dosing convention.
- Borrowing missed-dose rules, solvents or expiry dates from another drug. Those instructions depend on the exact molecule, formulation and supporting data.
- Converting a rodent exposure into a human regimen by simple body-weight arithmetic. Species, formulation, schedule and pharmacokinetics differ.
- Assuming that an unnamed substance is permitted in sport. WADA S0 applies to unapproved investigational substances without requiring an individual listing.

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Liraglutide

Victoza, Saxenda

GLP-1 receptor agonist

Module 2 · Recomposition

Goals: Fat loss

Route: SC daily

A once-daily GLP-1 receptor agonist with strong evidence for weight management in eligible patients, but no established role in lean athletic recomposition.

WHAT IT IS

An engineered analogue of human GLP-1 with arginine replacing lysine at position 34. A C16 fatty acid attaches through a glutamic acid spacer at lysine 26. Albumin binding and slower absorption prolong exposure, supporting daily administration (PMID 21923591).

Approved formulations are ready-to-use subcutaneous solutions. The Saxenda and Victoza US prescribing information describe different indications and dosing schedules for the same molecule. Their shared ingredient does not make their labeled regimens interchangeable.

Module 2, Recomposition. The relevant goal is weight reduction through lower energy intake. Evidence comes mainly from populations with obesity or type 2 diabetes. These studies do not establish improved physique, muscle retention, or performance in lean athletes.

MECHANISM

Liraglutide activates the GLP-1 receptor. Pancreatic effects include glucose-dependent insulin secretion and reduced glucagon secretion. Hypoglycemia risk rises with insulin or sulfonylureas, despite the glucose-dependent mechanism (Victoza US prescribing information).

Appetite and energy intake are central to its weight effect. A 49-person trial studied 1.8 mg or 3.0 mg subcutaneously once daily for five weeks (PMID 23999198). Both doses increased fullness and reduced subsequent unrestricted lunch intake by approximately 16 percent. Energy expenditure did not increase. The higher dose significantly slowed first-hour gastric emptying, while overall five-hour emptying was similar to placebo. This short experiment does not establish that gastric emptying effects always disappear after the first hour.

Rodent experiments identified liraglutide uptake in arcuate POMC/CART neurons and other brain sites (PMID 25202980). GLP-1 stimulated these neurons and indirectly inhibited NPY/AgRP signaling through GABA-dependent pathways. These findings support central appetite mechanisms. They do not establish one dominant human brain pathway or exclude peripheral contributions.

Cardiovascular benefit is demonstrated in high-risk type 2 diabetes, without establishing the responsible mechanism (PMID 27295427). Resting heart rate can increase despite cardiovascular benefit. Rodent thyroid C-cell proliferation explains the tumor warning; its relevance to humans remains uncertain (PMID 20203154).

EVIDENCE · GRADE A

Grade A for approved indications, supported by large randomized trials. SCALE studied 3,731 adults without diabetes; LEADER studied 9,340 adults with type 2 diabetes and high cardiovascular risk. Evidence strength does not eliminate limits of applicability. The studies reviewed here do not establish benefit in lean, trained adults. Weight reduction includes changes in fat and lean compartments, with substantial variation across populations and measurement methods.

Human data. SCALE compared liraglutide 3.0 mg subcutaneously once daily with placebo for 56 weeks, alongside lifestyle counseling (PMID 26132939). Mean weight loss was 8.4 versus 2.8 kg. At least 5 percent weight loss occurred in 63.2 versus 27.1 percent. Baseline mean BMI was 38.3. These are

Animal and mechanistic data. Candy-fed obese rats received liraglutide 0.2 mg/kg subcutaneously twice daily for 12 weeks (PMID 17192459). Weight and fat gains reversed alongside reduced calorie intake, without lower energy expenditure relative to candy-fed controls. This animal exposure is not a human

group averages, not predicted individual outcomes. A pooled SCALE analysis found that at least 4 percent weight loss by week 16 predicted later response (PMID 27804269). This means 16 weeks after initiation, including escalation. It does not mean 16 weeks at the maintenance dose. LEADER used liraglutide up to 1.8 mg subcutaneously once daily, or the maximum tolerated dose (PMID 27295427). Median follow-up was 3.8 years. Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke occurred in 13.0 versus 14.9 percent, hazard ratio 0.87. Pancreatitis was not significantly increased. These findings do not establish cardiovascular protection in healthy athletes. Lundgren randomized 195 adults after an eight-week diet produced mean weight loss of 13.1 kg (PMID 33951361). Treatment included liraglutide 3.0 mg subcutaneously once daily, structured exercise, both interventions, or placebo for one year. Weight differences versus placebo favored exercise by 4.1 kg, liraglutide by 6.8 kg, and their combination by 9.5 kg. Combination treatment reduced body-fat percentage by 3.9 percentage points, approximately twice either intervention alone. Its additional weight reduction versus liraglutide alone was not statistically significant. This was not an isolated trial of resistance training or protein supplementation. STEP 8 compared liraglutide 3.0 mg subcutaneously once daily with semaglutide 2.4 mg subcutaneously once weekly (PMID 35015037). At 68 weeks, mean losses were 6.4 and 15.8 percent, respectively. Treatment discontinuation for any reason was 27.6 and 13.5 percent, respectively. Discontinuation is not equivalent to withdrawal from study follow-up or discontinuation caused specifically by vomiting. A 2026 systematic review included 35 incretin studies and found widely variable reductions in muscle-related indices (PMID 41996180). Measurement heterogeneity prevented meta-analysis. Lean soft tissue, fat-free mass, and directly measured skeletal muscle are different outcomes. The review does not establish a fixed percentage of muscle loss for an individual.

dosing template. Arcuate-neuron experiments support appetite mechanisms (PMID 25202980). Thyroid experiments found important rodent-primate differences but did not resolve long-term human thyroid risk (PMID 20203154). In an angiotensin II mouse model, liraglutide improved aspects of diastolic dysfunction while reducing lean muscle mass relative to the disease-control group (PMID 37382868). The paper appeared online in 2023 and in its journal issue in 2024. This specific disease model does not quantify muscle loss in healthy human users.

REGULATORY STATUS AND SPORT

STATUS

Prescription liraglutide has US approvals for type 2 diabetes and chronic weight management under indication-specific labeling. The current weight-management label covers eligible adults and adolescents aged at least 12 years who meet its weight and obesity criteria. The diabetes label also includes cardiovascular risk reduction in adults with type 2 diabetes and established cardiovascular disease. Both carry a boxed warning for thyroid C-cell tumors. Label statements here were checked against current DailyMed prescribing information, including the Saxenda record published June 15, 2026. A research-use vial is not an FDA-approved presentation of the drug. Approval and availability outside the US require jurisdiction-specific verification.

WADA

Monitoring does not mean prohibition or establish that future prohibition will follow. The official 2026 WADA documents could not be retrieved successfully during this verification, so current status is supported here by published literature rather than independently confirmed against those

ROUTES	Approved administration is subcutaneous, with the abdomen, thigh, and upper arm listed in US prescribing information. Labels describe site rotation. No approved oral or intranasal liraglutide formulation was identified in the labeling reviewed. Route-specific efficacy and exposure cannot be inferred from an unapproved preparation.
HALF-LIFE	Approximately 13 hours after subcutaneous administration (PMID 21923591; Saxenda and Victoza US prescribing information). Peak concentrations occur around 11 hours in the weight-management label and 8 to 12 hours in the diabetes label. Half-life does not determine an exact time when all effects end. Label restart rules address gastrointestinal tolerability, not a guaranteed clearance deadline.
TIMING	US labels describe daily administration independent of meals. For a missed dose, they specify resuming with the next scheduled dose, without an extra replacement dose. After more than three days since the last administration, the Saxenda label specifies restarting at 0.6 mg subcutaneously once daily, followed by escalation. This is label documentation, not an individualized restart plan.
CYCLE LENGTH	There is no validated bodybuilding cycle in the evidence reviewed. Weight-management studies examined sustained treatment, including 56 weeks in SCALE and one year in the maintenance trial. LEADER's median follow-up was 3.8 years. The adult Saxenda response checkpoint is week 16 after initiation. Continued treatment depends on indication, response, and tolerability. These studies do not establish a tapering schedule or guarantee maintenance after withdrawal.
TITRATION	The Saxenda US label describes 0.6, 1.2, 1.8, 2.4, then 3.0 mg subcutaneously once daily, with weekly increases. It permits approximately one additional week before escalation when an increase is poorly tolerated. For adults, lower doses are escalation steps, and inability to tolerate maintenance treatment is a discontinuation criterion. The Victoza US label describes 0.6 mg subcutaneously once daily for one week, then 1.2 mg once daily. If needed, its maximum is 1.8 mg subcutaneously once daily after at least one week at the preceding dose. These are separate indication-specific label schedules.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Adult weight management. The US label evaluates response 16 weeks after initiation and specifies discontinuation below 4 percent baseline weight loss.	3.0 mg, equivalent to 3000 mcg, as adult maintenance treatment; Saxenda US prescribing information and SCALE, PMID 26132939.	Subcutaneous, as reported in the label and SCALE.	Once daily; SCALE treatment lasted 56 weeks.	Saxenda US prescribing information, sections 2.1 and 2.2; SCALE randomized trial, PMID 26132939. · PMID 26132939
Adult type 2 diabetes. The label distinguishes initiation for gastrointestinal tolerability from doses intended for glycemic control.	1.2 mg or 1.8 mg, equivalent to 1200 or 1800 mcg; Victoza US prescribing information. LEADER used up to 1.8 mg or maximum tolerated dosing, PMID 27295427.	Subcutaneous, as reported in the label and LEADER.	Once daily; LEADER median follow-up was 3.8 years.	Victoza US prescribing information, section 2.1; LEADER randomized trial, PMID 27295427. · PMID 27295427
Weight-loss maintenance after a supervised low-calorie diet, with or without structured exercise.	3.0 mg, equivalent to 3000 mcg; Lundgren randomized trial, PMID 33951361.	Subcutaneous.	Once daily for one year.	Lundgren randomized controlled trial, PMID 33951361. · PMID 33951361
Mechanistic human study of appetite, gastric emptying, and energy expenditure in adults with obesity without diabetes.	1.8 mg or 3.0 mg, equivalent to 1800 or 3000 mcg; van Can randomized trial, PMID 23999198.	Subcutaneous.	Once daily, with outcomes measured after five weeks.	van Can randomized incomplete crossover trial, PMID 23999198. · PMID 23999198
Animal experiment in candy-fed obese rats. These weight-adjusted exposures are not validated human regimens.	0.2 mg/kg, equivalent to 200 mcg/kg per administration; Raun animal study, PMID 17192459.	Subcutaneous.	Twice daily for 12 weeks.	Raun animal study, PMID 17192459. · PMID 17192459

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– Semaglutide

The Saxenda US label does not recommend coadministration with another GLP-1 receptor agonist. Added efficacy and the size of any added toxicity are not established. STEP 8 compared separate treatments, not concurrent administration.

– Tirzepatide

Its GLP-1 receptor activity overlaps with liraglutide. No controlled evidence supporting this combination was verified. The label's restriction on concurrent GLP-1 receptor agonists applies; gastrointestinal effects are a potential overlapping concern.

– Retatrutide

Its GLP-1 receptor activity overlaps with liraglutide. No combination trial was verified, and efficacy or tolerability cannot be inferred from separate-agent studies.

SAFETY

COMMON EFFECTS

Nausea, vomiting, diarrhea, constipation, dyspepsia, and abdominal discomfort are common. Headache, fatigue, and injection-site reactions also occur. Routine monitoring in adult weight-management trials found average resting heart-rate increases of 2 to 3 beats per minute (Saxenda US prescribing information). A meta-analysis also identified modest increases with liraglutide (PMID 26358202). Gastrointestinal symptoms may lessen over time, but persistent symptoms are clinically relevant. Hypoglycemia risk is greater with insulin or sulfonylureas.

SERIOUS SIGNALS

A meta-analysis of 76 randomized trials found increased gallbladder or biliary disease with GLP-1 receptor agonists (PMID 35344001). Relative risk was 1.37 overall and 2.29 in weight-loss trials. These are class-level relative risks, not an individual's absolute probability. US labels warn about pancreatitis, severe gastrointestinal reactions, dehydration-associated acute kidney injury, serious hypersensitivity, and aspiration during anesthesia or deep sedation. LEADER's pancreatitis result does not eliminate the warning. Rodent C-cell tumors support the boxed warning; human causality remains uncertain (PMID 20203154). The current Saxenda label records removal of the suicidal-behavior and ideation warning in February 2026. Lean-compartment reductions warrant attention, but available body-composition data do not prove drug-induced functional impairment in every patient (PMID 41996180).

CONTRAINDICATIONS

Formal US label contraindications include personal or family history of medullary thyroid carcinoma, MEN2, and serious hypersensitivity to liraglutide or formulation ingredients. Pregnancy is no longer listed as a formal Saxenda contraindication, but its pregnancy section still specifies discontinuation when pregnancy is recognized. Weight loss offers no pregnancy benefit. Breastfeeding data are insufficient and require an individualized clinical assessment. Severe gastroparesis is a labeled situation where use is not recommended. Pancreatitis history, gallbladder disease, dehydration risk, and concurrent insulin or sulfonylureas require clinical review. Other GLP-1 agonists are a coadministration limitation, not a formal contraindication.

STOP RULES

Severe persistent abdominal pain warrants urgent assessment for pancreatitis or other causes. Facial or throat swelling, breathing difficulty, collapse, or severe hypoglycemia require emergency care. Right upper abdominal pain with fever or jaundice, persistent vomiting, or reduced urine output also warrant prompt assessment. A neck mass, persistent hoarseness, or swallowing difficulty requires evaluation. The adult Saxenda label specifies discontinuation for insufficient week-16 response, inability to tolerate maintenance treatment, sustained resting heart-rate increase, or recognized pregnancy. Suspected pancreatitis and serious hypersensitivity also trigger discontinuation under labeling. Anesthesia planning requires the treating team to assess aspiration risk. The label does not establish a universal one-day interruption rule.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

Approved liraglutide presentations reviewed here are prefilled pens containing ready-to-use solution. The Saxenda and Victoza US labels specify 3 mL containing 18 mg at 6 mg/mL. No reconstitution is involved. An unapproved powder's printed mass does not establish its actual peptide content, formulation, sterility, or stability.

SOLVENT

Neither reviewed US label provides a solvent or reconstitution method for lyophilized liraglutide. The approved formulation contains buffering ingredients, propylene glycol, phenol, and water for injection, with pH approximately 8.15. Adding bacteriostatic water to an unknown powder does not reproduce the validated formulation. Visual clarity cannot establish sterility, potency, or absence of endotoxin.

STORAGE

US pen labels specify refrigeration at 2 to 8 C before first use. After first use, labeled storage is up to 30 days at 15 to 30 C or refrigerated. Freezing, excessive heat, and sunlight are excluded by labeling. These limits apply to the approved formulation and container. They do not establish a refrigerated shelf life or beyond-use date for reconstituted powder.

Formulation arithmetic only, using the labeled solution: 6 mg/mL multiplied by 3 mL equals 18 mg per pen (Saxenda US prescribing information). The labeled concentration also equals 6000 mcg/mL. The adult maintenance amount is 3.0 mg subcutaneously once daily, according to that label. Dividing 3.0 mg by 6 mg/mL gives an equivalent solution volume of 0.50 mL. This calculation explains concentration; it is not an instruction to extract pen contents or use a separate syringe.

Mass, concentration, and device markings describe different quantities. A pen setting expresses its labeled delivery amount. Syringe markings depend on the device's calibration and do not independently measure liraglutide potency. Without a validated preparation and measured concentration, mathematically correct division cannot establish what an unapproved vial delivers.

BUYING NOTES

Regulatory authorization, product identity, and batch testing answer different questions. An approved presentation has evaluated manufacturing, formulation, container, and stability specifications. Approval does not guarantee every item circulating outside an authorized supply chain is authentic.

A COA can describe the submitted sample, but its value depends on laboratory identity, methods, sampling, and batch traceability. Chromatographic purity alone does not establish peptide quantity, correct sequence, sterility, endotoxin limits, or clinical equivalence. A molecular-mass result may support identity but cannot resolve every impurity or formulation issue. A generic purity cutoff is not a complete release specification.

For this compound, the important distinction is between evidence for regulated liraglutide formulations and unsupported assumptions about an independently supplied powder. No vendor assessment or COA can convert that powder into the formulation tested in the cited trials.

COMMON MISTAKES

- Counting 16 weeks from the maintenance dose. The adult Saxenda response assessment occurs 16 weeks after treatment starts, including escalation.
- Treating initiation doses as validated long-term weight-management regimens for lean adults. The adult weight-management label uses lower steps for escalation, not established athletic protocols.
- Reading fat-free mass or lean soft tissue as a direct measurement of skeletal muscle. Measurement methods differ, and neither quantity alone establishes strength or physical function.
- Treating treatment discontinuation as study withdrawal. STEP 8 reported 27.6 percent treatment discontinuation with liraglutide, while most randomized participants completed trial follow-up.
- Interpreting the exercise trial as proof of statistically superior weight loss versus liraglutide alone. That comparison was not significant, although body-fat percentage results favored combination treatment.
- Assuming appetite suppression establishes an anabolic effect, or that an untested peptide stack prevents lean-compartment loss. No verified combination evidence supports that claim.
- Extending the pen's storage limits to reconstituted powder. Formulation and container stability require their own validation.
- Using a half-life estimate as a missed-dose rule or a fixed anesthesia interruption schedule. The current label provides specific restart language and acknowledges uncertainty about aspiration mitigation.

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AOD-9604

hGH fragment 177-191 analog

Modified GH C-terminal fragment

Module 2 · Recomposition

Goals: Fat loss

Route: SC

WADA prohibited

A modified growth hormone fragment with metabolic effects in rodents. Human oral development failed to establish useful weight loss, and subcutaneous efficacy remains unproven.

WHAT IT IS

AOD-9604 is a synthetic peptide containing 16 amino acids. It comprises human growth hormone residues 177 to 191 with an additional N-terminal tyrosine and an intramolecular disulfide bond. Its identity is described in the analytical literature (PMID 25208511).

AOD-9604, the unmodified hGH 177-191 fragment, and products labelled hGH 176-191 require careful distinction. These names overlap in commercial descriptions, but a name does not establish sequence, terminal chemistry, salt form or disulfide connectivity. AOD9401 is a related fragment studied in earlier experiments, not an interchangeable name for AOD-9604. Results from that precursor belong to the development history and require explicit attribution (PMID 11116208).

The development objective was to retain effects on lipid metabolism while limiting classical growth hormone receptor activity. Preclinical experiments supported aspects of this separation. They did not establish selective fat loss, muscle preservation or improved performance in humans. The oral obesity program subsequently failed to demonstrate sufficient efficacy for continued development.

Module 2, recomposition. Goal category: fat loss. Class: modified GH C-terminal fragment. AOD-9604 is not an established growth hormone secretagogue. Its biological origin does not justify applying secretagogue dosing, timing or cycling conventions to it.

MECHANISM

The early evidence concerns related fragments as well as AOD-9604 itself. Wu and Ng studied synthetic hGH 177-191 in rat adipose tissue. The fragment inhibited lipid synthesis, but did not significantly increase glycerol release in that assay (PMID 8358331). Inhibition of lipogenesis and stimulation of lipolysis describe different processes. Neither measurement alone establishes sustained loss of body fat in humans.

A subsequent study examined AOD9401, the related 177-191 domain. It stimulated hormone-sensitive lipase and inhibited acetyl-CoA carboxylase in isolated rat adipose tissue. Chronic treatment also reduced adipocyte size and weight gain in obese Zucker rats (PMID 11116208). These findings support the biological rationale for investigating GH fragments. They do not establish that every formulation labelled AOD-9604 reproduces the same enzyme effects.

Direct AOD-9604 experiments provide a separate line of evidence. In obese mice, treatment reduced weight gain and increased fat oxidation and plasma glycerol. Unlike intact growth hormone in that experiment, it did not induce hyperglycemia or reduce insulin secretion. In the accompanying cell assays, AOD-9604 did not compete for the human GH receptor or induce receptor-associated proliferation (PMID 11673763).

These results support activity outside classical GH receptor signalling under the tested conditions. They do not prove absence of every growth-related effect in every tissue. A negative proliferation assay also cannot exclude cancer risk during prolonged human exposure. The human observation of no significant IGF-1 increase is a separate clinical finding, not a complete safety mechanism.

The beta-3 adrenergic pathway was investigated as a possible contributor. Chronic treatment increased beta-3 receptor RNA expression in obese mice. Weight and lipolysis responses were absent in receptor knockout animals, but acute effects on energy expenditure and fat oxidation remained (PMID 11713213). The authors

concluded that the lipolytic effects were not mediated directly through beta-3 receptors. Increased receptor expression could contribute to downstream sensitivity without establishing direct receptor agonism.

A specific molecular receptor explaining AOD-9604 activity has not been established by these studies. Direct beta-3 agonism and a defined AMPK mechanism should not be presented as demonstrated targets. A plausible pathway diagram is weaker evidence than binding, functional target validation and reproducible clinical outcomes.

Conformation also requires precise interpretation. Reduced, S-carbamidomethylated GH fragments produced insulin-antagonistic effects in rats (PMID 6751009). A structural study characterized a related 15-residue cyclic fragment, rather than the complete 16-residue AOD-9604 molecule (PMID 11152298). These experiments show that sequence and chemical modification matter. They do not demonstrate that shaking an AOD-9604 vial breaks its disulfide bond or produces the insulin-antagonistic experimental derivative.

Established within specific experiments: rodent metabolic activity, lack of detectable GH receptor competition in the tested assay, and no significant human IGF-1 increase in summarized trials. Unresolved: the principal molecular target, clinically effective human exposure, long-term safety and efficacy through subcutaneous administration.

EVIDENCE · GRADE C

Grade C applies to the claimed fat-loss and recomposition benefits. Positive efficacy evidence is predominantly animal research. Human trials exist, but their existence does not establish benefit, and the larger oral obesity program was unsuccessful. The catalogue grade reflects support for the claimed outcome, rather than simply counting randomized studies.

Human safety observations are more extensive than for many experimental peptides, but remain limited by reporting quality, route and duration. They cannot establish the safety of repeated subcutaneous exposure. Joint-repair claims also remain preclinical. AOD-9604 therefore belongs in an evidence map as a compound with animal activity and an unsuccessful human obesity program, not as a validated recomposition intervention.

Human data. The historical clinical program included six controlled studies using intravenous or oral formulations. The largest randomized study assigned 502 adults with obesity and lasted 24 weeks. Its weight-loss findings did not demonstrate a significant advantage over placebo, and obesity development was discontinued. Dominikowski reports 534 participants before randomization, whereas FDA's review reports 536 enrolled. Both report 502 randomized. The randomized population is retained here because it is consistent and directly relevant to the treatment comparison. FDA describes the primary weight comparison at 12 weeks, with additional weight outcomes assessed at 24 weeks. Calling the study a 24-week trial does not mean its primary efficacy assessment occurred only at the final visit. Detailed efficacy reporting remains limited, with substantial dependence on conference material and sponsor disclosures. These limitations reduce confidence in precise effect estimates but do not supply evidence of benefit. The clinical summaries reported no significant differences in IGF-1 and no consistent deterioration in measured glucose outcomes. However, FDA identified incomplete adverse-event reporting and events requiring more cautious interpretation. Lack of significant laboratory differences does not establish absence of risk. No

Animal and mechanistic data. Direct AOD-9604 studies reported reduced weight gain, increased fat oxidation and increased glycerol in obese mice (PMID 11673763). Reduced weight gain is not necessarily weight loss from baseline. That distinction matters when translating an animal growth curve into a claim about adult body composition. In obese Zucker rats, AOD-9604 at 500 mcg/kg orally once daily for 19 days reduced weight gain versus controls (PMID 11146367). Insulin sensitivity was preserved in the reported clamp experiments. This is a species-specific experimental exposure, not a human dosing estimate. Related AOD9401 experiments reported enzyme changes and smaller adipocytes (PMID 11116208). The beta-3 receptor knockout work further defined possible pathway involvement without identifying a direct receptor target (PMID 11713213). These studies provide mechanistic consistency within selected rodent models, not evidence of clinical effectiveness across species. A randomized study in 32 rabbits examined collagenase-induced knee osteoarthritis. AOD-9604 at 0.25 mg per knee, administered intra-articularly weekly during post-induction weeks 4 through 7, improved cartilage-related scores (PMID 26275694). The combination arm received the same AOD-9604 exposure plus 6 mg hyaluronic acid per knee, intra-articularly on that

controlled human efficacy study of subcutaneous AOD-9604 for fat loss, recomposition, athletic performance or joint repair was identified in this review. Oral failure does not prove every other route ineffective. It also provides no evidence that an injectable route succeeds. Source: FDA's 2024 evaluation of the clinical program, supported by the historical and contemporary reviews (PMID 15134286, PMID 42395176). [FDA AOD-9604 briefing document] (<https://www.fda.gov/media/183584/download>).

weekly schedule (PMID 26275694). Combination outcomes exceeded either agent alone in that model. This rabbit result concerns a chemically induced joint injury and local administration. It does not establish human cartilage regeneration, systemic tissue repair, or benefit from combining AOD-9604 with another peptide.

REGULATORY STATUS AND SPORT

STATUS

AOD-9604 is not an FDA-approved drug. There is no approved US prescribing label establishing an indication, dose, formulation or administration schedule. FDA's 2024 evaluation recommended against adding its free base and acetate forms to the 503A bulks list. The current FDA safety page places AOD-9604 under substances whose nominations were withdrawn, following earlier Category 2 placement. Describing it as currently remaining in Category 2 is inaccurate. Withdrawal is not drug approval or authorization for routine compounding. The legal status of a preparation depends on the applicable statutory conditions, not its marketing description. Food-use GRAS claims require separate interpretation. An expert-panel determination or notification concerning specified food uses does not establish therapeutic efficacy or authorize injection. A research-use label likewise does not establish pharmaceutical quality or lawful human marketing. Regulatory status checked September 5, 2026. [FDA current compounding safety information] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>).

WADA

Prohibited at all times under the 2026 WADA Prohibited List, section S2.2.3, growth hormone analogues and fragments. AOD-9604 is explicitly named. The prohibition applies in and out of competition and does not depend on demonstrated performance benefit. Analytical publications establish that the compound has been investigated in anti-doping testing, but analytical findings do not alter its prohibited status (PMID 25208511, PMID 24124033). [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Oral administration was used in the obesity efficacy program. Intravenous administration was used in early human pharmacology and safety studies. These studies involved controlled formulations and selected populations; their results do not automatically transfer to differently manufactured preparations. Intra-articular administration was studied in the rabbit osteoarthritis model (PMID 26275694). Subcutaneous administration appears in non-clinical use descriptions, but no controlled human efficacy trial through that route was identified. The historical review documents early human development, while the contemporary review distinguishes clinical exposures from forum-derived practices (PMID 15134286, PMID 42395176). Route changes can alter absorption, peak exposure, metabolism and immune responses. Equal nominal peptide mass across routes does not imply equal systemic exposure or comparable risk. There is no validated conversion between the oral research doses and a subcutaneous regimen.

HALF-LIFE

A clinically established human elimination half-life suitable for scheduling repeated administration was not identified. FDA's preclinical review describes a short intravenous half-life in pigs, which cannot establish human subcutaneous pharmacokinetics. Analytical research documents metabolism and matrix-dependent degradation (PMID 25208511, PMID 42328738). These experiments answer questions about sample stability and analytical recovery. They do not establish how long a clinical effect lasts or how frequently a person would require administration. Elimination half-life, absorption time, duration of biological effect and storage stability are separate measurements. A number describing any one of them cannot substitute for the others. No validated human exposure-response model was identified that resolves these uncertainties for body composition.

TIMING

No validated meal, exercise or time-of-day schedule was identified. Claims favouring fasted mornings or pre-exercise administration derive from non-clinical conventions. General knowledge about insulin and fat metabolism does not establish an AOD-9604 timing effect. AOD-9604 has not been established as a ghrelin-receptor or GHRH-receptor agonist. Evidence about those pathways cannot validate timing for this fragment. Conversely, lack of GH receptor binding alone does not

determine whether meals affect absorption or downstream physiology. Timing would require direct comparison of relevant formulations, exposures and outcomes. Changes in transient fat oxidation would still need to translate into sustained body-composition benefit. Neither a plausible metabolic explanation nor repeated anecdotal use supplies that comparison.

CYCLE LENGTH

Cycles of 8 to 12 weeks are commonly cited in non-clinical use; not validated in trials (PMID 42395176). The oral research program included treatment lasting up to 24 weeks, but that duration does not validate a subcutaneous cycle. No controlled evidence establishes a washout interval, a recovery period, or an on-off schedule that improves outcomes or reduces harm. The absence of documented endogenous-axis suppression does not prove that uninterrupted exposure is harmless. Receptor adaptation and longer-term immune effects are insufficiently characterized. A study's follow-up period also differs from treatment duration. Short observation after treatment cannot reliably exclude delayed adverse effects. The available human record therefore cannot define an evidence-based cycle for performance or recomposition.

TITRATION

No validated titration schedule for human subcutaneous use was identified. Early human studies included dose escalation for research purposes. That design does not establish a titration strategy for routine use. Oral dose-ranging reports did not demonstrate a simple, reproducible relationship between increasing exposure and greater weight loss. Limited reporting, variability and subgroup findings prevent interpreting this as proof that the lowest exposure is optimal. There is no established therapeutic target concentration, effective maintenance exposure or clinically validated maximum for body composition. Lack of response cannot distinguish inadequate exposure from an ineffective intervention, an unsuitable formulation or measurement noise. Dose escalation therefore lacks an established benefit-risk rationale for this claimed use.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Early human intravenous pharmacology, adults with obesity	25, 50 or 100 mcg/kg per intravenous administration in the study summarized by Wilding (PMID 15134286), with weekly study visits across four periods.	Intravenous	Single study administrations separated by approximately one week, with active doses and placebo evaluated across four periods.	Wilding 2004, PMID 15134286, describes the early study. FDA's 2024 briefing corroborates the weight-based units and weekly schedule. These were experimental pharmacology exposures, not established weight-loss doses. · PMID 15134286
Human oral obesity program, one studied treatment arm	1 mg orally once daily for 12 weeks, as summarized in Dominikowski 2026 (PMID 42395176).	Oral	Once daily for 12 weeks.	PMID 42395176 reports this oral regimen. FDA's review confirms it was one arm of a larger dose-ranging trial. Early findings were incompletely reported, and the subsequent program failed to establish sufficient weight-loss efficacy. · PMID 42395176
Chronic oral experiment in obese Zucker rats	500 mcg/kg orally once daily for 19 days, as reported by Ng and colleagues (PMID 11146367).	Oral	Once daily for 19 days.	PMID 11146367 directly reports this animal dose and schedule. Weight gain was lower than in controls, and the reported insulin-sensitivity measurements were preserved. Species differences, formulation and oral absorption prevent direct conversion into a human regimen. · PMID 11146367

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Collagenase-induced knee osteoarthritis in rabbits	0.25 mg AOD-9604 per knee intra-articularly once weekly during post-induction weeks 4 through 7; the combination arm also received 6 mg hyaluronic acid per knee on that schedule (PMID 26275694).	Intra-articular under ultrasound guidance	Weekly during weeks 4 through 7 after the first collagenase administration, with assessment at week 8.	Kwon and Park 2015, PMID 26275694. The timing refers to post-induction weeks, not a variable treatment duration of four to seven weeks. The findings concern local treatment of rabbit joints and do not define a systemic or human protocol. · PMID 26275694
Non-clinical body-composition practices described in a narrative review	250 to 500 mcg total per day subcutaneously, divided into 2 to 3 administrations; commonly cited in non-clinical use; not validated in trials (PMID 42395176).	Subcutaneous	Daily totals divided into 2 to 3 administrations; commonly cited in non-clinical use; not validated in trials.	Dominikowski 2026, PMID 42395176, explicitly derives this pattern from non-clinical sources. The numbers describe reported behaviour rather than a tested regimen. The stated total is a daily amount, not the amount of every divided administration. · PMID 42395176

STACKING

+ CJC-1295	Proposed pairing, not demonstrated synergy. The rationale combines a GH-axis agent with a fragment intended to affect lipid metabolism through another pathway. No controlled human study establishing an incremental AOD-9604 benefit was identified. Lack of an IGF-1 rise with AOD-9604 alone cannot establish the endocrine profile of the combination. Mechanistic complementarity remains a hypothesis rather than an outcome.	– HGH Fragment 176-191	Identity and duplication concern. Commercial fragment names overlap, but they do not prove chemical equivalence. Exact sequence, terminal chemistry, salt form and disulfide state require verification. If both preparations contain the same active peptide, coadministration duplicates exposure. If they differ, there is still no established complementary benefit. The analytical literature cannot authenticate a preparation from its label alone (PMID 25208511).
+ Ipamorelin	Proposed pairing with no established human combination benefit. A GH secretagogue and a GH-derived fragment need not share the same target, but distinct targets do not establish compatible exposures or additive fat loss. No controlled combination data were identified that quantify body composition, glucose effects or longer-term safety. A dosing convention cannot supply those missing measurements.	– IGF-1 LR3	No established combination benefit or safety profile. AOD-9604's lack of a significant IGF-1 increase in summarized trials does not neutralize another agent's pharmacology. An IGF-1 analogue introduces a separate growth-factor exposure requiring independent assessment. The AOD-9604 receptor experiments cannot justify a claim that the combination preserves the fragment's proposed metabolic separation (PMID 11673763).
+ BPC-157	Proposed tissue-repair pairing without a supporting human combination trial. The cited rabbit experiment tested AOD-9604 with hyaluronic acid, not BPC-157 (PMID 26275694). Its results cannot establish synergy between these peptides. Differences in injury model,	– Tesamorelin	No controlled evidence establishes an AOD-9604 contribution to this combination. Evidence supporting another agent in a defined indication does not transfer to the added fragment. Concurrent exposure also complicates interpretation of laboratory changes, adverse effects and weight outcomes.

	species and administration route further limit extrapolation. The orthopaedic review provides research context, not validation of this stack (PMID 41490200).	This is an evidence-gap concern, not a demonstrated pharmacokinetic interaction or a formally established combination contraindication.
+ Semaglutide	No demonstrated incremental benefit from adding AOD-9604 was identified. A separate proposed mechanism does not establish additional weight loss, muscle preservation or improved tolerability. Any change during simultaneous treatment would be difficult to attribute without an appropriate comparator. The relevant question is the measured benefit of the addition, which remains unanswered, rather than whether the mechanisms can be described differently.	

SAFETY

COMMON EFFECTS

Human study summaries describe headache, gastrointestinal symptoms, fatigue and dizziness. Early intravenous studies also reported local reactions and bruising. Attribution was often uncertain because detailed event breakdowns by dose and treatment were incomplete. The clinical summaries generally reported no significant IGF-1 differences and no consistent adverse trend in measured glucose outcomes. These findings apply to the populations, formulations and observation periods studied. They do not establish absence of endocrine effects during unstudied exposure patterns. The frequency and severity of adverse effects from repeated subcutaneous administration cannot be estimated reliably from this record. Oral trial tolerability and brief intravenous observations are insufficient substitutes. FDA's detailed review is more cautious than the broad reassurance in some secondary summaries.

SERIOUS SIGNALS

FDA identifies potentially associated serious adverse events, while stating that causality remains unclear. Its clinical review describes serious diarrhea considered possibly related to oral treatment and severe chest tightness considered possibly related to intravenous treatment. Several neoplastic diagnoses were reported during an oral trial. Investigators considered these unrelated, but FDA found the available case information insufficient for firm reassurance. These observations do not establish that AOD-9604 causes cancer. They also make a categorical statement of no serious safety concerns inappropriate. Additional concerns include immunogenicity, aggregation, peptide-related impurities and uncertain product characterization. The older chemically modified fragment experiments do not demonstrate the clinical toxicity of an ordinarily mishandled AOD-9604 preparation (PMID 6751009). The intrinsic peptide risks and manufacturing risks remain separate uncertainties. Attributing all realistic danger to contamination would understate the incomplete clinical evidence. [FDA review of AOD-9604 safety] (<https://www.fda.gov/media/183584/download>).

CONTRAINDICATIONS

There is no approved AOD-9604 label establishing formal contraindications. Pregnancy, breastfeeding and pediatric exposure lack an adequate clinical safety basis. Active or recent malignancy also warrants particular caution because clinical oncologic risk is unresolved. Previous hypersensitivity to the peptide or formulation components is a reason to avoid re-exposure pending medical assessment. Significant metabolic disease and concurrent investigational agents further limit the applicability of the available trial observations. A normal IGF-1 result cannot exclude immune, cardiovascular or oncologic risk. Anti-doping prohibition is a sporting restriction rather than a medical contraindication. Unverified identity or sterility is a product-quality hazard, not a substitute category for patient contraindications.

STOP RULES

Breathing difficulty, throat swelling, fainting, generalized hives or significant chest symptoms warrant discontinuation and urgent medical assessment. A suspected systemic allergic reaction is not an appropriate setting for unsupervised rechallenge. Spreading redness, warmth, increasing pain, fever or chills after an injection require prompt evaluation. Possible explanations include infection, inflammatory reactions and contamination. Appearance and timing alone cannot determine which explanation is correct. Persistent severe diarrhea, dehydration, new neurological symptoms or sustained unexplained systemic symptoms also warrant discontinuation and clinical review. Headache or fatigue alone does not identify a specific peptide reaction, but persistent

symptoms should not be dismissed. A certificate of analysis cannot exclude clinical toxicity. Conversely, a missing certificate does not diagnose the cause of a reaction. Assessment depends on symptoms, examination, exposure history and appropriate testing.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved standard AOD-9604 vial presentation. Neither nominal vial mass nor the appearance of a white cake establishes identity, sterility, peptide content or disulfide integrity. Total powder mass, peptide content and chromatographic purity are different quantities. Counterions, residual water and excipients may contribute to total mass. A meaningful specification states what the mass represents and how it was measured. A chromatographic percentage cannot automatically be used as a correction factor for labelled mass. The relevant analytical questions concern the tested lot and final preparation, rather than a generic expectation for research powders.

SOLVENT

No validated general-purpose diluent, concentration or reconstitution procedure for non-clinical subcutaneous use was identified. Historical intravenous trial preparation does not validate a multidose preparation intended for another route. Bacteriostatic water does not sterilize a contaminated powder or guarantee peptide stability. Sterile water and saline also do not confer a universal storage period after mixing. Compatibility depends on formulation, pH, concentration, container, preservative and intended use. The structural literature characterizes a related cyclic fragment but does not test shaking, foaming or routine reconstitution handling (PMID 11152298). Potential aggregation, precipitation and chemical degradation require formulation-specific testing. A clear solution is not proof of sterility or molecular integrity. A visible precipitate is a quality concern, but absence of visible particles does not establish that the preparation meets injectable-product standards.

STORAGE

No universal storage interval for reconstituted AOD-9604 was established by the cited research. A general convention for multidose containers cannot establish chemical stability or microbial control for this peptide preparation. One analytical study found substantial AOD-9604 degradation after a week in serum and plasma held at 4 or 22 degrees C (PMID 42328738). Those biological matrices contain components absent from a simple laboratory diluent. Their degradation rates cannot be converted into a beyond-use date for a different formulation. The same study reports different stability under other sample-storage conditions. That variation reinforces the importance of matrix and method, rather than establishing a preferred home-storage procedure. Detection after storage also does not necessarily demonstrate unchanged potency or suitability for administration. Validated storage specifications require testing of the actual formulation, concentration, container and handling conditions. Refrigeration alone cannot verify intact peptide, absence of aggregates or sterility.

Illustrative concentration arithmetic only, using hypothetical quantities rather than a preparation or administration protocol. If an independently confirmed 5 mg peptide amount were present in a final solution volume of 2 mL, the calculated concentration would be 2.5 mg/mL. Converting mass units gives the same concentration as 2500 mcg/mL.

If that same confirmed 5 mg amount were instead present in a final volume of 5 mL, the concentration would be 1 mg/mL. These hypothetical mass and volume values are calculation inputs, not doses, approved formulation specifications or instructions to mix a product.

The calculation is confirmed peptide mass divided by final solution volume. It does not use vial capacity, total powder weight or a purity percentage as interchangeable inputs. Final solution volume also needs to be distinguished from the amount of liquid initially added when displacement matters.

The resulting concentration establishes only an arithmetic relationship between mass and volume. It does not establish a clinically justified amount, route, frequency, device marking or shelf life. No syringe-unit conversion is provided because there is no validated human subcutaneous regimen to which it could be applied. A calculator can expose unit errors while leaving efficacy and formulation questions completely unresolved.

BUYING NOTES

Supplier evaluation begins with a limitation: documentation cannot establish clinical effectiveness. A technically convincing certificate does not reverse the unsuccessful obesity program or validate a subcutaneous regimen. Product quality and therapeutic evidence answer different questions.

Identity requires more than a familiar name. AOD-9604 is a defined modified fragment, whereas GH fragment labels may describe different sequences or use imprecise shorthand. A useful analytical record specifies sequence, terminal groups, salt or counterion, and relevant disulfide characterization. FDA identified inconsistencies in public chemical descriptions and supporting documentation during its review.

Lot traceability matters because results apply to the tested material. A generic certificate reused across lots does not characterize each supplied preparation. The report's laboratory, sample identification, dates, methods and acceptance criteria determine how much can reasonably be concluded from it.

Chromatography and mass spectrometry provide complementary information. A chromatographic purity result estimates components resolved and detected under that method. Mass spectrometry supports molecular identification, but an expected intact mass alone may not resolve every sequence, stereochemical or structural uncertainty. Neither test establishes sterility, endotoxin control or clinical potency.

Disulfide characterization is relevant to identity, but its interpretation should remain proportionate. The related-fragment structural paper does not provide a commercial release specification for AOD-9604 (PMID 11152298). The insulin-antagonistic chemically modified fragment is not a demonstrated routine storage product (PMID 6751009).

Separate analytical questions include actual peptide content, residual solvents, aggregation, endotoxin and sterility. A high purity percentage cannot substitute for these assessments. Results from bulk material also do not automatically characterize a finished preparation after filling, shipment or reconstitution.

Regulatory descriptions require equal precision. Food-use safety claims, withdrawn compounding nominations and drug approval are different statuses. None should be used as shorthand for the others. No supplier documentation can establish an approved human indication or an evidence-based personal protocol where neither exists.

COMMON MISTAKES

- Treating AOD-9604, AOD9401 and every preparation labelled GH fragment as chemically interchangeable. Related sequences can inform a research hypothesis without establishing identical pharmacology. Product names alone cannot establish sequence, disulfide state or equivalence (PMID 11116208, PMID 25208511).
- Presenting reduced weight gain in rodents as demonstrated human fat loss. The animal findings are positive within their models, while the larger human oral program failed to establish efficacy. Neither finding cancels the other, and each requires its species and outcome to remain visible (PMID 11146367, PMID 42395176).
- Using a GRAS claim or historical compounding category as evidence of drug approval. Food-use assessments do not validate injection or weight-loss efficacy. FDA currently lists AOD-9604 among withdrawn nominations, which does not establish routine compounding eligibility.
- Assuming that subcutaneous administration solves the oral program's efficacy problem. A route change can alter exposure, but improved exposure is not itself proven clinical benefit. The missing comparison is a controlled human study of the actual formulation and route.
- Extending a rabbit joint result to systemic human repair. The study used 0.25 mg AOD-9604 per knee intra-articularly each week during post-induction weeks 4 through 7 (PMID 26275694). It did not establish a subcutaneous protocol or synergy with another peptide.
- Borrowing timing, cycling or titration rules from GH secretagogues. AOD-9604 has not been established to act through their receptors. Neither fasting conventions nor a plausible lipid-metabolism explanation can replace an actual comparison of schedules and clinical outcomes.
- Assuming that a GH fragment is permitted in sport because it lacks a demonstrated performance benefit. AOD-9604 is explicitly prohibited under WADA S2.2.3 at all times. Analytical research and clinical efficacy are separate from that classification.
- Converting biological-sample stability findings into a reconstituted-vial shelf life. Serum and plasma degradation experiments do not validate a multidose preparation in another solvent. Visible clarity, refrigeration and preservative content cannot individually establish acceptable quality (PMID 42328738).
- Escalating exposure because early changes are absent or inconsistent. No validated subcutaneous dose-response relationship was identified. A weight trend also cannot isolate treatment effects from diet, training,

hydration and measurement variation without an appropriate comparison.

- Copying a dose from a review without checking its units. Dose verification requires the compound, amount, weight basis, route, frequency, population and original research context to remain connected.

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HGH Fragment 176-191

Frag 176-191

GH C-terminal fragment

Module 2 · Recomposition

Goals: Fat loss

Route: SC

WADA prohibited

A sixteen amino acid growth hormone fragment with limited direct research. Its evidence must be separated from AOD9604 and the shorter fragment hGH 177-191.

WHAT IT IS

A synthetic peptide corresponding to residues 176 through 191 of mature human growth hormone. The native sequence is FLRIVQCRSVEGSCGF, beginning with phenylalanine. AOD9604 contains the fifteen residues of hGH 177-191 preceded by tyrosine, giving YLRIVQCRSVEGSCGF. Both contain sixteen amino acids, but they are chemically different. Cox and colleagues explicitly describe the tyrosine-containing structure of AOD9604 (PMID 25208511). A third peptide, AOD9401, corresponds to hGH 177-191 and contains fifteen residues (PMID 11116208). Commercial terminology and some reviews blur these distinctions. A name on a container therefore cannot establish which sequence it contains. The development rationale for this peptide family was to investigate lipid metabolism effects associated with the growth hormone C-terminal region. The human oral obesity programme belonged to AOD9604. Its clinical history cannot be assigned to native hGH 176-191.

MECHANISM

Direct evidence for native hGH 176-191 includes an early experiment in normal rats. It produced a short-lived blood glucose increase and a more sustained insulin increase. Insulin tolerance testing also showed reduced insulin sensitivity after exposure to active C-terminal fragments, including hGH 176-191 (PMID 645904). These findings prevent a blanket claim that native Frag lacks the glucose effects of growth hormone. They do not establish the size or frequency of any corresponding human effect.

The frequently cited receptor experiments tested AOD9604. In transfected cells, AOD9604 did not compete for the growth hormone receptor or induce proliferation through that receptor. In the accompanying mouse experiment, it increased fat oxidation and reduced weight gain without the hyperglycaemia observed with intact growth hormone (PMID 11673763). These are compound-specific laboratory observations, not proof of human metabolic neutrality or absence of cancer risk.

The enzyme findings also need correct attribution. AOD9401 stimulated hormone-sensitive lipase and inhibited acetyl-CoA carboxylase in isolated rat adipose tissue (PMID 11116208). Another AOD9401 study reported increased lipolysis and decreased lipogenesis in isolated human adipose tissue (PMID 10950816). Isolated human tissue is laboratory evidence, not evidence from people receiving treatment. Neither experiment establishes these effects for native hGH 176-191.

The beta3-adrenergic experiments used AOD9604. Chronic treatment effects differed between normal and receptor-knockout mice, while some acute metabolic effects persisted without the receptor. The authors concluded that the lipolytic actions were not mediated directly through beta3 receptors, although receptor expression increased (PMID 11713213). This supports pathway involvement under those experimental conditions. It does not establish a direct receptor target, predictable interactions, or a clinically useful response in humans.

No validated human target-engagement marker or clinical exposure-response relationship for native hGH 176-191 was identified. An incompletely characterized mechanism increases uncertainty, but does not itself prove that dose-response relationships cannot exist.

EVIDENCE · GRADE C

Grade C reflects direct animal evidence for biological activity, including adverse glucose effects. It does not establish fat loss efficacy. No human efficacy trial of sequence-defined native hGH 176-191 was identified.

Human data. The focused PubMed search did not identify a clinical efficacy, safety, or pharmacokinetic study administering sequence-defined native hGH 176-191 to humans. A study using material described as hGH fragment 176-191 examined nanoparticle formulations in cultured breast cancer cells and computational models (PMID 35783198). That is laboratory research, not a cancer treatment trial or human safety evidence. AOD9604 has a separate human development history. A 2026 review describes a 24-week obesity study with 534 participants, including 502 randomized, that failed its primary weight-loss endpoint (PMID 42395176). The review cites a published human safety analysis as well as sponsor-reported efficacy outcomes. Neither the negative efficacy programme nor its safety findings establishes the effects of native Frag.

Animal and mechanistic data. Native hGH 176-191 caused transient hyperglycaemia, increased insulin concentrations, and reduced insulin sensitivity in normal rats (PMID 645904). This is direct evidence relevant to safety, not evidence of useful fat loss. Related AOD9604 studies reported reduced weight gain and increased fat oxidation in obese mice, and preserved insulin sensitivity in obese Zucker rats (PMID 11673763, PMID 11146367). AOD9401 studies reported changes in adipose metabolism and reduced weight gain (PMID 11116208, PMID 10950816). These findings cannot be pooled as if they tested one molecule.

REGULATORY STATUS AND SPORT

STATUS

No approved medicinal product or regulatory dosing label for native hGH 176-191 was identified. The AOD9604 development programme and its compounding assessment concern a related, distinct substance. FDA currently lists AOD-9604 among bulk substances whose nominations were withdrawn, following previous Category 2 placement. FDA retains concerns about immunogenicity, impurities, characterization, and serious adverse events with uncertain causality. This is not equivalent to approval or a universal statement about compounding legality. A research-use label does not itself authorize sale for human treatment. Source: [FDA compounding safety assessment] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>).

WADA

Prohibited at all times, both in and out of competition, under S2.2.3, growth hormone, its analogues and fragments. WADA explicitly names both AOD-9604 and hGH 176-191. The prohibition does not depend on demonstrated fat loss or on a particular route. Source: [WADA Prohibited List] (<https://www.wada-ama.org/en/prohibited-list>).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

No clinically validated administration route for native hGH 176-191 was identified. Subcutaneous use appears in non-clinical accounts, but those accounts often leave chemical identity unresolved. Related-compound experiments used oral administration, intraperitoneal administration, and continuous delivery by osmotic pumps. The cited rabbit joint experiment used intra-articular AOD9604, not native Frag (PMID 26275694). Route-specific results do not establish equivalent exposure by another route.

HALF-LIFE

No reliable human elimination half-life for sequence-defined native hGH 176-191 was identified. The AOD9604 metabolism paper describes laboratory degradation and metabolites, not clinical pharmacokinetics of native Frag (PMID 25208511). Stability in a biological sample, disappearance in a laboratory incubation, and elimination from a living person are different measurements.

TIMING

No human trial establishes an advantage from fasting, morning administration, exercise timing, or separation from meals for native Frag. Experimental effects on fat metabolism do not demonstrate that a particular meal schedule improves clinical outcomes. The direct rat glucose findings also make a simple insulin-based timing rationale unreliable (PMID 645904).

CYCLE LENGTH

No validated treatment cycle, maintenance schedule, or washout interval for native Frag was identified. The 24-week human programme described in PMID 42395176 concerned oral AOD9604. It cannot establish a native Frag cycle. Eight to twelve weeks is commonly cited in non-clinical use; not validated in trials. Observation periods in animal experiments describe study design rather than a schedule for people.

TITRATION

No validated titration schedule or clinical target for native Frag was identified. IGF-1 is not an established response marker for this compound. A normal IGF-1 result would not establish efficacy or exclude glucose effects, immune reactions, or contamination.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Native hGH 176-191, approved human use	None established. No approved drug label was identified.	Not established	Not established	No regulatory label or validated clinical regimen for native hGH 176-191 was identified.
Native hGH 176-191, direct animal study	No transferable human dose established. The animal experiment is relevant to metabolic effects, not clinical dosing.	Administration route not established from the retrieved abstract	Acute experimental exposure	PMID 645904 reports experiments in normal rats. A complete dose-route specification was not available in the retrieved abstract. · PMID 645904
Related compound AOD9604, obese Zucker rats	500 mcg/kg orally once daily for 19 days, reported in PMID 11146367.	Oral	Once daily for 19 days	PMID 11146367. This animal regimen tested AOD9604 and is not a native Frag regimen or human dose. · PMID 11146367
Related compound AOD9604, rabbit osteoarthritis model	0.25 mg AOD9604 per treated knee, alone or with 6 mg hyaluronic acid, intra-articularly once weekly, reported in PMID 26275694.	Intra-articular, ultrasound guided	Weekly during weeks 4 through 7 after the initial collagenase injection	PMID 26275694. The treatment occurred during weeks 4 through 7, rather than lasting an interchangeable 4 to 7 weeks. It tested AOD9604. · PMID 26275694
Non-clinical reports using the ambiguous Frag name	250 to 500 mcg subcutaneously once daily, commonly cited in non-clinical use; not validated in trials.	Subcutaneous	Once daily in non-clinical accounts	Commonly cited in non-clinical use; not validated in trials. These accounts do not reliably distinguish native hGH 176-191 from AOD9604. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– AOD-9604

No combination benefit is established. Native Frag and AOD9604 differ chemically, but ambiguous labeling can also conceal duplicate exposure. Sequence identity determines which problem applies.

– Semaglutide

No controlled evidence establishes an added benefit from native Frag. Changes in appetite, weight, or glucose during combined exposure would not identify the fragment's contribution.

– Tirzepatide

No clinical interaction or combination trial with native Frag was identified. Additional exposure would introduce uncertainty without an established incremental fat loss benefit.

– Tesamorelin

A distinct hormonal mechanism does not establish synergy. Combined effects on glucose regulation and endocrine

– CJC-1295

measurements have not been characterized for native Frag.

No validated combination regimen exists. Growth hormone axis stimulation complicates interpretation of metabolic symptoms, and native Frag cannot be assumed metabolically neutral.

– Ipamorelin

No demonstrated synergy or clinical interaction dataset supports this pairing. Receptor selectivity of one component does not establish the tolerability of combined exposure.

– GHRP-6

Appetite and endocrine effects create additional variables without an established combination benefit. The original claim of a predictable opposing effect was too categorical.

– IGF-1 LR3

No human combination evidence supports this pairing. Additional IGF-related activity introduces metabolic and proliferative uncertainty, without evidence that native Frag offsets those risks.

SAFETY

COMMON EFFECTS

The frequency of adverse effects in humans receiving native hGH 176-191 is unknown. Direct rat findings include increased blood glucose and insulin, with reduced insulin sensitivity (PMID 645904). Injection-site pain, inflammation, and infection are route-related concerns, but their frequency cannot be quantified for this compound. The related AOD9604 programme included human safety reporting; those results cannot establish the tolerability of native Frag or uncharacterized preparations.

SERIOUS SIGNALS

Human risks remain inadequately characterized. The direct animal glucose findings undermine claims of assured metabolic neutrality. The absence of receptor-mediated proliferation in an AOD9604 cell assay cannot exclude cancer-related effects of native Frag. FDA identifies immunogenicity concerns and potentially associated serious adverse events for related AOD-9604, with causality unresolved. Incorrect identity, inaccurate content, endotoxin, and microbial contamination introduce separate risks that purity percentages alone cannot resolve.

CONTRAINDICATIONS

No approved label defines formal contraindications. Pregnancy, breastfeeding, childhood, active malignancy, and a history of serious peptide hypersensitivity are precautionary exclusions because relevant safety data are missing. Diabetes, impaired glucose regulation, and endocrine disease require particular clinical assessment given the rat findings. These are precautionary boundaries, not a validated contraindication list. Anti-doping restrictions are separate from medical contraindications.

STOP RULES

Breathing difficulty, facial or throat swelling, collapse, or rapidly spreading inflammation with fever warrant cessation of exposure and urgent medical assessment. New marked thirst, frequent urination, or unexplained weakness also warrants assessment for glucose disturbance. A changed reaction after a new lot may indicate a product problem, but symptoms cannot identify its cause. Lack of measurable benefit does not establish a reason to escalate exposure.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved standard vial presentation for native Frag. Container size and labeled mass are commercial attributes, not evidence of identity, potency, or sterility. A label using Frag, hGH 176-191, or AOD9604 does not resolve the sequence. Total powder mass may also include counterions, water, and excipients rather than only peptide.

SOLVENT

No validated clinical reconstitution solvent or multidose preparation specification for native Frag was identified. A preservative does not establish peptide stability, eliminate endotoxin, or sterilize

contaminated material. Compatibility depends on sequence, formulation, concentration, pH, and container conditions.

STORAGE

Dry-powder stability and solution stability require separate data. Temperature, light, pH, container, concentration, and handling can influence degradation. A clear solution does not prove chemical integrity or microbiological quality. A defensible storage period requires validated stability and contamination-control data for the actual formulation.

Concentration arithmetic can be explained without establishing an administration regimen.

Hypothetical laboratory example: 5 mg of verified peptide in a final solution volume of 2 mL equals 2.5 mg/mL, or 2500 mcg/mL. These numbers describe an illustrative concentration, not a studied dose, administration route, or frequency.

The denominator is final solution volume, which is not automatically identical to the volume of solvent added. The numerator must represent verified peptide content rather than total powder weight. A calculated concentration cannot establish identity, biological activity, sterility, or an appropriate exposure. Syringe markings represent volume on a specified device and do not measure peptide activity in IU. The original injection-volume examples have therefore been removed.

BUYING NOTES

Identity is the first analytical question. Native hGH 176-191, AOD9604, and AOD9401 have different sequences and cannot be treated as interchangeable solely because naming overlaps. Useful documentation identifies the exact sequence, chemical form, lot, test date, methods, and laboratory responsible.

Mass spectrometry supports identity assessment, while chromatographic purity describes the relative signal from detected components under a particular method. Neither measurement alone establishes peptide content per container, sterility, endotoxin control, or clinical suitability. Sequence confirmation may require more than a matching intact mass. A certificate should also be traceable to the tested lot and distinguish measured results from acceptance criteria. Independent testing reduces some uncertainty but cannot establish clinical efficacy.

COMMON MISTAKES

- Calling hGH 176-191 a fifteen amino acid peptide. The native fragment contains sixteen residues; hGH 177-191 contains fifteen.
- Treating native hGH 176-191, AOD9604, and AOD9401 as the same molecule. Different sequences require separate attribution of experimental findings.
- Assigning AOD9604's failed human obesity programme to native Frag. That programme concerns a related compound and cannot establish native Frag efficacy.
- Claiming the fragment cannot affect glucose. Direct native-fragment experiments reported hyperglycaemia and reduced insulin sensitivity in rats (PMID 645904).
- Converting a related compound's animal exposure into a human regimen. Species, sequence, route, formulation, and exposure all matter.
- Interpreting increased fat oxidation or reduced weight gain as proof of clinically meaningful fat loss in trained adults.
- Treating isolated human adipose tissue as a human clinical trial. The cited experiment used AOD9401 in laboratory tissue preparations (PMID 10950816).
- Assuming an abdominal administration site produces local fat reduction. No controlled human evidence establishes that effect for native Frag.
- Interpreting the AOD9604 rabbit joint experiment or the Frag cancer-cell formulation study as evidence of human treatment benefit.
- Treating a purity certificate, an unchanged appearance, or a normal IGF-1 result as proof of clinical suitability.
- Using laboratory degradation results to claim a human half-life, storage period, administration interval, or anti-doping clearance window.

REFERENCES

1. Ng FM et al. Hyperglycemic action of synthetic C-terminal fragments of human growth hormone.. *The American journal of physiology*, 1978. PMID 645904 DOI 10.1152/ajpendo.1978.234.5.E521 (Direct experiments including native hGH 176-191 in normal rats. Reports transient hyperglycaemia, increased insulin, and reduced insulin sensitivity. Does not establish human risk magnitude or fat loss efficacy.)
2. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Related-compound context: summarizes the AOD9604 human obesity programme, its unsuccessful primary endpoint, and published safety reporting. Its naming convention does not establish identity with native Frag, and current regulatory status requires the FDA source.)
3. Heffernan MA et al. Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment.. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 2001. PMID 11673763 DOI 10.1038/sj.ijo.0801740 (Related-compound context: AOD9604 mouse metabolism and laboratory growth hormone receptor assays. Does not establish receptor behavior or metabolic neutrality of native hGH 176-191 in humans.)
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5. Ng FM et al. Molecular and cellular actions of a structural domain of human growth hormone (AOD9401) on lipid metabolism in Zucker fatty rats.. *Journal of molecular endocrinology*, 2000. PMID 11116208 DOI 10.1677/jme.0.0250287 (Identifies AOD9401 as hGH 177-191 and reports adipose enzyme and rat metabolic findings. Retained to distinguish this fifteen-residue peptide from native Frag and AOD9604.)
6. Ng FM et al. Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone.. *Hormone research*, 2000. PMID 11146367 DOI 10.1159/000053183 (Related AOD9604 study: 500 mcg/kg orally once daily for 19 days in obese Zucker rats. Reports reduced weight gain and preserved insulin sensitivity, not a native Frag or human regimen.)
7. Heffernan MA et al. Effects of oral administration of a synthetic fragment of human growth hormone on lipid metabolism.. *American journal of physiology. Endocrinology and metabolism*, 2000. PMID 10950816 DOI 10.1152/ajpendo.2000.279.3.E501 (Related AOD9401 study in obese mice and isolated rodent and human adipose tissue. Supports attribution correction and the distinction between human tissue experiments and clinical trials.)
8. Cox HD et al. Detection and in vitro metabolism of AOD9604.. *Drug testing and analysis*, 2015. PMID 25208511 DOI 10.1002/dta.1715 (Defines AOD9604 as hGH 177-191 with an additional N-terminal tyrosine. Reports laboratory metabolism, not a human elimination half-life for native Frag.)
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10. Habibullah MM et al. Human Growth Hormone Fragment 176-191 Peptide Enhances the Toxicity of Doxorubicin-Loaded Chitosan Nanoparticles Against MCF-7 Breast Cancer Cells.. *Drug design, development and therapy*, 2022. PMID 35783198 DOI 10.2147/DDDT.S367586 (Computational and cultured-cell study using material described as hGH fragment 176-191 in a nanoparticle formulation. Does not establish human anticancer efficacy, fat loss, or safety.)

CJC-1295

Mod GRF 1-29 (no DAC), CJC-1295 DAC

GHRH analog

Module 2 · Recomposition

Goals: Hypertrophy, Recovery, Sleep

Route: SC

WADA prohibited

An albumin-binding GHRH analog that prolonged GH and IGF-1 elevation in small human studies. Muscle gain, recovery and sleep benefits remain unproven.

WHAT IT IS

CJC-1295 is a synthetic analog of the first 29 amino acids of human growth hormone releasing hormone, abbreviated GHRH. The studied molecule has four amino acid substitutions and an additional modified lysine at its C terminus. Its reactive maleimide group permits covalent attachment to circulating albumin, extending exposure after administration (PMID 15817669).

The name requires qualification. CJC-1295 in the pivotal clinical papers refers to the albumin-binding molecule, commonly distinguished as CJC-1295 DAC, meaning drug affinity complex. Modified GRF 1-29, often called CJC-1295 no DAC, lacks the albumin-binding extension. These are distinct active molecules, not interchangeable formulations. Salt identity is a separate issue: an acetate designation does not establish whether DAC is present.

The human half-life and sustained hormone responses described here belong to the DAC molecule. They do not establish the pharmacokinetics, efficacy or appropriate administration schedule of modified GRF 1-29. No human pharmacokinetic study establishing a half-life for the no DAC variant was identified in this verification.

Module 2. Commonly proposed goals include hypertrophy, body recomposition, recovery and sleep. These are proposed applications, not demonstrated clinical outcomes. The documented human research route is subcutaneous administration. There is no approved CJC-1295 regimen for these goals.

MECHANISM

CJC-1295 stimulates the GHRH receptor on pituitary somatotrophs, the cells that produce growth hormone. GHRH receptor signaling increases intracellular cAMP and supports GH synthesis and secretion. This mechanism depends on functioning pituitary tissue and available secretory capacity. A response in healthy volunteers does not establish treatment efficacy in someone with structural pituitary disease.

The defining modification concerns duration of exposure. The maleimide-bearing terminal extension can react with the free thiol at cysteine 34 of albumin. Albumin attachment changes the peptide's stability and disposition. The foundational study demonstrated receptor activity in cultured rat pituitary cells and enhanced resistance of albumin conjugates to dipeptidylpeptidase IV. CJC-1295 remained detectable in rat plasma beyond 72 hours. Albumin-associated immunoreactivity was demonstrated separately by Western blot, including persistence beyond 24 hours (PMID 15817669).

In healthy adults, the estimated terminal half-life was 5.8 to 8.1 days. After single subcutaneous administrations, mean GH concentrations increased 2 to 10 fold for at least six days. Mean IGF-1 increased 1.5 to 3 fold for 9 to 11 days. These are study-level ranges, not expected responses for every individual or every amount administered (PMID 16352683).

A separate study measured overnight GH secretion before administration and one week afterward. Pulse frequency and magnitude were unchanged, while trough GH increased approximately 7.5 fold. Mean GH and IGF-1 also increased. However, the investigators found no correlation between IGF-1 increases and the measured GH secretion parameters. Their suggestion that elevated trough GH contributed to IGF-1 production was an interpretation, not a demonstrated causal relationship (PMID 17018654).

GH stimulates hepatic and peripheral IGF-1 production and influences lipid and glucose metabolism. These pathways provide a biological rationale for body composition claims. They do not demonstrate added muscle,

improved training performance or faster tissue healing with CJC-1295.

Sleep requires separate evidence. A GHRH antagonist experiment suppressed the GH response to a challenge while leaving measured slow-wave sleep unchanged. This study did not administer CJC-1295 and cannot establish whether CJC-1295 improves or worsens sleep. It does show why GH secretion and sleep quality cannot be treated as interchangeable outcomes (PMID 15538933).

EVIDENCE · GRADE B

Grade B applies to the short-term GH and IGF-1 response in small human studies. Although the pivotal publication contains two randomized trials, their limited duration and biomarker endpoints fit the scale's small-trial category. This grade does not establish therapeutic benefit or long-term safety.

Direct evidence for hypertrophy, athletic recovery and improved sleep remains insufficient. For these specific applications, the rationale is predominantly mechanistic, grade D. Growth restoration in genetically deficient mice is animal evidence, grade C, for that experimental setting. It is not evidence of enhancement in healthy adults.

A 2026 scoping review included CJC-1295 among six emerging compounds. Across the review, 67 percent of publications used animal models. That percentage describes the pooled literature, not CJC-1295 alone. The authors found that claimed musculoskeletal benefits remained unsupported by adequate human trials (PMID 42578445). A separate narrative review described GH-axis secretagogues as investigational for sports medicine, with uncertain safety and product quality concerns (PMID 42160466).

Human data. The pivotal publication reported two randomized, double-blind, placebo-controlled trials lasting 28 and 49 days. Participants were healthy adults aged 21 to 61. Outcomes centered on pharmacokinetics, GH, IGF-1 and short-term tolerability. No serious adverse reactions were reported in those trials, which does not exclude uncommon or delayed harm (PMID 16352683). An additional study examined overnight GH pulsatility in healthy men aged 20 to 40. Measurements occurred before administration and one week afterward (PMID 17018654). A subsequent serum proteomics analysis evaluated samples from 11 healthy men and identified changes in several protein spots. This was exploratory biomarker research, not evidence of muscle growth or recovery (PMID 19386527). These publications do not establish improvements in strength, injury healing, body composition or sleep. Participants were described as healthy; their training status should not be assumed. Trial duration also differs from duration of repeated exposure. Describing the published studies as seven weeks of continuous treatment would be inaccurate. The published papers do not represent every human exposure during development; FDA also reviewed reports of a longer, unpublished trial.

Animal and mechanistic data. The foundational pharmacology experiment used normal male Sprague Dawley rats, not GH-deficient animals. CJC-1295 produced approximately four times the GH area under the curve over two hours compared with unmodified hGRF(1-29). It also showed prolonged plasma persistence (PMID 15817669). A separate study treated neonatal GHRH-knockout mice for five weeks. Daily treatment normalized body weight and length, while longer intervals produced incomplete growth normalization. Relative lean mass and subcutaneous fat mass were normal in all treated groups. Increased pituitary RNA, GH mRNA and immunohistochemical findings supported somatotroph proliferation (PMID 16822960). The rat study establishes pharmacological activity in normal animals. The mouse study establishes growth restoration in a specific deficiency model. Neither demonstrates improved training adaptation, tendon healing or sleep in healthy humans.

REGULATORY STATUS AND SPORT

STATUS

CJC-1295 is not an FDA-approved drug. FDA's evaluation identifies distinct DAC and non-DAC substances and notes the absence of an applicable USP or NF drug substance monograph. Review for possible use in compounding is not marketing approval. A nomination, committee discussion or research designation does not establish that a particular human-use preparation is lawful. [FDA CJC-1295 evaluation](<https://www.fda.gov/media/183819/download>). The sports medicine review describes investigational use and quality concerns; its conclusions are indication-specific and cannot establish worldwide legal status (PMID 42160466). An analytical paper identified a 29-amino-acid, C-terminally amidated peptide in an unknown preparation. Its sequence

matched material marketed as CJC-1295. This illustrates naming ambiguity and unregulated supply, but does not establish that the seized material was the albumin-binding clinical molecule (PMID 21204297).

WADA

Prohibited at all times, both in competition and out of competition. The 2026 WADA Prohibited List explicitly names CJC-1295 under S2.2.4, growth hormone releasing factors, within the GHRH analog category. The prohibition does not depend on demonstrated performance improvement, a research-use label or a particular administration schedule. [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). The older analytical paper also identifies CJC-1295 as prohibited under S2 (PMID 21204297). That historical statement is consistent with the current list. Neither plasma half-life nor albumin binding establishes an individual testing outcome. No detection window or assurance about whether a test will identify exposure is provided.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Subcutaneous administration was used in the verified human clinical studies of the DAC molecule (PMID 16352683, PMID 17018654). The foundational rat study also used subcutaneous administration (PMID 15817669). In the knockout-mouse experiment, administration was subcutaneous during the first treatment week and intraperitoneal during treatment weeks two through five (PMID 16822960). No human comparison establishing an advantage for intramuscular administration was identified. No validated oral, intranasal or transdermal formulation with equivalent exposure was identified. Poor absorption is a formulation problem; it should not be converted into a universal claim that alternative delivery is physically impossible. Route alone also does not establish equivalence between different chemical variants or preparations.

HALF-LIFE

The estimated terminal half-life was 5.8 to 8.1 days for the DAC molecule in healthy adults (PMID 16352683). This is an elimination estimate, not a guarantee of constant concentrations or a recommended interval between administrations. Concentrations can rise after administration, decline between administrations and accumulate with repeated exposure. The same publication reported sustained GH and IGF-1 elevations, with mean IGF-1 remaining above baseline for up to 28 days in the multiple-dose study. This should not be rewritten as a universal 28-day elevation after the final administration. The published abstract does not establish that interpretation. Drug elimination, hormone normalization and recovery from an adverse effect are separate processes. No human half-life for modified GRF 1-29 was verified. Removing the albumin-binding extension prevents transfer of the DAC pharmacokinetic estimate. An exact duration in minutes or hours would require separate evidence for that molecule and formulation.

TIMING

No comparative human trial identified here established an advantage for bedtime administration, fasting or separation from carbohydrate intake. The long DAC half-life reduces the plausibility of treating clock time as the main determinant of overall exposure. It does not make plasma concentrations flat or eliminate acute endocrine responses (PMID 16352683). GH secretion still varies with physiological context, including sleep and metabolic signals. Mechanistic observations about short-acting secretagogues cannot supply a validated timing protocol for CJC-1295. The same limitation applies to the no DAC molecule: a shorter presumed duration does not establish that a particular meal or bedtime schedule improves outcomes.

CYCLE LENGTH

No validated cycle or recovery interval exists. The pivotal published studies lasted 28 and 49 days, with single or limited repeated administrations. These durations should not be interpreted as continuous exposure throughout each study (PMID 16352683). FDA also reviewed reports of a longer, unpublished development trial, so seven weeks is not an accurate upper bound for all human exposure. Published long-term efficacy and safety data remain inadequate. Non-clinical courses of 8 to 12 weeks with a similar break are commonly cited in non-clinical use; not validated in trials. A calendar break does not demonstrate that drug exposure or hormone concentrations have normalized. Conversely, the reported IGF-1 findings do not establish that everyone requires a month to return to baseline. Neither a fixed washout period nor repeated cycling has been validated as a way to prevent adverse effects.

TITRATION

No validated individual titration algorithm exists for CJC-1295. The absence of a significant difference between single subcutaneous doses of 60 and 90 mcg/kg in PMID 17018654 does not establish an optimal dose. Small samples can fail to detect meaningful differences. IGF-1 was a pharmacodynamic endpoint in the clinical studies, not a validated target for fitness-oriented dose adjustment. An age-referenced IGF-1 result can help a clinician assess exposure, but it cannot quantify every relevant risk. Baseline and follow-up glucose measures may support metabolic assessment. Normal laboratory values do not establish long-term tolerability, product quality or freedom from cardiovascular reactions. No evidence-based monitoring schedule for unsupervised use was identified.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Selected dose levels explicitly discussed in the pivotal healthy-adult clinical report, DAC molecule.	30 or 60 mcg/kg per single subcutaneous administration, study-reported levels in PMID 16352683. These were selected levels within a broader ascending-dose investigation.	Subcutaneous.	Single administration in the single-dose study.	Human randomized trial, PMID 16352683. The abstract specifically discusses these levels when describing tolerability. They are not an established effective range for hypertrophy, recovery or sleep. · PMID 16352683
Repeated-administration component of the pivotal clinical program, DAC molecule.	The numeric dose allocation across repeated-administration groups is not enumerated in the fetched PubMed abstract. It cannot be described as the same ascending doses without verification.	Subcutaneous.	Two or three administrations at weekly or every-two-week intervals, depending on the study group.	Human randomized trial, PMID 16352683. The verified abstract establishes the route, number of administrations, intervals and cumulative hormone response. · PMID 16352683
Overnight GH pulsatility study in healthy men, DAC molecule.	60 or 90 mcg/kg as a single subcutaneous administration, study-reported doses in PMID 17018654.	Subcutaneous.	Single administration, with repeat overnight sampling one week later.	Human clinical study, PMID 17018654. No statistically significant difference between these small dose groups was observed. That finding does not establish equivalence, receptor saturation or a dose-response plateau. · PMID 17018654
Neonatal GHRH-knockout mice treated for five weeks, growth restoration model.	2 mcg per mouse per administration, every 24, 48 or 72 hours, study-reported dose in PMID 16822960. Administration was subcutaneous initially and subsequently intraperitoneal.	Subcutaneous during treatment week one; intraperitoneal during treatment weeks two through five.	Every 24, 48 or 72 hours, in separate experimental groups.	Animal study, PMID 16822960. The dose is per animal, not per kg. The mixed route schedule is described in FDA's review of the study. These amounts cannot be converted directly into a human regimen. · PMID 16822960
Unvalidated non-clinical reporting for the DAC molecule.	1000 to 2000 mcg total per week by subcutaneous administration, reported once weekly or divided between two weekly administrations; commonly cited in non-clinical use; not validated in trials.	Subcutaneous, as described in non-clinical reporting.	Once or twice weekly, with the stated amount representing the weekly total.	commonly cited in non-clinical use; not validated in trials. This is a description of circulating practice, not a verified prevalence estimate or an efficacy-supported schedule. Trial results cannot be assumed at these exposures. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.
Unvalidated non-clinical reporting for modified GRF 1-29, also called no DAC.	100 mcg per subcutaneous administration, one to three times daily; commonly cited in non-clinical use; not validated in trials.	Subcutaneous, as described in non-clinical reporting.	One to three times daily.	commonly cited in non-clinical use; not validated in trials. The DAC clinical papers do not validate this separate molecule, its half-life or this schedule. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ Ipamorelin

Proposed receptor complementarity: ipamorelin acts through the ghrelin receptor, while CJC-1295 targets the GHRH receptor. This provides a mechanistic hypothesis, not evidence that the specific pair improves recovery or hypertrophy. No verified combination trial established those outcomes.

+ GHRP-2

A second proposed GHRH-plus-ghrelin-receptor combination. Different receptors do not establish a favorable benefit-risk balance. Additional GH stimulation and other endocrine effects are plausible concerns. No verified study supports choosing this pair for a larger pulse, and no comparative outcome evidence establishes superiority over another combination.

+ BPC-157

The recovery rationale combines systemic GH-axis stimulation with separate preclinical tissue-repair hypotheses. Complementary narratives do not demonstrate additive healing. No verified human study tested this pair. The scoping review's overall conclusion was that musculoskeletal claims for these emerging compounds remain unsupported by adequate human trials (PMID 42578445).

+ Semaglutide

The proposed goal is preservation of lean tissue during weight loss. No verified trial establishes that CJC-1295 achieves this when combined with semaglutide. GH-axis stimulation can raise metabolic concerns, but opposing physiological effects cannot predict the pair's net glucose response. There is no evidence that one compound reliably offsets adverse effects from the other.

– Sermorelin

Both target the GHRH receptor. Combining them duplicates a pharmacological pathway without verified additional clinical benefit. The available evidence does not establish continuous receptor saturation from CJC-1295, so redundancy should not be explained through an assumed occupied receptor at every moment. Added exposure and uncertain tolerability remain the relevant concerns.

– Tesamorelin

Another GHRH analog adds overlapping stimulation. Its evidence for a specific clinical indication cannot be transferred to a CJC-1295 combination or to athletic enhancement. No verified combination trial establishes added benefit, appropriate exposure or long-term tolerability.

– IGF-1 LR3

This would add direct IGF-receptor activity downstream of GH release. The specific combination lacks verified human efficacy and safety data. Concern centers on additional, poorly characterized signaling and possible metabolic effects.

SAFETY

COMMON EFFECTS

Reported human effects include injection-site redness, tenderness, itching or swelling, flushing, headache and gastrointestinal symptoms. Increased heart rate was also reported in the pulsatility study. Frequency and severity varied across study groups (PMID 16352683, PMID 17018654). Fluid retention, joint discomfort, nerve-compression symptoms and reduced insulin sensitivity are GH-axis concerns. Their incidence with CJC-1295 is not established by these small studies. They should not all be presented as commonly observed CJC-1295 effects. Appetite changes were not established as a consistent finding in the verified clinical abstracts. Long exposure may prolong

some problems, but neither symptom duration nor resolution can be predicted solely from plasma half-life.

SERIOUS SIGNALS

FDA identifies serious adverse events associated with CJC-1295, including increased heart rate and systemic vasodilatory reactions. It also flags possible immunogenicity and difficulties characterizing peptide impurities. The published trials' absence of serious reactions does not negate these broader concerns. [FDA peptide safety information] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>). FDA's development review describes reports of an unpublished trial stopped after a participant died following an acute myocardial infarction. Temporal association does not establish that CJC-1295 caused the event. The incomplete record cannot quantify causality or risk. [FDA CJC-1295 evaluation] (<https://www.fda.gov/media/183819/download>). Elevated IGF-1 and impaired glucose regulation are additional concerns, not the only signals that matter. Pituitary growth findings in deficient mice require caution but do not establish human tumor formation (PMID 16822960). Long-term malignancy risk remains unresolved. Risks pooled across different secretagogues in reviews should not be attributed automatically to CJC-1295 (PMID 42578445).

CONTRAINDICATIONS

There is no approved CJC-1295 label establishing formal contraindications. Relevant exclusion concerns arise from GH-axis pharmacology, limited clinical evidence and unknown reproductive safety. Active malignancy, an unexplained mass, pregnancy, breastfeeding, childhood and acute critical illness are major concerns. A prior malignancy requires individualized assessment; every remote cancer history should not be presented as an established permanent CJC-1295 contraindication. Pituitary tumors, previous pituitary surgery or radiation, diabetes, impaired glucose tolerance and proliferative retinopathy require specialist assessment. Existing edema or carpal tunnel symptoms may worsen with GH-axis stimulation. Cardiovascular disease, unexplained palpitations, hypotensive episodes and previous serious hypersensitivity reactions also matter. These distinctions separate formal labeled contraindications from precautionary exclusions for an investigational compound.

STOP RULES

Chest pain, fainting, breathing difficulty, severe palpitations, facial or throat swelling, or severe headache with visual disturbance warrant urgent medical evaluation and no further exposure. Persistent edema, worsening hand numbness, limiting joint pain or new glucose abnormalities warrant prompt clinical review. An IGF-1 result above the age-referenced range is a reason to reassess exposure, not a validated signal for a particular dose reduction. Abnormal glucose or HbA1c also requires evaluation. Urgent symptoms should not wait for repeat laboratory confirmation. Baseline results help identify change, but an abnormal follow-up result remains interpretable against clinical context and reference ranges without a baseline. No monitoring checklist makes an unapproved regimen validated. The long half-life means stopping exposure does not immediately remove the compound or guarantee prompt symptom resolution.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

Nominal vial contents of 2 mg or 5 mg are commonly cited in non-clinical use; not validated in trials. These are packaging amounts, not clinical doses or approved presentations. A printed mass does not establish actual peptide content, exact molecular identity or suitability for administration. DAC status and salt form require separate identification. A label saying CJC-1295 acetate cannot, by itself, resolve whether the albumin-binding extension is present. The analytical report on an unknown preparation illustrates the ambiguity around the CJC-1295 name (PMID 21204297). It does not quantify how frequently labels are incorrect.

SOLVENT

No approved CJC-1295 reconstitution instructions establish a universal diluent, concentration or multidose procedure. Bacteriostatic water is commonly mentioned in non-clinical descriptions, but that does not establish compatibility with every CJC-1295 preparation. A preservative does not sterilize contaminated powder or neutralize endotoxin. Solvent choice depends on the exact formulation, pH, excipients, container and validated stability data. Sterile water also does not make a preparation suitable for single-use administration merely because it lacks preservative. Peptide aggregation can depend on formulation and mechanical stress. It is not established that any shaking necessarily denatures this peptide. Clear appearance likewise cannot confirm identity, potency, sterility or absence of soluble degradation products.

STORAGE

No formulation-specific stability study was verified that supports a universal refrigerated shelf life for reconstituted CJC-1295. Storage requirements for dry material cannot automatically be applied to a prepared solution. DAC and non-DAC materials, different salts, solvents and containers may behave differently. Claims of three to four weeks after preparation are commonly cited in non-clinical use; not validated in trials. A preservative's presence does not establish peptide potency throughout that period. Chemical stability, aggregation, sterility and container integrity are separate quality questions. Temperature limits and permitted freeze-thaw cycles require data for the actual

formulation. Visible cloudiness, particles, discoloration or loss of container integrity indicate a quality problem. Normal appearance cannot establish that a preparation remains suitable for administration.

Concentration arithmetic only, using hypothetical laboratory quantities. A nominal 2 mg sample in a final solution volume of 2 mL corresponds to 2000 mcg divided by 2 mL, or 1000 mcg/mL. The nominal sample size is commonly cited in non-clinical use; not validated in trials. The chosen final volume is illustrative, not a verified formulation instruction.

At that assumed concentration, a 0.1 mL analytical aliquot contains 100 mcg. These are sample quantities for arithmetic, not an administration dose. No route or frequency applies to this example. A different final volume changes concentration without changing the total nominal mass. For the same hypothetical 2 mg sample in a final volume of 1 mL, concentration would be 2000 mcg/mL.

The calculation assumes the stated peptide mass is correct, dissolution is complete and the final volume is known. Volume of diluent added and final solution volume are not conceptually identical. Counterions, residual water and an inaccurate content claim can also undermine the calculation.

Mass, concentration and volume are different quantities. Device markings are not peptide activity units, and IU should not replace mcg for CJC-1295. Arithmetic does not establish molecular identity, clinical dose, solvent compatibility, sterility or stability. The published human study amounts remain separately documented under reported_doses, with their routes and frequencies (PMID 16352683).

BUYING NOTES

The central documentation problem is exact identity. The name CJC-1295 has been applied to related but distinct molecules. The expected sequence, terminal modification and salt form therefore matter more than an abbreviated label. A mass spectrometry result can support identity, but molecular mass alone may not resolve every sequence, stereochemical or impurity question. The analytical paper used high-resolution tandem mass spectrometry to characterize an unknown preparation, illustrating the value of structural analysis rather than a name alone (PMID 21204297).

A useful certificate links results to a specific batch and states the laboratory, methods, dates and reference standards. Identity testing and purity testing answer different questions. An HPLC purity percentage describes the measured chromatographic profile under a particular method. It does not independently establish the correct molecule, absolute peptide content or freedom from contaminants outside that method's detection scope.

Net peptide content is another separate measurement. Counterions and residual water can contribute to dry material mass. A high chromatographic purity result therefore does not prove that nominal vial mass equals active peptide mass. Quantitative content testing needs an appropriate analytical method and reference material.

For material intended for parenteral administration, relevant quality attributes also include sterility, bacterial endotoxins, particulates, residual solvents and aggregation. A certificate containing identity and purity alone does not address all of these. Independent laboratory involvement adds traceability only when the report can be authenticated and linked to the tested batch. A laboratory name or logo is not sufficient evidence by itself.

A certificate for a raw powder does not automatically describe the final filled preparation. Subsequent processing, packaging and storage can introduce additional uncertainty. The sports medicine review identifies product quality as a recurring concern for investigational injectable peptides (PMID 42160466). Documentation can reduce specific uncertainties, but it cannot establish clinical efficacy, regulatory approval or a validated human-use regimen.

COMMON MISTAKES

- Treating DAC, no DAC and acetate as interchangeable labels. DAC describes a structural extension; acetate describes a salt form. Neither term substitutes for complete molecular identification.
- Applying the DAC half-life to modified GRF 1-29. The verified human pharmacokinetic findings belong to the albumin-binding molecule, not every preparation called CJC-1295.

- Assuming a long half-life means flat concentrations. Prolonged exposure still permits peaks, troughs, acute hormone responses and accumulation with repeated administration.
- Interpreting no significant difference between small dose groups as proof of a plateau. Statistical non-significance does not establish equivalence, saturation or an optimal amount.
- Treating higher GH or IGF-1 as demonstrated muscle gain. The clinical papers measured biomarkers, not training adaptation, strength or accelerated injury recovery.
- Calling the published study durations continuous treatment periods or the complete human exposure record. Limited repeated administrations and an unpublished development trial require separate descriptions.
- Assuming a fixed break resets the axis. The verified findings do not establish an individual normalization time or a validated cycle-and-washout strategy.
- Treating theoretical receptor complementarity as demonstrated combination efficacy. Different mechanisms do not establish better outcomes or predictable combined adverse effects.
- Using the GHRH antagonist sleep experiment as a CJC-1295 sleep trial. It tested a different intervention and cannot establish this compound's effect on sleep quality.
- Equating clear solution, high HPLC purity or preservative content with an acceptable injectable preparation. Identity, content, sterility, endotoxin and stability require separate evidence.

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the International IGF Research Society, 2009. PMID 19386527 DOI 10.1016/j.ghir.2009.03.001 (Exploratory serum proteomics analysis in 11 healthy men before and one week after CJC-1295 administration.)

Ipamorelin

Selective ghrelin receptor agonist (GHRP)

Module 2 · Recomposition

Goals: Hypertrophy, Recovery, Sleep

Route: SC

WADA prohibited

A ghrelin receptor agonist with documented short-term GH release in humans, animal evidence of endocrine selectivity, and no established benefit for muscle, recovery or sleep.

WHAT IT IS

A synthetic pentapeptide with the sequence Aib-His-D-2-Nal-D-Phe-Lys-NH₂, also identified as NNC 26-0161 (PMID 9849822, PMID 9879640). It belongs to the growth hormone secretagogue family and acts through the ghrelin receptor pathway rather than the GHRH receptor. Its original distinguishing feature was preferential GH release in animal experiments. In swine, ipamorelin did not increase ACTH or cortisol significantly beyond responses to GHRH. GHRP-2 and GHRP-6 did increase those hormones. None of the tested secretagogues increased prolactin, FSH, LH or TSH in that experiment (PMID 9849822). Consequently, that study does not establish a unique prolactin advantage over those comparators. Its placement under Hypertrophy, Recovery and Sleep describes proposed applications, not demonstrated human outcomes.

MECHANISM

Receptor pharmacology. Ipamorelin activates the growth hormone secretagogue receptor pathway, conventionally described as GHS-R1a agonism. The original experiments demonstrated GH release from rat pituitary cells. GHRP antagonists blocked the response, whereas a GHRH antagonist did not. The reported cellular EC₅₀ was 1.3 nmol/L, with maximal activity approximately 85 percent of the GHRP-6 response (PMID 9849822). These results establish secretagogue activity through a receptor pathway distinct from GHRH. They do not directly map every intracellular signaling step in humans.

Human hormone response. In healthy men, a single intravenous infusion over 15 minutes produced one measured GH episode, peaking approximately 0.67 hours after infusion began. GH then declined toward negligible concentrations. The pharmacodynamic model estimated half-maximal stimulation at an ipamorelin plasma concentration of 214 nmol/L (PMID 10496658). This describes an acute experimental response. It does not establish the response to repeated subcutaneous exposure, bedtime administration or prolonged combinations.

Downstream rationale. GH signaling can influence IGF-1, substrate metabolism and tissue growth. However, a GH pulse is a surrogate measurement, not evidence of increased strength or accelerated recovery. Rat studies found longitudinal bone growth without a measurable increase in total circulating IGF-I (PMID 10373343). A glucocorticoid-treated rat model found improved muscle tension and bone formation with ipamorelin (PMID 11735244). These findings support biological activity but cannot determine outcomes in healthy adults who train.

Competing metabolic effects. In mice, ipamorelin increased adiposity through mechanisms that did not require normal GH production. Increased food intake and leptin accompanied some responses (PMID 11162489). Therefore, GH release does not establish a net fat-loss effect. Endocrine selectivity in swine also does not exclude appetite changes, metabolic disturbances or adverse effects after longer human exposure.

EVIDENCE · GRADE C

Grade C applies to hypertrophy, bone and recovery claims because the relevant direct evidence is preclinical. Sleep claims remain grade D, with no direct ipamorelin sleep trial identified. Acute GH release has small human pharmacology studies consistent with grade B evidence for that specific physiological effect. The postoperative ileus trial did not demonstrate a statistically significant clinical benefit (PMID 25331030). A 2026 scoping review found predominantly animal evidence across several peptides, including ipamorelin. Its aggregate findings must not be presented as ipamorelin-specific human results (PMID 42578445).

Human data. A pharmacokinetic study used single intravenous infusions over 15 minutes at five dose levels, 4.21 to 140.45 nmol/kg, approximately 3 to 100 mcg/kg, with eight healthy men per level (PMID 10496658). It reported dose-proportional pharmacokinetics, a terminal half-life near 2 hours and an acute GH peak near 40 minutes. In a phase 2 randomized trial, 117 bowel-resection patients enrolled and 114 entered the safety and modified intention-to-treat populations. Ipamorelin was administered at 0.03 mg/kg intravenously twice daily, from postoperative day 1 through day 7 or discharge (PMID 25331030). Any treatment-emergent adverse event occurred in 87.5 percent of the ipamorelin group and 94.8 percent of placebo recipients. Median time to a tolerated meal was 25.3 versus 32.6 hours, respectively, with $p = 0.15$. Neither the key nor secondary efficacy analyses showed significant differences. A separate analytical study included nasal ipamorelin administration to one volunteer, correcting the claim that every published human exposure was intravenous (PMID 25869809). No controlled human evidence for ipamorelin-induced muscle gain, strength, recovery or improved sleep was identified. Human sleep findings with GHRP-6 concern a different compound and cannot establish ipamorelin efficacy (PMID 7617137).

Animal and mechanistic data. Adult female rats received 18, 90 or 450 mcg per rat per day subcutaneously, divided into three daily injections for 15 days (PMID 10373343). Longitudinal bone growth increased dose-dependently, without a change in total IGF-I. In glucocorticoid-treated female rats, ipamorelin 100 mcg/kg subcutaneously three times daily for 3 months improved maximum calf-muscle tetanic tension and periosteal bone formation relative to glucocorticoid alone (PMID 11735244). This model does not reproduce resistance training in healthy humans. Another study administered 0.5 mg/kg/day continuously through subcutaneous osmotic minipumps for 12 weeks in female rats (PMID 10828840). Bone mineral content increased primarily through larger bone dimensions, while volumetric mineral density remained unchanged. In GH-intact and GH-deficient mice, repeated subcutaneous ipamorelin increased relative fat-pad weight. Food intake and leptin also increased in GH-intact mice (PMID 11162489). These experiments demonstrate context-dependent growth and metabolic effects, not a reliable recomposition outcome.

REGULATORY STATUS AND SPORT

STATUS

No FDA-approved ipamorelin drug or approved dosing label was identified. FDA currently lists ipamorelin acetate in Category 2 under its 503B interim compounding policy, with a September 29, 2023 listing date. It also appears in FDA's safety-risk table for substances whose 503A nominations were withdrawn. Compounding eligibility and drug approval are separate questions. The evidence reviewed does not justify a definitive statement about every country's law or every possible supply arrangement. Source: [FDA compounding safety-risk information] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>).

WADA

Prohibited at all times, both in and out of competition. The 2026 WADA Prohibited List explicitly names ipamorelin under S2.2.4, growth hormone releasing factors, within growth hormone secretagogues and their mimetics. Pharmacokinetic half-life does not alter prohibited status. Source: [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

The principal human pharmacology and postoperative ileus studies used intravenous infusions (PMID 10496658, PMID 25331030). A human analytical study also documented nasal administration, with one volunteer receiving ipamorelin (PMID 25869809). This was not a therapeutic efficacy trial. Subcutaneous injections and continuous subcutaneous infusion appear in animal research (PMID 10373343, PMID 10828840). Rat nasal bioavailability was approximately 20 percent, which cannot be assigned to humans (PMID 9879640). No validated human subcutaneous pharmacokinetic profile was identified. Different routes cannot be treated as interchangeable on the basis of an equal nominal amount.

HALF-LIFE

Approximately 2 hours terminal elimination half-life after intravenous infusion in healthy men. Reported clearance was 0.078 L/h/kg and steady-state distribution volume was 0.22 L/kg (PMID 10496658). The GH response peaked around 0.67 hours after infusion began. Drug elimination and the hormone-response time course describe different processes. These measurements do not establish a subcutaneous half-life, repeated-dose exposure or duration of clinical benefit.

TIMING

The acute intravenous study recorded the GH peak approximately 0.67 hours after infusion began (PMID 10496658). It did not compare bedtime, waking, fasting or post-training schedules. Claims

that meal spacing or bedtime administration improve ipamorelin outcomes are commonly cited in non-clinical use; not validated in trials. General hormone physiology cannot establish an effective schedule for muscle gain, recovery or sleep.

CYCLE LENGTH

The cited postoperative trial administered treatment for up to 7 days or until discharge (PMID 25331030). This defines that trial's exposure, not a supported duration for performance-related use. Animal studies lasted 15 days, 12 weeks or 3 months, depending on the model (PMID 10373343, PMID 10828840, PMID 11735244). Those durations cannot validate human cycles. Online descriptions of 8 to 12 week blocks and subsequent breaks are commonly cited in non-clinical use; not validated in trials. No evidence establishes that cycling prevents metabolic effects, desensitization or other harm.

TITRATION

The acute human study compared assigned dose levels across groups; it did not validate a home titration schedule (PMID 10496658). No evidence-based subcutaneous escalation or maintenance algorithm was identified. A larger measured GH response does not identify an optimal clinical dose. Symptoms, body weight and isolated IGF-1 measurements also do not establish product identity, effective exposure or a validated adjustment rule.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Healthy male volunteers, acute pharmacokinetic and pharmacodynamic study	4.21, 14.02, 42.13, 84.27 or 140.45 nmol/kg, approximately 3, 10, 30, 60 or 100 mcg/kg (study, PMID 10496658)	Intravenous infusion over 15 minutes	Single infusion at the assigned dose level	Gobburu JV, 1999, Pharmaceutical research. Eight participants were studied at each dose level. These experimental intravenous doses do not establish a subcutaneous regimen. · PMID 10496658
Adults following bowel resection, phase 2 randomized placebo-controlled trial	0.03 mg/kg, equivalent to 30 mcg/kg, per infusion (study, PMID 25331030)	Intravenous infusion	Twice daily, postoperative day 1 through day 7 or hospital discharge	Beck DE, 2014, International journal of colorectal disease. The trial did not demonstrate significant differences in its key or secondary efficacy analyses. · PMID 25331030
Adult female rats, longitudinal bone growth	18, 90 or 450 mcg per rat per day, total daily amount (study, PMID 10373343)	Subcutaneous injection	Daily amount divided into three injections for 15 days	Johansen PB, 1999, Growth hormone & IGF research. Animal exposure only. The listed amounts are daily totals, not amounts per injection. · PMID 10373343
Female rats receiving glucocorticoid treatment, muscle tension and bone formation	100 mcg/kg per injection, totaling 300 mcg/kg/day (study, PMID 11735244)	Subcutaneous injection	Three times daily for 3 months	Andersen NB, 2001, Growth hormone & IGF research. Outcomes were measured in a glucocorticoid-treated animal model. · PMID 11735244
Young adult female rats, bone mineral content and dimensions	0.5 mg/kg/day (study, PMID 10828840)	Continuous subcutaneous delivery through osmotic minipumps	Continuous delivery for 12 weeks	Svensson J, 2000, The Journal of endocrinology. Greater bone mineral content reflected increased bone dimensions rather than greater volumetric mineral density. · PMID 10828840
Reported non-clinical self-administration patterns	100 to 300 mcg per administration, commonly cited in non-clinical use; not validated in trials	Subcutaneous administration, as described in non-clinical accounts	One to three times daily, commonly cited in non-clinical use; not validated in trials	An unvalidated usage claim, not an approved label or a study-derived dose. No primary trial validating this range, frequency or route was identified.

	+ CJC-1295 A GHRH analogue acts through a different receptor pathway, creating a plausible class-level rationale for amplified GH release. Direct human outcome evidence for this pair was not identified. Longer GHRH-analogue exposure also cannot be described as proven replacement of GH pulses with continuous GH secretion.	– Hexarelin	Both stimulate the secretagogue receptor pathway. No clinical evidence establishes additional benefit from combining them. Shared endocrine effects and greater exposure make the resulting response harder to predict or attribute.
+ Sermorelin	Complementary GHRH and secretagogue pathways provide a mechanistic hypothesis, not a validated ipamorelin combination. No direct human trial of this pair was identified. Any increase in hormone stimulation would require separate evaluation of clinical benefit and metabolic effects.	– GHRP-6	This duplicates secretagogue receptor stimulation without demonstrated combination benefit. GHRP-6 increased ACTH and cortisol in a human study (PMID 7617137).
+ Tesamorelin	Different receptor pathways create a theoretical interaction. Evidence for a GHRH analogue alone does not establish efficacy, dose equivalence or safety when combined with ipamorelin. No direct clinical outcome evidence for this pair was identified.	– IGF-1 LR3	Adding an IGF-1 analogue creates a different endocrine exposure with no validated ipamorelin combination regimen. Feedback regulation discussed for secretagogues alone cannot establish protection for this combination (PMID 28400207).

SAFETY

COMMON EFFECTS

A reliable frequency profile for repeated subcutaneous ipamorelin has not been established. Injection-site reactions, appetite changes, fluid retention, musculoskeletal symptoms and dysglycemia appear in broader peptide and secretagogue reviews (PMID 42395176, PMID 28400207). They should not be presented as quantified ipamorelin-specific adverse effects. The postoperative trial's high overall event rates occurred in recently operated patients and included events unrelated to treatment (PMID 25331030). Increased adiposity was demonstrated in mice, not established as a common human outcome (PMID 11162489).

SERIOUS SIGNALS

FDA identifies serious adverse events, including death, in literature involving intravenous ipamorelin for gastric motility. This does not establish that ipamorelin caused those events. FDA also highlights potential immunogenicity from aggregation or peptide impurities and inadequate safety information for certain other injectable routes. Source: [FDA safety-risk assessment] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>). Broader secretagogue literature raises concerns about glucose regulation and insufficient long-term cancer and mortality data (PMID 28400207).

CONTRAINDICATIONS

There is no approved ipamorelin label establishing formal contraindications. Clinically important concerns include active malignancy, uncontrolled glucose disorders, proliferative diabetic retinopathy and acute critical illness, extrapolated from GH-axis pharmacology rather than validated ipamorelin trials. A cancer history requires individualized assessment and is not equivalent to proven active malignancy. Pregnancy, breastfeeding and pediatric use lack adequate clinical evidence. Animal bone-growth findings do not establish pediatric suitability (PMID 10373343). Hypersensitivity and uncertain formulation composition are additional concerns. Anti-doping prohibition is a sporting restriction, not a medical contraindication.

STOP RULES

Breathing difficulty, facial or tongue swelling, fainting, chest pain, or severe headache with visual changes warrant urgent medical evaluation and no further exposure pending assessment. Persistent edema, numbness, abnormal glucose readings, or a hot, spreading, painful injection-site reaction also warrant medical review. These are general clinical escalation criteria, not validated ipamorelin monitoring thresholds. No competition-related stopping interval is provided because ipamorelin is prohibited at all times.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved ipamorelin presentation or standardized vial strength was identified. A labeled mass is not independent confirmation of peptide content, salt composition or usable concentration. Salt, water content and assay conventions can affect how reported mass is interpreted.

SOLVENT

No approved reconstitution solvent or validated multidose preparation procedure was identified in the cited human studies. Sterile water and bacteriostatic water are not interchangeable evidence of formulation compatibility. A preservative does not establish peptide stability, remove endotoxin or make an unverified powder suitable for administration.

STORAGE

No formulation-specific post-reconstitution stability or beyond-use period was established by the references reviewed. Storage requirements depend on formulation, container, sterility assurance and validated stability data. Refrigeration or freezing does not independently establish suitability, and repeated freezing may affect peptide preparations. Visible cloudiness or particles indicate a problem, but a clear solution can still contain contaminants or degraded material.

Hypothetical concentration arithmetic only: 5 mg of analytically confirmed peptide in a final solution volume of 2.5 mL equals 2 mg/mL, or 2000 mcg/mL. These are assumed quantities for a calculator example, not a documented formulation, dose, route or administration frequency. The denominator is final solution volume, which is not automatically identical to the volume of solvent added. This calculation does not establish recovery after dissolution, stability, sterility or biological activity. No syringe setting or human dose is inferred. The intravenous research doses cannot be converted into a validated subcutaneous regimen merely by matching mass or adjusting for body weight.

BUYING NOTES

A certificate of analysis can support particular analytical claims; it does not confer drug approval or establish suitability for human administration. Useful document fields include the batch identifier, sampling date, analytical method, laboratory identity, peptide identity and measured content. HPLC peak-area purity does not by itself measure the amount of intended peptide in a vial. Mass spectrometry addresses identity differently from a purity chromatogram. Salt form, water content and related impurities can complicate interpretation. Sterility and endotoxin are separate attributes, neither established by an HPLC percentage. A fixed purity threshold cannot substitute for those assessments. A primary analytical study identified glycine-extended secretagogues, including Gly-Ipamorelin, in illicit-market material (PMID 29864719). That finding demonstrates an analogue-identification problem; it does not establish a contamination rate or prove that every sample was mislabeled as ordinary ipamorelin. Supplier documents also do not independently establish the custody or representativeness of the tested sample.

COMMON MISTAKES

- Treating a GH pulse as proof of hypertrophy, better recovery or better sleep. The human pharmacology study measured hormone release, not those outcomes (PMID 10496658).
- Transferring results from glucocorticoid-treated rats to healthy adults who train. The cited muscle-tension result used a specific animal disease model (PMID 11735244).
- Assuming intravenous pharmacokinetics describe subcutaneous exposure. The reported 2-hour terminal half-life and approximately 40-minute GH peak came from intravenous infusions (PMID 10496658).
- Interpreting selectivity as an absence of adverse effects. The original swine study addressed selected hormone responses, and its prolactin findings were shared by the tested comparators (PMID 9849822).
- Assuming greater bone mineral content means denser bone. In the cited rat study, larger bone dimensions explained the increase while volumetric density remained unchanged (PMID 10828840).
- Using a normal IGF-1 result to authenticate a product or prove an absence of biological effects. Rat bone growth occurred without increased total IGF-I (PMID 10373343).
- Reading the ileus trial as either proof of efficacy or proof of no possible effect. Its primary and secondary comparisons were not statistically significant (PMID 25331030).
- Inferring permission to use a prohibited substance from its elimination half-life. WADA prohibition applies both in and out of competition.

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GHRP-2 (Pralmorelin)

Pralmorelin

Ghrelin receptor agonist

Module 2 · Recomposition

Goals: Hypertrophy

Route: SC

WADA prohibited

A synthetic ghrelin-receptor agonist with an approved Japanese diagnostic use. Small human studies document increased GH, IGF-I and appetite, but do not establish muscle-building benefits in trained adults.

WHAT IT IS

GHRP-2 is a synthetic hexapeptide from the growth hormone releasing peptide family. Its development preceded the discovery of ghrelin, the receptor's endogenous ligand (PMID 22975043). It has no structural homology with growth hormone releasing hormone, abbreviated GHRH (PMID 9186261).

GHRP-2 activates the growth hormone secretagogue receptor, commonly called the ghrelin receptor. It stimulates pituitary GH secretion through a system involving both pituitary and hypothalamic signaling. Its effect depends on physiological context, including pituitary reserve, GHRH signaling, age and exposure duration (PMID 11443201, PMID 15126555).

Japan authorizes pralmorelin for diagnosing GH deficiency. That indication concerns a supervised stimulation test, rather than repeated treatment for physique or performance. Research has also examined appetite, pediatric growth and sustained hormone responses. These endpoints do not establish improved training adaptation, strength or body composition in healthy athletes.

MECHANISM

Receptor activity. GHRP-2 acts through the growth hormone secretagogue receptor rather than the GHRH receptor. Rat receptor cloning demonstrated a functional, seven-transmembrane receptor expressed in the pituitary and hypothalamus (PMID 9092793). That study supports receptor biology, but does not independently establish every proposed signaling step for GHRP-2 in human tissues.

Dependence on GHRH signaling. Eleven people with an inactivating GHRH-receptor mutation retained a small GH response to GHRP-2. GH increased 4.5-fold from baseline, compared with 79-fold in controls (PMID 11443201). This supports a GHRH-independent component alongside a much larger response when the signaling system is intact. Congenital deficiency also affects pituitary development, so these fold changes cannot precisely divide the response into anatomical mechanisms.

Interaction with GHRH. In critically ill adults, adding GHRH to GHRP-2 approximately doubled mean GH relative to GHRP-2 alone. IGF-I increased by a further 40 percent (PMID 9024260). A separate older-adult study also demonstrated greater GH stimulation with combined GHRH and GHRP-2 under selected experimental conditions (PMID 15126555). These findings establish endocrine synergy, not improved muscle outcomes or the effectiveness of every commercial GHRH analog combination.

Hypothalamic mechanisms. Historical reviews discuss reduced somatostatin inhibition and increased GHRH activity as candidate explanations (PMID 9186261). Experiments involving GHRP-6 altered hypothalamic GHRH and somatostatin expression in rats (PMID 8950613). Those results provide related-compound context. They do not directly demonstrate the same changes after GHRP-2 in humans.

GH secretion patterns. Seven postmenopausal women received continuous IV GHRP-2 at 1 mcg/kg per hour for 24 hours in a randomized comparison with saline (PMID 10372723). GH secretory burst mass increased approximately sevenfold, burst amplitude tenfold and basal secretion 4.5-fold. Pulse frequency and calculated GH half-life did not change. This describes one infusion experiment, not a universal rule that GHRP-2 only enlarges physiological pulses.

Other endocrine and appetite effects. Single IV doses of 1 or 2 mcg/kg increased prolactin, ACTH and cortisol in an acute human study (PMID 9285939). Continuous SC infusion at 0.1 or 1 mcg/kg per hour for 270 minutes increased food intake in a dose-dependent manner (PMID 16861611). These are clinically relevant effects alongside GH stimulation. Rat lung-injury and heart-failure experiments suggest additional actions, but human therapeutic benefits remain unestablished (PMID 20805679, PMID 15951341).

EVIDENCE · GRADE A

Grade A applies to the approved Japanese diagnostic indication under this catalog's grading definition. Evidence for repeated administration to alter hormones or appetite is grade B, based on small human studies. Muscle-growth findings in growth-retarded yaks are grade C and do not establish benefit in trained adults. A human case report describing improved strength during recovery from severe anorexia nervosa is too weak to establish an anabolic treatment effect. No controlled trial establishing hypertrophy or recomposition in trained adults was identified.

Human data. Diagnostic validation included 77 healthy participants and 58 patients with severe GH deficiency. A single 100 mcg IV bolus after overnight fasting produced GH peaks within 60 minutes (PMID 17609397). The diagnostic cutoff depended on assay calibration, illustrating why a numerical GH result requires clinical and laboratory context. A comparison in 71 Japanese patients with pituitary tumors reported a median GHRP-2-stimulated peak GH of 28.88 mcg/L. Sensitivity was 81.3 percent and specificity 94.5 percent against the study's insulin-tolerance-test definition of severe deficiency (PMID 23079545). In 17 older adults, continuous SC infusion at 1 mcg/kg per hour for 30 days sustained increased GH and IGF-I (PMID 15126555). GH stimulation exceeded threefold on day 1 and 1.8-fold on days 14 and 30. IGFBP-3 and IGFBP-5 also increased, and screening laboratory tests remained normal. These biochemical findings do not demonstrate muscle gain or establish long-term safety. Seven lean men received continuous SC infusion at 1 mcg/kg per hour for 270 minutes and consumed 35.9 percent more food than during saline (PMID 15699539). In 19 lean and obese adults, continuous SC infusion for 270 minutes increased intake by 10.2 percent at 0.1 mcg/kg per hour. Intake increased by 33.5 percent at 1 mcg/kg per hour in the same randomized study (PMID 16861611). Fifteen children with short stature received intranasal GHRP-2 at 5 to 15 mcg/kg per administration, twice daily initially and subsequently three times daily (PMID 9390009). Height velocity increased, but the uncontrolled design and pediatric population limit interpretation. Ten GH-deficient children received oral GHRP-2 at 900 mcg/kg twice daily for 12 months. Appetite increases were usually transient, and BMI changes were not statistically significant (PMID 14513874). A separate adult case report described one year of intranasal administration before meals in severe anorexia nervosa. Weight increased by 6.7 kg over 14 months, with reported improvements in strength and activity (PMID 26401470). Concurrent care and nutritional recovery prevent attribution of these outcomes to a direct

Animal and mechanistic data. In rats, a single SC dose of 100 mcg/kg given 30 minutes before an endotoxin challenge reduced lung-injury measures and NF-kappaB activation (PMID 20805679). In pressure-overload heart failure, SC GHRP-2 at 100 mcg/kg twice daily for three weeks improved cardiac-function measures within a study of several GHRPs (PMID 15951341). A small study in growth-retarded yaks found increased skeletal-muscle fiber diameter and area after GHRP-2 administration. Changes in GH, IGF-I and muscle protein-synthesis signaling accompanied the findings (PMID 26894743). This is direct animal muscle evidence, but the developmental and nutritional setting differs substantially from resistance-trained adults. Rat feeding experiments found that GHRP-2 responses depended on strain, feeding state and preferred diet (PMID 15572207). A mouse social-defeat study did not find improved depressive-like behavior with chronic GHRP-2 (PMID 30758330). Rat pharmacokinetic experiments demonstrated biexponential plasma decline and substantial nasal absorption (PMID 9879640). Neither animal bioavailability nor animal treatment doses establish a corresponding human regimen.

anabolic action. This report means that 30 days is not the longest documented adult exposure.

REGULATORY STATUS AND SPORT

STATUS	Pralmorelin is approved in Japan for diagnosis of GH deficiency. The adult diagnostic regimen is a single 100 mcg IV administration, also documented in the validation study (PMID 17609397). This approval does not cover chronic physique, performance, anti-aging or weight-management treatment. No FDA-approved therapeutic indication for GHRP-2 was identified. FDA specifically flags injectable and nasal compounded GHRP-2 for potential significant safety risks. Regulatory authorization, access and compounding rules are separate questions and vary by jurisdiction. [FDA compounding safety information](https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks).
WADA	Prohibited at all times, both in and out of competition, under S2.2.4, Growth Hormone Releasing Factors. GHRP-2, also named pralmorelin, is explicitly listed among GH-releasing peptides. Diagnostic approval does not remove anti-doping obligations. Analytical detection research exists, but detection timing does not define permission to use the substance (PMID 20552695). [WADA Prohibited List](https://www.wada-ama.org/en/prohibited-list).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Documented human routes include IV bolus for diagnostic testing, IV infusion for physiological experiments, SC infusion, SC bolus, intranasal administration and oral administration. The supporting records include PMID 17609397, PMID 10372723, PMID 15126555, PMID 11322505, PMID 9390009 and PMID 14513874. These routes have different absorption and exposure characteristics. Activity after oral or nasal administration does not make their doses interchangeable with IV or SC doses. Trial formulations also cannot be assumed equivalent to an unidentified research preparation.
HALF-LIFE	The Japanese pralmorelin hydrochloride diagnostic injection label reports a terminal elimination half-life of approximately 0.42 to 0.69 hours after IV administration in healthy men. This is approximately 25 to 41 minutes. It is distinct from GH peak timing and does not establish SC or intranasal kinetics. [Japanese diagnostic injection label, July 2025] (https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/200022_7223407D2023_1_01).
TIMING	The diagnostic validation used overnight fasting before testing (PMID 17609397). Historical GHRP research describes reduced GH responses under some glucose, fatty-acid and glucocorticoid conditions (PMID 9186261). Appetite experiments included meals during infusion, showing that fasting is not a universal feature of every research design (PMID 16861611). No controlled evidence identified here establishes bedtime or workout timing as superior for muscle outcomes. A timing rationale based on normal GH rhythms remains an extrapolation.
CYCLE LENGTH	Thirty days is the duration of a verified continuous SC infusion study in older adults, not the maximum documented adult exposure (PMID 15126555). A separate severe-anorexia case report describes one year of intranasal administration (PMID 26401470). Pediatric studies extended to 12 months orally and up to 24 months intranasally (PMID 14513874, PMID 9390009). Their longer duration does not validate repeated exposure in healthy adults. Non-clinical cycles of 8 to 12 weeks are conventions without demonstrated performance efficacy or an established safety boundary.
TITRATION	The cited studies used prespecified experimental doses rather than a validated symptom-guided escalation protocol. Continuous SC infusion at 0.1 versus 1 mcg/kg per hour for 270 minutes produced different appetite and GH responses (PMID 16861611). One acute comparison described a single 2 mcg/kg IV dose as maximally effective for GH in that experimental context (PMID 10195374). That wording does not establish a universal ceiling across routes, populations or exposure patterns. It also does not prove that every higher dose produces only adverse effects.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human diagnostic validation in adults	100 mcg total as a single IV bolus after overnight fasting, reported in PMID 17609397.	IV bolus	Once per diagnostic test	PMID 17609397 studied 77 healthy participants and 58 patients with severe GH deficiency. Blood sampling continued for two hours. This dose concerns diagnostic testing, not repeated treatment. · PMID 17609397

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Acute human endocrine-response study	1 or 2 mcg/kg as a single IV bolus per experimental session, reported in PMID 9285939.	IV bolus	Single administration per experimental session	PMID 9285939 compared GHRP-2 with other endocrine stimuli in small groups of young and older adults. GH, prolactin, ACTH and cortisol were measured. · PMID 9285939
Human GH secretion-pattern experiment	1 mcg/kg per hour by continuous IV infusion for 24 hours, reported in PMID 10372723.	IV infusion	Continuous for 24 hours	PMID 10372723 used a randomized paired comparison with saline in seven postmenopausal women. This experiment measured secretion patterns and circulating hormones. · PMID 10372723
Repeated exposure in older adults	1 mcg/kg per hour by continuous SC infusion for 30 days, reported in PMID 15126555.	SC infusion	Continuous throughout the 30-day exposure	PMID 15126555 documented sustained hormone changes in 17 older adults. Continuous pump exposure differs from intermittent SC boluses. · PMID 15126555
Human appetite dose-response experiment	0.1 or 1 mcg/kg per hour by continuous SC infusion for 270 minutes per study visit, reported in PMID 16861611.	SC infusion	One 270-minute infusion per assigned study condition	PMID 16861611 compared both doses with placebo in 19 lean and obese adults. Both food intake and GH responses increased with dose. · PMID 16861611
Exploratory SC bolus study in older adults	10 mcg/kg as a single SC bolus during experimental testing, reported in PMID 11322505.	SC bolus	Single administration during the acute experiment	PMID 11322505 describes acute and chronic studies in older adults. Its abstract does not clearly assign an SC route to every lower-dose comparator, so no universal SC dose-response ceiling is inferred. · PMID 11322505
Historical pediatric intranasal study	5 to 15 mcg/kg intranasally per administration, twice daily for three months and then three times daily, reported in PMID 9390009.	Intranasal	Twice daily initially, then three times daily	PMID 9390009 followed 15 children for six months, with six continuing for 18 to 24 months. Pediatric growth findings do not establish adult performance effects. · PMID 9390009
Historical pediatric oral study	900 mcg/kg orally per administration, twice daily for 12 months, reported in PMID 14513874.	Oral	Twice daily for 12 months	PMID 14513874 evaluated appetite and BMI in ten children with GH deficiency. The route and formulation prevent direct comparison with injectable quantities. · PMID 14513874
Rat acute lung-injury experiment	100 mcg/kg SC once, 30 minutes before the experimental endotoxin challenge, reported in PMID 20805679.	SC	Single pretreatment administration	PMID 20805679 measured experimental lung injury and inflammatory signaling. No human-equivalent treatment dose is established. · PMID 20805679
Rat pressure-overload heart-failure experiment	100 mcg/kg SC per administration, twice daily for three weeks, reported in PMID 15951341.	SC	Twice daily for three weeks	PMID 15951341 compared several GHRPs in diseased rats. These results do not establish a human cardiac treatment regimen. · PMID 15951341
Non-clinical dosing claims	100 to 300 mcg SC per administration, one to three times daily: commonly cited in non-clinical use; not validated in trials.	SC	One to three times daily in non-clinical descriptions	Commonly cited in non-clinical use; not validated in trials. These schedules have not been established as effective or tolerable regimens for hypertrophy or recomposition. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation .

STACKING

+ CJC-1295

GHRH and GHRP-2 produced endocrine synergy in human experiments (PMID 9024260, PMID 15126555). Those findings do not directly establish the response to CJC-1295, whose exposure profile differs. No verified combination trial here demonstrates improved body composition or defines the safety of this pairing.

– GHRP-6

Both compounds stimulate the ghrelin-receptor pathway. There is no verified evidence here that combining them improves outcomes. Shared receptor activity creates potential overlapping exposure, but does not establish a specific increase in adverse-event rates or desensitization.

+ Sermorelin

A historical review reports GH synergy between GHRP-2 and GHRH 1-29 NH₂, the peptide sequence used for sermorelin (PMID 8950613). Sequence correspondence supports mechanistic relevance. It does not validate a chronic combination schedule or establish a training benefit.

– Hexarelin

Separate administrations of hexarelin and GHRP-2 produced similar GH, prolactin, ACTH and cortisol responses in acute comparisons (PMID 9285939, PMID 10195374). These were not combination studies. Added benefit, interaction magnitude and effects on desensitization remain unestablished.

+ Tesamorelin

GHRH-receptor stimulation offers a plausible mechanism for additional GH release alongside GHRP-2. The verified studies used GHRH rather than tesamorelin itself (PMID 9024260, PMID 15126555).

– Semaglutide

GHRP-2 increased food intake in controlled experiments (PMID 16861611), creating a potential conflict with an appetite-reduction goal. This is a concern about competing treatment objectives. No verified combination study here establishes a direct toxic interaction or proves loss of semaglutide efficacy.

SAFETY

COMMON EFFECTS

Increased hunger and food intake are demonstrated human effects (PMID 15699539, PMID 16861611). Acute experiments also documented increased prolactin, ACTH and cortisol (PMID 9285939). The Japanese diagnostic label lists warmth, gastrointestinal symptoms, sleepiness and hypotension. Edema, hand tingling, joint symptoms and impaired glucose regulation are broader GH-axis concerns. Their incidence during chronic GHRP-2 exposure is not established by the small studies reviewed here (PMID 42395176).

SERIOUS SIGNALS

FDA reports increased insulin requirements, infections, pancreatitis and deaths among critically ill recipients of GHRP-2; causality has not been established. It also identifies potential immunogenicity associated with aggregation and peptide-related impurities. Normal screening results in 17 older adults cannot exclude uncommon or delayed harm (PMID 15126555). [FDA GHRP-2 safety information](<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>).

CONTRAINDICATIONS

Pregnancy or possible pregnancy is a formal contraindication in the Japanese diagnostic label. Lactation requires an individualized assessment. The label also notes pituitary-apoplexy reports with similar stimulation agents in pituitary adenoma patients. Active malignancy, uncontrolled diabetes, proliferative retinopathy and unexplained pituitary symptoms are important GH-axis clinical concerns, rather than a verified GHRP-2-specific contraindication list for chronic treatment. Anti-doping prohibition is a separate restriction. [Japanese diagnostic injection label] (https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/200022_7223407D2023_1_01).

STOP RULES

Breathing difficulty, facial or throat swelling, collapse, or sudden severe headache with visual changes warrant emergency assessment and no further exposure. Severe persistent abdominal pain, repeated vomiting or fever also requires prompt evaluation. Persistent edema, numbness, breast discharge or deteriorating glucose control warrants discontinuation pending clinical review. These are clinical escalation signals, not a validated monitoring protocol that makes continued non-clinical use acceptable.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No universal research-vial strength or formulation is established. Package mass is a content claim, not evidence of identity, potency or sterility. The Japanese diagnostic formulation contains 100 mcg per vial according to its pralmorelin hydrochloride injection label. Its specifications cannot be transferred to another preparation.

SOLVENT

The Japanese pralmorelin hydrochloride diagnostic injection label specifies 10 mL of physiological saline for preparation immediately before administration. It does not validate bacteriostatic water, repeated vial entry or extended storage for unrelated research formulations.

STORAGE

The Japanese diagnostic label specifies storage at or below 10 C, avoiding freezing. No formulation-specific evidence reviewed here validates freezing research powders or keeping reconstituted research material for four weeks. A clear solution can still be contaminated or degraded. Appearance alone does not establish suitability, and preservative content does not substitute for validated stability and sterility data.

Concentration arithmetic only: a hypothetical preparation containing 5 mg in a final volume of 5 mL contains 1 mg/mL, equivalent to 1000 mcg/mL. These figures are calculation inputs, not an administration dose or a preparation specification. If the final volume were 2 mL, the calculated concentration would be 2.5 mg/mL, equivalent to 2500 mcg/mL. This illustrates why a concentration requires both a verified amount and a final volume.

The arithmetic assumes that the stated amount represents actual peptide content and that the final volume is known. Neither assumption can be confirmed from powder appearance. Gross powder mass may include water, counterions and excipients. A mass calculation also cannot establish sterility, compatibility or stability.

The conversion is 1 mg equals 1000 mcg. Syringe markings indicate volume according to the device calibration; they are not peptide potency units. A correctly calculated volume can still contain the wrong amount if the material is mislabeled. Diagnostic IV quantities cannot be converted into a validated SC regimen simply by changing concentration.

BUYING NOTES

A certificate of analysis describes the submitted sample and the tests performed. It does not establish regulatory approval, clinical suitability or that every container matches the tested sample. A useful assessment distinguishes identity, purity, actual peptide content, sterility, endotoxin burden and stability.

HPLC area purity describes relative chromatographic signals under a particular method. It does not directly measure the amount of peptide in a container, and a high percentage can coexist with missing quality information. Mass spectrometry can support molecular identity, but a matching mass alone cannot establish every structural feature or exclude all impurities. Net-content testing addresses a different question from chromatographic purity.

Batch identifiers, sample dates, analytical methods and an identifiable testing laboratory improve traceability. Independent confirmation of a report can address authenticity, but cannot establish conditions after testing. Sterility and endotoxin assessments are distinct from chemical identity testing. Their absence is not resolved by an attractive chromatogram or a research-use statement.

For mixtures, each ingredient requires separate identity and content characterization. A single combined purity number cannot establish the amount of each component. Shipping temperature claims require formulation-specific stability support. No generic purity threshold makes an unidentified preparation equivalent to the medicine used in a clinical study.

COMMON MISTAKES

- Treating increased GH or IGF-I as proof of muscle gain. The major repeated-exposure trial measured hormones, not established training outcomes (PMID 15126555).
- Assuming there is no muscle evidence of any kind. A yak experiment measured larger muscle fibers, but it does not establish efficacy in trained adults (PMID 26894743).
- Calling 30 days the longest adult exposure. A one-year intranasal case report exists, with substantial limitations for causal interpretation (PMID 26401470).
- Ignoring appetite as an outcome. Controlled infusion studies demonstrated increased food intake, which can conflict with an energy deficit goal (PMID 16861611).

- Treating a GH peak as the drug's elimination half-life. Hormone-response timing, drug clearance and route-dependent absorption describe different processes.
- Assuming diagnostic approval authorizes repeated treatment. The approved Japanese indication concerns testing GH secretory capacity.
- Assuming all ghrelin-receptor agonists have identical selectivity or that two agonists must work better together. Acute comparisons do not answer combination questions.
- Interpreting normal laboratory screening in a small study as evidence that serious adverse events do not occur.
- Using a certificate's purity percentage as proof of net content, sterility, endotoxin control and stability. These require different evidence.
- Treating a short elimination half-life as permission to use a prohibited substance. WADA prohibition applies at all times.
- Confusing mg, mcg, concentration and volume. A correct unit conversion cannot compensate for an unverified content claim.

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GHRP-6

Ghrelin receptor agonist

Module 2 · Recomposition

Goals: Hypertrophy

Route: SC

WADA prohibited

A ghrelin receptor agonist with documented human growth hormone responses, additional endocrine effects, and no established benefit for muscle gain or recomposition.

WHAT IT IS

GHRP-6 is a synthetic hexapeptide with the sequence His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂ and molecular weight 872.44 Da (PMID 23099431). It was among the first growth hormone releasing peptides studied extensively in humans. Its development helped establish a receptor system subsequently linked to the natural hormone ghrelin (PMIDs 9186261 and 16906274).

GHRP-6 is neither growth hormone nor a growth hormone releasing hormone analog. It stimulates endogenous growth hormone secretion through the growth hormone secretagogue receptor. Growth hormone releasing hormone, abbreviated GHRH, contributes substantially to the resulting response. Pituitary function, hypothalamic signaling, metabolic conditions and route of administration influence the response.

This card addresses the recomposition and hypertrophy goals commonly associated with GHRP-6. The human literature establishes changes in circulating hormones after experimental administration. The studies reviewed here do not establish increased muscle size, improved strength, reduced fat mass or better recovery in trained adults.

An increase in growth hormone or IGF-1 is a biological effect, not a demonstrated training outcome. Acute endocrine experiments cannot establish the benefit or safety of repeated exposure over a training block. Describing GHRP-6 as a natural pulse does not resolve those limitations.

GHRP-6 also affects hormones outside the growth hormone axis. Human experiments document prolactin, ACTH and cortisol responses under some conditions. Appetite stimulation is biologically plausible and supported by animal findings, but its frequency and magnitude in human non-clinical use are not established.

MECHANISM

GHRP-6 activates the growth hormone secretagogue receptor type 1a, abbreviated GHS-R1a. Ghrelin also activates this receptor. Secretagogue signaling involves calcium-dependent pathways and protein kinase systems at the pituitary, together with hypothalamic regulation. The receptor system differs from the GHRH receptor system (PMIDs 9186261 and 16906274).

The peptide family was developed from structures related to enkephalins. Structural ancestry does not make the growth hormone response an opioid effect. The class review reports that opioid antagonists such as naloxone do not block its growth hormone releasing activity (PMID 9186261).

Both pituitary and hypothalamic actions contribute. The relative importance of these sites depends on the experimental question and physiological setting. The reviewed literature supports hypothalamic participation, but does not justify assigning a universal percentage of the response to either site. Functional antagonism of somatostatin has been proposed. It remains a mechanistic interpretation rather than a complete account of GHRP-6 activity.

A human antagonist experiment provides direct evidence for GHRH dependence. Nine healthy men received a single intravenous GHRP-6 bolus of 1 mcg/kg per test session after antagonist or saline pretreatment (PMID 9543138). GHRH blockade reduced the maximal growth hormone increment from 33.8 to 6.2 mcg/L. This establishes that endogenous GHRH supports most of the response under those conditions. The remaining response means that complete dependence would overstate the finding.

GHRP-6 and GHRH produced synergistic growth hormone release in an acute human experiment (PMID 2108187). A later multicenter study evaluated their combination as a diagnostic stimulus in adults with suspected growth hormone deficiency (PMID 11030292). These findings establish endocrine synergy for the studied preparations. They do not validate chronic combinations with every GHRH analog in the catalog.

During a 34-hour intravenous infusion, growth hormone pulse amplitude increased without a significant change in pulse frequency or interpulse concentration (PMID 7903313). IGF-1 increased from 252 to 312 mcg/L. However, the response to an additional GHRP bolus was smaller during the infusion. Continued secretion and partial desensitization can occur together. This experiment does not support a claim that responsiveness remains completely unchanged.

Selectivity is limited. Acute human studies found prolactin and cortisol increases, while an overnight experiment also found increased ACTH (PMIDs 2108187 and 7617137). These responses vary with exposure and experimental conditions. The literature reviewed here does not establish that adrenal responses always increase after growth hormone responses reach a plateau.

Animal tissue-protection studies describe additional actions in experimental injury models. Those findings do not establish a clinically effective cardiovascular, kidney or lung treatment. A proposed secondary receptor mechanism cannot be used to predict human protection from training stress or disease.

EVIDENCE · GRADE C

Grade C applies to the recomposition and hypertrophy claim addressed by this card. Human endocrine studies exist, but their surrogate outcomes are insufficient to establish that claim. Acute growth hormone stimulation has substantially stronger support, consistent with grade B evidence from small, short human experiments. The grade does not imply that GHRP-6 has only been studied in animals.

No controlled trial establishing improved muscle mass, strength or body composition in trained adults was identified in this review. This was a targeted literature check, not a systematic review proving that no relevant publication exists. The retrieved clinical studies mainly examine endocrine responses, pharmacokinetics, sleep physiology and diagnostic testing. Class-level results from other secretagogues cannot be assigned automatically to GHRP-6.

The distinction between endpoint and compound is essential. A real study can support an acute growth hormone response while providing no evidence for the advertised physique outcome. Animal injury experiments also cannot establish human recovery or organ protection. The references below identify the exact studies supporting each retained claim.

Human data. In 18 healthy men, single intravenous GHRP-6 boluses of 0.1, 0.3 and 1.0 mcg/kg per test session produced dose-related growth hormone responses (PMID 2108187). Mean peak concentrations were 7.6, 16.5 and 68.7 mcg/L, respectively, compared with 1.2 mcg/L after placebo. Prolactin and cortisol approximately doubled at the highest studied dose. These are group hormone measurements, not expected individual responses or muscle outcomes. An overnight placebo comparison administered four intravenous boluses of 50 mcg each during one experimental night (PMID 7617137). Growth hormone, ACTH and cortisol increased, and stage 2 sleep duration increased. Slow-wave sleep did not increase. More stage 2 sleep cannot be assumed to mean better restorative sleep or athletic recovery. A 34-hour infusion in nine young men increased growth hormone pulse amplitude and IGF-1, while the response to an additional GHRP challenge was reduced (PMID 7903313). Six men received seven intranasal administrations of 15 mcg/kg every 8 hours in a separate experiment (PMID

Animal and mechanistic data. In a rat hepatic ischemia and reperfusion model, a single intraperitoneal pretreatment of 120 mcg/kg reduced several injury measurements (PMID 16417467). Reported reductions of 50 to 85 percent applied to specific experimental endpoints, including tissue injury, inflammatory infiltration and lipid peroxidation. They are not estimates of human benefit. The paper also included cell experiments and an epidermal growth factor combination. A mouse study reported reduced acute lung injury and subsequent fibrotic changes across experimentally induced injury models (PMID 41534456). A separate study used a self-assembling GHRP-6 hydrogel in mice with acute kidney injury (PMID 41327290). The hydrogel affected tubular-cell metabolism and mTOR-P70 signaling. A locally acting or sustained-release formulation cannot be treated as equivalent to an ordinary peptide solution. In ovariectomized rats receiving placebo rather than estradiol replacement, GHRP-6 increased high-fat diet intake and activated arcuate nucleus neurons (PMID 32224927). The estradiol-treated

1915110). IGF-1 increased from 94.5 to 125.8 mcg/L. In seven elderly women, oral GHRP-6 at 300 mcg/kg twice daily for 4 days maintained the acute growth hormone response without significantly increasing IGF-1 (PMID 7952160). A pharmacokinetic study examined single intravenous boluses of 100, 200 and 400 mcg/kg across nine healthy male volunteers (PMID 23099431). These unusually high experimental doses were used for plasma pharmacokinetic characterization. They do not define a therapeutic range. The publication year is 2013, with online publication in 2012. A multicenter diagnostic study included 125 patients with organic pituitary disease and 125 healthy controls (PMID 11030292). Its purpose was distinguishing growth hormone deficiency through an acute stimulation test. Diagnostic performance does not demonstrate that repeated administration improves training outcomes.

animals responded differently. This supports context-dependent appetite signaling in that model, not a universal human hunger response. That study administered hexarelin and another secretagogue, while using a modified GHRP-6 analog as an antagonist. Neither related compounds nor antagonists establish the effects of unmodified GHRP-6 on human muscle. The retained animal studies primarily concern injury biology and appetite.

REGULATORY STATUS AND SPORT

STATUS

GHRP-6 is investigational and has no FDA-approved therapeutic dosing label. Published experimental administration and diagnostic research do not establish marketing approval. The current FDA compounding risk page lists GHRP-6 under 503B category 2. It identifies potential immunogenicity from aggregation or peptide-related impurities, together with cortisol and glucose-related concerns. [FDA compounding safety assessment](<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>). Requirements differ by jurisdiction, intended use and supply pathway. A research-use label does not establish authorization for human treatment. A certificate of analysis likewise does not establish regulatory approval, pharmaceutical manufacturing compliance or clinical suitability.

WADA

Prohibited at all times, both in competition and out of competition, under S2.2.4, Growth hormone releasing factors. The 2026 list explicitly names GHRP-6 among growth hormone releasing peptides. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Published analytical research demonstrates identification of GHRP-6 and related compounds in human urine (PMID 25869809). Detection is not limited to measuring circulating growth hormone. No detection windows, clearance schedules or timing advice are provided. Prohibited status does not depend on whether an individual notices an endocrine or performance effect.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Human studies document intravenous bolus, intravenous infusion, oral, intranasal and sublingual administration. The class review also discusses subcutaneous activity, but class-level statements do not establish a specific GHRP-6 subcutaneous regimen (PMID 9186261). No validated subcutaneous dose for recomposition was identified. Route and formulation materially change the response. An oral study estimated about 0.3 percent of intravenous growth hormone releasing activity from its dose comparison (PMID 1730807). This was relative pharmacodynamic activity, not a measured absolute oral bioavailability applicable to all preparations. An enteric-coated oral preparation later failed to reproduce an endocrine response in a nocturnal experiment (PMID 10336729). Intranasal administration produced dose-related responses in one small study (PMID 1915110). Sublingual administration produced only a trend toward increased growth hormone in another (PMID 10336729). Neither finding supplies a conversion between intravenous study doses and non-clinical subcutaneous use.

HALF-LIFE

The LC-MS pharmacokinetic study reported a distribution half-life of 7.6 plus or minus 1.9 minutes and an elimination half-life of 2.5 plus or minus 1.1 hours (PMID 23099431). These estimates followed single intravenous boluses of 100, 200 or 400 mcg/kg in nine healthy men, as reported in that study. They are model-based estimates averaged across the three dose levels. An earlier immunoassay study estimated a serum half-life of about 20 minutes (PMID 1730807). Differences in assay, exposure and pharmacokinetic modeling limit direct comparison. Neither value establishes subcutaneous dosing frequency. The oral study reported a detectable growth hormone rise around 30 minutes, a peak at 60 to 75 minutes and return toward baseline by 150 to 180 minutes. Those

timings describe its oral experiment. They are not a universal GHRP-6 effect curve or an estimate of drug elimination.

TIMING

No study establishes an optimal relationship to training, meals or bedtime for muscle gain. The class literature reports modulation of endocrine responses by glucose, free fatty acids, glucocorticoids and growth hormone feedback (PMID 9186261). Experimental inhibition does not establish a practical fasting interval or predict the effect of a particular mixed meal. Overnight administration altered both endocrine secretion and sleep architecture (PMID 7617137). A later route-comparison study found different nocturnal responses with oral, intranasal and sublingual preparations (PMID 10336729). These findings argue against treating bedtime as an inherently beneficial administration window. Age and endocrine disease also influence growth hormone responsiveness. An altered acute response does not identify who will gain muscle or benefit clinically. Timing changes cannot compensate for the absence of trials measuring the intended outcome.

CYCLE LENGTH

No validated cycle length for recomposition or hypertrophy was identified. The cited repeated-exposure experiments include a 34-hour infusion, seven intranasal administrations over approximately 2 days, and 4 days of oral treatment. Their endpoints and preparations differ, so they do not form a continuous escalation of evidence toward longer treatment. Non-clinical subcutaneous cycles of 8 to 12 weeks are commonly cited in non-clinical use; not validated in trials. The cited human studies do not establish efficacy, safety, monitoring intervals or recovery after that duration. No optimal interval between cycles has been demonstrated. Preserved secretion during short exposure does not exclude partial desensitization. The infusion study directly found a smaller response to an additional GHRP challenge (PMID 7903313). The class review also describes partial desensitization, particularly during continuous administration (PMID 9186261). These observations do not establish how responsiveness changes over months.

TITRATION

No evidence-based titration schedule exists for a fitness application. The acute intravenous dose-response study establishes increasing hormone responses within its tested conditions (PMID 2108187). It does not establish an effective starting dose, a subcutaneous escalation sequence or a symptom-based endpoint. Hunger, flushing, drowsiness or tingling are not validated markers of a productive growth hormone exposure. Absence of symptoms cannot establish normal glucose handling, appropriate IGF-1 concentrations or product identity. Increasing frequency after a tolerated administration has not been validated as a clinical strategy. A universal saturation threshold and predictable off-target response cannot be assigned from the retrieved studies. Titration based on those assumptions would present mechanistic speculation as an established protocol.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Acute endocrine dose-response study in 18 healthy men. Growth hormone increased with dose, and prolactin and cortisol increased at the highest studied dose. No physique endpoint was measured.	0.1, 0.3 or 1.0 mcg/kg, single intravenous bolus per test session, PMID 2108187.	Intravenous bolus	Single dose per test session	Bowers CY, 1990, The Journal of clinical endocrinology and metabolism, PMID 2108187. Experimental endocrine challenge, not a treatment recommendation. · PMID 2108187
Phase I pharmacokinetic study in nine healthy male volunteers. The high experimental exposures support pharmacokinetic estimates, not a dose for muscle gain or repeated use.	100, 200 or 400 mcg/kg, single intravenous bolus, PMID 23099431.	Intravenous bolus	Single administration at the studied dose level	Cabrales A, 2013, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, PMID 23099431. · PMID 23099431

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Nine healthy young men underwent prolonged exposure. Pulse amplitude and IGF-1 increased, while responsiveness to an additional GHRP challenge decreased.	1 mcg/kg intravenous loading bolus once, followed by continuous intravenous infusion at 1 mcg/kg per hour for 34 hours, PMID 7903313.	Intravenous loading bolus followed by infusion	One loading bolus followed by continuous infusion for 34 hours	Jaffe CA, 1993, The Journal of clinical endocrinology and metabolism, PMID 7903313. · PMID 7903313
Oral endocrine study in normal men. A separate pediatric group was included in the publication, but pediatric findings do not establish adult fitness applications.	100 or 300 mcg/kg orally, single administration per test session in the adult experiment, PMID 1730807.	Oral	Single administration per test session	Bowers CY, 1992, The Journal of clinical endocrinology and metabolism, PMID 1730807. · PMID 1730807
Short repeated-exposure study in seven elderly women. Growth hormone responsiveness persisted, but IGF-1 did not increase significantly.	300 mcg/kg orally twice daily for 4 days, PMID 7952160.	Oral	Twice daily for 4 days	Ghigo E, 1994, European journal of endocrinology, PMID 7952160. · PMID 7952160
Repeated intranasal exposure in six healthy men. IGF-1 increased, without detectable attenuation of the growth hormone response across the reported administrations.	15 mcg/kg intranasally every 8 hours for seven consecutive administrations, PMID 1915110.	Intranasal	Every 8 hours for seven administrations	Hayashi S, 1991, Endocrinologia japonica, PMID 1915110. · PMID 1915110
Placebo-controlled overnight physiology experiment. Increased stage 2 sleep occurred alongside increased growth hormone, ACTH and cortisol.	50 mcg per intravenous bolus, four boluses during one experimental night, PMID 7617137.	Intravenous bolus	Four administrations during one experimental night	Frieboes RM, 1995, Neuroendocrinology, PMID 7617137. The retrieved abstract specifies four boluses without establishing an exact interval. · PMID 7617137
Rat hepatic ischemia and reperfusion model. Injury-marker reductions do not establish human efficacy or a human equivalent dose.	120 mcg/kg intraperitoneally as a single pretreatment before experimental injury, rats, PMID 16417467.	Intraperitoneal, rats	Single pretreatment	Cibrián D, 2006, Clinical science (London, England : 1979), PMID 16417467. · PMID 16417467
A range circulated in non-clinical discussions. It is included to distinguish convention from study evidence. This review did not validate its prevalence, effectiveness or safety.	100 to 200 mcg subcutaneously per administration, one to three times daily, commonly cited in non-clinical use; not validated in trials.	Subcutaneous	One to three times daily, commonly cited in non-clinical use; not validated in trials.	commonly cited in non-clinical use; not validated in trials. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ CJC-1295

Mechanistic rationale only. GHRP-6 and GHRH produced acute endocrine synergy in humans, but the cited study did not test CJC-1295 (PMID

– GHRP-2

Overlapping secretagogue mechanisms and untested combined exposure provide no demonstrated advantage. GHRP-2 can stimulate prolactin,

	2108187). GHRH antagonist data support interaction between the two signaling systems (PMID 9543138). They do not establish the magnitude, duration or clinical benefit of this specific combination. Its adverse effects cannot be calculated by adding the profiles of the individual compounds.		ACTH and cortisol in acute human experiments (PMID 9285939). That study did not test coadministration with GHRP-6. Claims that the combination doubles hormonal adverse effects or cannot increase growth hormone are unsupported. The practical limitation is absent combination evidence, not a proven arithmetic rule.
+ Sermorelin	Sermorelin belongs to the GHRH signaling pathway, making endocrine interaction plausible. However, the cited Bowers synergy experiment used GHRH-(1-44)-NH ₂ , not a chronic sermorelin regimen (PMID 2108187). The diagnostic combination study likewise does not establish a training protocol (PMID 11030292). Claims of a more physiological pulse, lower total exposure or fewer adverse effects require direct comparative evidence.	– Hexarelin	Hexarelin has overlapping endocrine effects, including prolactin, ACTH and cortisol responses (PMID 9285939). An overnight study also found reduced slow-wave sleep and increased endocrine secretion (PMID 15177700). Those are findings for hexarelin, not measured outcomes of a GHRP-6 combination. No established physique benefit offsets the uncertainty of combined exposure.
+ Tesamorelin	Interaction is plausible through GHRH receptor stimulation, but no direct GHRP-6 plus tesamorelin fitness trial was identified. Evidence for GHRP-6 plus another GHRH preparation cannot establish this combination's effectiveness (PMID 2108187). Potentially greater growth hormone and IGF-1 exposure raises metabolic concerns. Neither those concerns nor possible benefits have been quantified for this pair.	– IGF-1 LR3	No human evidence supporting this combination was identified. Direct IGF-1 receptor stimulation would add a different exposure to secretagogue-driven endocrine signaling. Potential hypoglycemic and growth-signaling effects require separate evaluation. Neither an unlimited response nor a quantified cancer risk has been demonstrated.

SAFETY

COMMON EFFECTS

Human incidence rates for adverse effects during repeated non-clinical use are unknown. The acute Bowers experiment reported no adverse clinical effects or laboratory abnormalities attributable to GHRP-6 (PMID 2108187). That observation concerns a small, short experiment. Its reported facial flushing occurred with GHRH, so it cannot establish a GHRP-6 flushing rate. Appetite stimulation is plausible through ghrelin receptor signaling. Direct GHRP-6 evidence cited here comes from an animal model with hormone-dependent differences in response (PMID 32224927). Hunger should therefore not be described as inevitable or precisely quantified in humans. Edema, joint discomfort and hand paresthesia are concerns associated with growth hormone excess and broader secretagogue exposure. Their frequency during a GHRP-6 training cycle is not established by these studies. Similarly, anecdotal warmth, drowsiness and head pressure do not have reliable incidence estimates. A symptom list should not imply that long-term surveillance has been performed.

SERIOUS SIGNALS

The clearest directly observed signals are endocrine. GHRP-6 increased cortisol and prolactin in an acute dose-response experiment, and increased ACTH and cortisol during overnight administration (PMIDs 2108187 and 7617137). The duration and clinical consequences of these changes during sustained use remain uncertain. Glucose regulation is a separate concern. One small study found no acute glucose increase after GHRP-6 in healthy controls or patients with thyrotoxicosis (PMID 17410412). That result does not exclude impaired insulin sensitivity during repeated exposure. The secretagogue safety review identifies glucose effects and inadequate long-term safety characterization as unresolved issues (PMID 28400207). Potential effects on existing malignancy are mechanistic concerns, not demonstrated GHRP-6 cancer-incidence findings. The reviewed

studies do not establish long-term cancer, cardiovascular or mortality outcomes. Endogenous feedback limits some endocrine responses but does not establish protection from clinically important adverse effects. Product-related risks are additional to pharmacology. Aggregation, peptide impurities, microbial contamination and endotoxin are distinct hazards. A clean-looking solution or an apparent hormonal response cannot exclude them.

CONTRAINDICATIONS There is no approved GHRP-6 label supplying a validated contraindication list. The following are clinical risk considerations based on endocrine mechanisms, missing safety data and product uncertainty. Active or suspected malignancy, unexplained growth hormone or IGF-1 elevation, acromegaly, and pituitary disease require specialist assessment. A past cancer diagnosis requires individualized evaluation rather than an unsupported claim that every history represents the same risk. Diabetes or impaired glucose tolerance increases concern about metabolic effects. Pregnancy, breastfeeding and pediatric use lack evidence supporting this fitness application. Severe acute illness also differs substantially from the healthy-volunteer setting. An investigational diagnostic test in patients with pituitary disease does not validate ongoing unsupervised exposure in that population. Known hypersensitivity to the peptide or preparation components is another concern. Anti-doping prohibition is a sporting restriction, separate from a medical contraindication. Neither normal baseline tests nor absence of these conditions establishes suitability for non-clinical use.

STOP RULES After exposure, breathing difficulty, facial or tongue swelling, collapse, severe headache with visual disturbance, or marked confusion warrants urgent medical assessment. Fever with increasing local redness, pain or swelling raises concern for infection. Persistent edema, hand numbness, joint pain or worsening glucose measurements warrants cessation and clinical evaluation. These findings have multiple possible causes and should not be diagnosed automatically as growth hormone excess. New unexplained masses or weight loss also require assessment, without implying that GHRP-6 caused them. No GHRP-6-specific laboratory threshold or monitoring schedule has been validated for a training cycle. Baseline and follow-up measurements can help clinical interpretation, but monitoring cannot establish an unproven regimen's safety. The cited short studies do not support a self-managed protocol based on symptoms alone.

RECONSTITUTION AND STORAGE

TYPICAL VIAL No approved GHRP-6 vial presentation or standard concentration was established by the sources reviewed here. A stated vial mass describes nominal contents, not measured concentration, potency or sterility. Lyophilized material may include counterions, residual water and formulation ingredients. Gross powder mass and net peptide content are different measurements. A concentration calculation is only as reliable as the stated content and final solution volume. A research label cannot establish that a preparation is appropriate for human administration.

SOLVENT No validated universal reconstitution solvent for non-clinical GHRP-6 preparations was identified. Solvent compatibility depends on the exact formulation, pH, excipients, container and intended analytical or clinical application. An experimental peptide cannot inherit another injectable medicine's preparation instructions. Bacteriostatic water does not sterilize contaminated powder or remove endotoxin. A preservative also does not establish chemical stability after reconstitution. Appearance is a limited quality observation. Visible particles or discoloration can indicate a problem, but a clear solution can still contain contamination or degraded peptide. There is no verified visual test that establishes acceptable identity, potency and sterility.

STORAGE The claimed refrigerated shelf life after mixing was not supported by the cited studies. A preservative's presence cannot establish peptide potency over that interval. Temperature, light, pH, concentration, container adsorption and freeze-thaw exposure can affect stability. Appropriate limits require data for the exact preparation, including chemical integrity and microbiological quality. Findings for dry peptide cannot automatically be applied to reconstituted solution. A clear appearance does not establish acceptable storage history. Refrigeration cannot reverse degradation or sterilize a contaminated preparation. No universal freezer rule, shipping tolerance or multiweek storage window is supplied here.

Concentration arithmetic only, using hypothetical analytical sample quantities rather than a proposed administration. If a sample contains 5 mg of verified net peptide and its final solution volume is 2 mL, its calculated concentration is 2.5 mg/mL. Because 1 mg equals 1000 mcg, that is 2500 mcg/mL. These quantities are illustrative assumptions, not a study dose or an approved preparation. If the same hypothetical 5 mg sample instead has a final volume of 5 mL, the concentration is 1 mg/mL, or 1000 mcg/mL. The amount of peptide in the container has not changed. Its concentration has changed because the final volume differs. Final volume matters, which is not always identical to the volume of liquid initially added. The general relationship is concentration equals verified peptide mass divided by final solution volume. For an analytical aliquot, peptide mass equals concentration multiplied by aliquot volume. These relationships describe dimensional arithmetic; they do not establish a route, frequency or clinically appropriate amount. A

BUYING NOTES

Supplier documentation can be evaluated without treating it as proof of clinical suitability. A useful certificate of analysis identifies the tested batch, laboratory, methods, dates and acceptance criteria. A generic certificate or unrelated batch report cannot establish the contents of another sample. Independent testing improves traceability only when sample identity and custody are documented.

Identity, chromatographic purity and peptide content answer different questions. Mass spectrometry can support molecular identity, but interpretation requires attention to charge state, adducts and the reported mass convention. A raw mass-to-charge peak need not equal the peptide's neutral molecular weight. The sequence and stereochemistry also matter because similarly named peptides and antagonists can have different biological actions.

An HPLC area percentage describes the detected chromatographic signal under a particular method. It does not automatically equal peptide mass fraction, exclude every impurity or establish sterility. Coelution and method sensitivity affect interpretation. A bare purity percentage without method details provides limited evidence.

Net peptide content, residual water, counterions, residual solvents and related impurities require appropriate measurements. No universal percentage deduction for water and counterions is justified. Missing information means the property is unestablished; it does not prove that the manufacturer never measured it.

Sterility and endotoxin testing are separate from identity and purity testing. Their relevance depends on the intended preparation and route. A vacuum seal, intact cake, attractive packaging or cold shipment cannot substitute for validated testing. Likewise, a collapsed cake alone does not identify the peptide or quantify degradation.

Documentation can reveal gaps and inconsistencies. It cannot establish an effective fitness dose, long-term clinical benefit or legal authorization for human treatment. None of the references validates a particular commercial source or preparation.

COMMON MISTAKES

- Reading hormone concentrations as muscle outcomes. The measured growth hormone peaks in PMID 2108187 establish an acute endocrine response. They do not measure hypertrophy, strength, recovery or fat loss.
- Treating receptor-mediated hunger as either guaranteed or harmless. Appetite signaling is relevant to energy intake, but the cited GHRP-6 animal findings varied with hormonal context. Human incidence and effect size remain uncertain.
- Turning experimental metabolic inhibition into a fasting protocol. Glucose and free fatty acids can influence secretagogue responses, but the cited literature does not establish a meal interval that improves physique outcomes.
- Escalating exposure based on subjective effects. Hunger, flushing or tingling cannot identify a productive dose or a validated saturation point. A tolerated administration does not establish that repeated exposure is appropriate.
- Assuming shared receptors prove a precise combination outcome. Related secretagogues can have different endocrine profiles. Neither guaranteed synergy nor a doubled adverse-effect burden has been demonstrated for the proposed pairs.
- Expecting every repeated exposure to increase IGF-1. The short oral experiment in elderly women did not show a significant increase, while other preparations and schedules did. Route, population and exposure are material differences.
- Equating preserved pulses with absence of desensitization. The infusion study preserved pulsatile secretion while reducing the response to an additional GHRP challenge. Those findings are compatible, not contradictory.

- Generalizing an oral hormone-response curve to every route. The timing reported in PMID 1730807 describes its oral experiment. Plasma half-life, growth hormone response duration and administration frequency are different concepts.
- Treating calculator precision as preparation quality. Arithmetic can be correct while net peptide content, final volume, identity or sterility remains uncertain. An instrument scale does not establish a biologically validated amount.
- Confusing GHRP-6 with GHRP-2, hexarelin or a modified GHRP-6 antagonist. Similar names do not establish equivalent pharmacology. The removed skeletal-muscle citation illustrates why the actual administered compound must be checked.
- Treating a short healthy-volunteer experiment as long-term surveillance. Small studies cannot quantify uncommon adverse events, cancer incidence, chronic metabolic effects or outcomes during months of use.
- Assuming endogenous hormone release avoids anti-doping rules. GHRP-6 itself is explicitly prohibited at all times. Analytical detection is documented independently of any claimed performance benefit.

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Hexarelin

Examorelin

Ghrelin receptor agonist

Module 2 · Recomposition

Goals: Hypertrophy

Route: SC

WADA prohibited

A potent growth hormone secretagogue with small human studies, but no established adult muscle benefit. A 16-week study found no significant body-composition improvement.

WHAT IT IS

Hexarelin is a synthetic hexapeptide growth hormone releasing peptide, also called examorelin. Its sequence is His-D-2-methyl-Trp-Ala-Trp-D-Phe-Lys-NH₂. It belongs to the same broad secretagogue family as GHRP-2 and GHRP-6. Its endocrine activity involves the growth hormone secretagogue receptor, GHSR1a, which also responds to ghrelin (PMID 7957536, PMID 25278975).

Human investigations include acute endocrine testing, repeated administration, diagnostic studies and small pediatric growth studies. Populations included healthy adults, elderly volunteers, children with short stature and patients with hypothalamic-pituitary disorders. Other studies examined beta-thalassemia, anorexia nervosa and adult growth hormone deficiency (PMID 9814463, PMID 9364340, PMID 9231048, PMID 10443652).

The relevant adult repeated-treatment study lasted 16 weeks. Its companion report identifies 12 healthy elderly participants. Growth hormone responses became partially attenuated, while lean mass, total body fat and bone mineral density did not change significantly. IGF-1 and IGF binding protein 3 also remained statistically unchanged (PMID 9589671, PMID 10990150).

That study was not the longest human exposure reported. Small intranasal studies in prepubertal children lasted up to 8 months and 6 to 10 months. They reported increased growth velocity, and one also reported increased IGF-1. These pediatric observations cannot establish adult hypertrophy, recovery or performance benefits (PMID 8548949, PMID 8766941).

Hexarelin also has a substantial cardiovascular research literature. Much of it concerns rodent disease models, isolated hearts and cultured cells. A cardiac binding target, CD36, provides a mechanism distinct from pituitary growth hormone release. Its physiological consequences depend on the experimental setting (PMID 11988484, PMID 25278975).

For a recomposition module, the defensible framing is a studied endocrine tool with unproven adult training outcomes. Increased growth hormone release does not establish increased muscle size, strength or fat loss. The negative adult body-composition findings matter, but a small study cannot exclude every possible effect in every population.

MECHANISM

Hexarelin activates GHSR1a, a G protein coupled receptor involved in growth hormone release. Its signaling includes phospholipase C activation and intracellular calcium mobilization. These pathways support secretion from pituitary somatotrophs. Hypothalamic regulation also contributes to the response, rather than the peptide acting only at the pituitary (PMID 25278975).

Several human findings support this integrated mechanism. Hexarelin produced larger acute growth hormone responses than GHRH under the conditions tested. The magnitude varied with age and with the endpoint used. These comparisons establish pharmacological activity, not a fixed potency ratio that applies to every route or population (PMID 8126144, PMID 7962341).

Coadministration with GHRH(1-29)-NH₂ produced peak growth hormone secretion rates greater than the arithmetic sum of the separate responses. This demonstrated acute endocrine synergy in six healthy men. A

second combined challenge lost statistically demonstrable synergy, showing that the interaction depended on recent exposure (PMID 8762732).

An imaging-characterized study of growth hormone deficient patients provided another line of evidence. Patients without a visible pituitary stalk had very low responses to both hexarelin and GHRH. Patients with a residual vascular connection retained larger responses. These findings support a requirement for hypothalamic-pituitary integrity for the full effect, while underlying pituitary disease complicates causal interpretation (PMID 9814463).

Hexarelin does not bypass normal inhibitory physiology. Oral glucose and a lipid-heparin infusion reduced its growth hormone response in healthy men. These interventions suppressed the GHRH response more strongly under the same experimental conditions. Separate somatostatin studies showed that hexarelin remained susceptible to inhibition, including during combined GHRH administration (PMID 7854159, PMID 7731498, PMID 9425393).

Functional interaction with somatostatin is therefore supported, but complete blockade of somatostatin action is not. The studies do not establish a simple mechanism in which hexarelin switches off inhibitory feedback. Different challenge designs, infusion conditions and exposure intervals produced different response patterns.

Hexarelin also stimulates prolactin and the hypothalamic-pituitary-adrenal axis. Human dose-response work documented increases in prolactin and cortisol alongside growth hormone. A separate volunteer study found that CRH augmented the ACTH and cortisol response, while desmopressin did not. The authors interpreted this pattern as evidence that vasopressin release may contribute to adrenal stimulation. It was not direct proof that vasopressin explains every endocrine effect (PMID 8954038, PMID 10404825).

Feedback remains relevant. Prior recombinant growth hormone reduced the subsequent response to hexarelin. Recombinant human IGF-1 also inhibited stimulated growth hormone release, with greater reported inhibition of the hexarelin response than the GHRH response. These experiments studied specific hormones and short challenge protocols. They do not directly establish interactions with IGF-1 LR3 or chronic combinations (PMID 8548947, PMID 9920097).

The cardiac mechanism includes CD36. Investigators isolated an approximately 84 kDa binding protein from rat cardiac membranes using a photoactivatable hexarelin derivative. Its N-terminal sequence identified CD36. Hexarelin increased coronary perfusion pressure in isolated perfused hearts, and this response was absent in CD36-deficient preparations. The findings support CD36-mediated coronary vasoconstriction in that experimental system (PMID 11988484).

Other experiments found protection against ischemia-reperfusion injury in hearts from hypophysectomized rats treated with hexarelin. This supports an action that does not require pituitary growth hormone release. It does not establish that every protective effect uses CD36 exclusively or predicts clinical benefit in coronary disease (PMID 10465272).

CD36-related metabolic signaling, including proposed connections with PPARgamma, has also been investigated in experimental models. These pathways offer hypotheses about lipid handling and adipocyte biology. Their relevance to adult human recomposition remains uncertain (PMID 18288286).

EVIDENCE · GRADE C

Grade C applies to adult hypertrophy, strength and recomposition claims. Human endocrine activity is reproducible, but the available clinical evidence does not establish these training outcomes. The adult 16-week study found no statistically significant change in lean mass, total body fat or bone mineral density (PMID 9589671).

The narrow claim of acute growth hormone release has human evidence consistent with grade B: small, short pharmacology studies with controlled comparisons. Their endocrine endpoints do not upgrade the evidence for muscle gain. The placebo-controlled rising-dose study randomized placebo placement, while active doses increased sequentially for safety (PMID 7957536).

Small pediatric studies reported increased growth velocity during several months of intranasal treatment. These are human outcome data and must not be omitted. They remain limited by size, design and population. They do not demonstrate adult hypertrophy or long-term clinical safety (PMID 8548949, PMID 8766941).

The adult findings are negative evidence within one regimen, not proof that hexarelin can never affect body composition. Conversely, positive animal findings and pediatric growth observations cannot substitute for controlled trials in adults who train.

Human data. Acute studies establish substantial growth hormone releasing activity. Twelve adult men participated in a double-blind, placebo-controlled rising-dose experiment. Another study compared intravenous, subcutaneous, intranasal and oral administration in 12 healthy young volunteers. A separate investigation mapped growth hormone, prolactin and cortisol responses across increasing intravenous exposures (PMID 7957536, PMID 8126144, PMID 8954038). Mechanistic studies examined metabolic inhibition, somatostatin interactions, age-related differences and feedback from recombinant growth hormone or IGF-1. These generally involved small samples and brief observation periods. They identify physiological responses rather than durable improvements in health or performance (PMID 7854159, PMID 7731498, PMID 9425393, PMID 7962341, PMID 8548947, PMID 9920097). A 24-hour study in six healthy young men compared two and three daily subcutaneous administrations. Both schedules increased integrated growth hormone secretion and secretory burst mass to a similar extent. Neither changed IGF-1 or integrated prolactin, ACTH and cortisol secretion over that observation period. This directly contradicts claims that three daily administrations have never been studied in humans (PMID 11888836). The 16-week elderly-adult study found partial attenuation of the response to a hexarelin challenge. Mean growth hormone response area fell from 19.1 to 10.5 mcg/L/h, approximately 45 percent. Four weeks after treatment ended, it was 19.4 mcg/L/h. These measurements describe stimulated response area, not a 45 percent reduction in all daily growth hormone secretion (PMID 9589671, PMID 10990150). Lean mass, total body fat, bone mineral density, IGF-1 and IGF binding protein 3 did not change significantly. One bone formation marker, C-terminal propeptide of type I collagen, increased. A companion endocrine report found no significant increase in urinary free cortisol or prolactin response area. These related publications should not be counted as independent efficacy replications (PMID 9589671, PMID 10341859). In eight prepubertal children with short stature, intranasal treatment for up to 8 months increased reported mean growth velocity from 5.3 to 8.3 cm/year. IGF-1 also increased. Another report in seven children found increased growth velocity over 6 to 10 months despite reduced growth hormone challenge responses. The reports may include overlapping participants and should not be added together as independent large cohorts (PMID 8548949, PMID 8766941). Additional human

Animal and mechanistic data. The cardiovascular literature includes several distinct experimental settings. CD36 identification and isolated-heart perfusion experiments provide receptor-level evidence. Hypophysectomized-rat experiments support growth hormone independent protection against ischemia-reperfusion injury. Neither demonstrates reduced cardiac events in humans (PMID 11988484, PMID 10465272). Other studies examined obese Zucker rats, myocardial infarction in ghrelin knockout mice, oral exposure after mouse myocardial infarction and neuroinflammatory pathways after mouse ischemia-reperfusion. Rat investigations also addressed interleukin-1 signaling and PTEN-related pathways in cardiac injury. These studies support further investigation of context-specific cardiac actions (PMID 10974647, PMID 23861368, PMID 24747279, PMID 32403043, PMID 28321024, PMID 31091855). Vascular models include experimentally induced atherosclerosis in rats and abdominal aortic aneurysm formation in mice. These disease models cannot establish preventive benefit in healthy adults or determine the clinical significance of the isolated-heart vasoconstriction finding (PMID 19931584, PMID 34856183). Metabolic findings differ across models. Obese Zucker rats developed higher glucose and insulin concentrations during repeated treatment. Nonobese insulin-resistant MKR mice showed improved glucose and insulin tolerance, reduced triglycerides and altered body composition. Differences in species, disease biology, route and exposure limit comparisons (PMID 10974647, PMID 28977588). Muscle evidence is mixed and includes work beyond growth hormone measurements. An aged-dog study reported improvement in selected muscle indices in three of six animals. A rat skeletal muscle study found that chronic secretagogue treatment failed to restore electrical and contractile properties. Neither result establishes improved human training performance (PMID 8914494, PMID 12788817). Attenuated growth hormone responsiveness has been reported in young-adult rats and dogs. Aged dogs showed changing responses across treatment and interruption periods. These observations help characterize adaptation, but do not validate a human cycling schedule (PMID 9067986, PMID 10474131, PMID 8914494). Cell studies require separate classification. H9C2 experiments addressed angiotensin II-induced hypertrophy and doxorubicin-induced cell death. A human neuroblastoma cell model examined mutant SOD1-associated injury. These are mechanistic, grade D observations. Neonatal rat brain injury research provides animal,

studies investigated short stature, structural pituitary abnormalities, beta-thalassemia, anorexia nervosa and diagnostic testing for adult growth hormone deficiency. Their existence does not establish efficacy for bodybuilding. No controlled trial establishing improved adult strength or skeletal muscle hypertrophy was identified in this verification search (PMID 7955465, PMID 9814463, PMID 9364340, PMID 9231048, PMID 10443652).

grade C evidence for that specific model (PMID 31526442, PMID 11322493, PMID 36674509, PMID 16081643).

REGULATORY STATUS AND SPORT

STATUS

Hexarelin is an investigational growth hormone secretagogue without an identified approved human prescribing label in this review. No FDA-approved hexarelin medicine or approved dose was identified. Historical human research does not itself establish marketing authorization. The reviewed records do not support a precise claim that all development ended in the 1990s. They also do not justify certifying approval status in every jurisdiction, declaring all available material non-GMP, or asserting identical possession and importation rules worldwide. A research-use designation does not establish identity, pharmaceutical quality or suitability for human administration. Compounding eligibility depends on jurisdiction-specific rules and cannot be inferred solely from the presence or absence of an approved reference product. The literature summarized here supplies no approved treatment regimen.

WADA

Prohibited at all times, in competition and out of competition. The 2026 WADA Prohibited List explicitly names examorelin (hexarelin) under S2.2.4, growth hormone releasing factors, within the growth hormone releasing peptides group. This is an S2 classification, not S4. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Published analytical research documents detection of hexarelin-related substances in human urine (PMID 25869809). No detection interval or clearance strategy is provided. Workplace and military testing policies are separate from WADA rules and cannot be inferred from the sports classification.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Human studies used intravenous, subcutaneous, intranasal and oral administration. Subcutaneous administration was used in the adult 16-week study. Intranasal administration was used in pediatric studies lasting several months, so repeated human exposure was not limited to the subcutaneous route (PMID 9589671, PMID 8548949, PMID 8766941). The four-route study reported biological bioavailability estimates of 77.0 percent subcutaneous, 4.8 percent intranasal and 0.3 percent oral. These estimates were derived from growth hormone responses. They are not direct measurements of the fraction of intact peptide reaching systemic circulation (PMID 8126144). Oral administration produced measurable endocrine responses at the experimental exposures used. Low biological bioavailability does not mean complete inactivity. Experimental absorption research identified intestinal degradation, terminal lysine deamidation and low epithelial permeability as relevant limitations (PMID 11578108). Comparable responses under selected intravenous and intranasal test conditions do not establish a universal route-conversion factor. Formulation, population and nonlinear hormone responses affect comparisons. The doses below preserve the actual study routes rather than treating them as interchangeable.

HALF-LIFE

A directly measured human plasma elimination half-life for intact hexarelin was not established by the records retrieved in this verification. This is a limitation of the verified evidence, not proof that no such measurement exists anywhere. In rats, intravenous terminal half-life was 75.9 plus or minus 9.3 minutes. Reported systemic clearance was 7.6 mL/min/kg, and steady-state distribution volume was 744 mL/kg. Subcutaneous bioavailability was 64 percent in that animal pharmacokinetic study. Biliary excretion was prominent, with substantial recovery of unchanged peptide (PMID 10611139). A dog pharmacokinetic study reported an intravenous terminal half-life of approximately 120 minutes. Species-specific clearance and assay methods prevent treating either animal estimate as a validated human value (PMID 8545255). Human growth hormone kinetics are better documented. In the adult rising-dose study, growth hormone peaked around 30 minutes and returned to baseline within 240 minutes. The approximately 55-minute half-life described there concerns the growth hormone response, not hexarelin elimination (PMID 7957536). In a separate pediatric diagnostic study, growth hormone peaks occurred at 15 to 30 minutes after intravenous administration and 30 to 60 minutes after intranasal administration. These are pharmacodynamic observations. They do not determine an injection interval or a peptide clearance window (PMID 7955465).

TIMING Experimental metabolic conditions influence growth hormone responses. Oral glucose and a lipid-heparin infusion reduced the response to a single 2 mcg/kg IV hexarelin administration in six healthy men (PMID 7854159). These challenge conditions are not equivalent to every ordinary meal. They do not establish a clinically beneficial fasting interval. A study of eight men compared morning wakefulness with administration shortly after sleep onset. Peak growth hormone concentrations were similar, but integrated response was larger during sleep. Slower growth hormone disappearance contributed to the difference (PMID 9156035). A larger acute hormone area does not demonstrate better sleep, recovery or hypertrophy. The studies therefore describe timing effects without establishing an optimal clock time for clinical or performance outcomes. The claim that every human study dosed participants while fasting is incorrect; the IGF-1 feedback experiment explicitly described fed conditions (PMID 9920097).

CYCLE LENGTH No validated adult performance cycle has been established. The 16-week study demonstrated partial attenuation of stimulated growth hormone release, with significant reductions at weeks 4 and 16. The challenge response was not significantly different from baseline four weeks after treatment ended (PMID 9589671, PMID 10990150). This does not establish four weeks as a universal stopping threshold or prove that repeated interruption preserves clinical benefit. The measured endpoint was endocrine responsiveness. No comparison demonstrated superior muscle outcomes from continuous versus intermittent adult use. Adaptation also appeared during closely spaced acute challenges. A second hexarelin challenge after 120 minutes produced a lower peak secretion rate, while combined hexarelin-GHRH synergy was no longer statistically demonstrable after repeat administration (PMID 8762732). Aged-dog experiments documented changing responses across treatment and interruption periods, but animal scheduling cannot supply a human protocol. Pediatric intranasal treatment continued for 6 to 10 months with increased growth velocity despite attenuated challenge responses. Reduced hormone responsiveness therefore cannot automatically be equated with loss of every biological effect (PMID 8914494, PMID 8766941).

TITRATION No validated titration schedule exists for adult hypertrophy or recomposition. Human dose-response curves characterize acute hormone release and cannot define a therapeutic target for training outcomes. In one single-administration IV study, growth hormone ED50 estimates were 0.50 mcg/kg for peak concentration and 0.64 mcg/kg for integrated response (PMID 7957536). These are modeled pharmacological parameters, not prescribed doses. Peak growth hormone changed little between the upper tested exposures, but response area continued to increase. A separate single-administration IV study reported an ED50 of 0.48 mcg/kg for growth hormone and 0.39 mcg/kg for prolactin (PMID 8954038). It observed a cortisol response increase at 0.5 mcg/kg IV given once during testing (PMID 8954038). These results show overlapping endocrine effects, not a precise boundary separating useful and harmful exposure. The studies do not support the categorical statement that every higher exposure produces only cortisol and prolactin. They also do not justify converting intravenous response thresholds into a universal subcutaneous ceiling. Acute GHRH synergy is documented, but adding another agent is not an evidence-based substitute for a missing adult efficacy regimen.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Twelve adult male volunteers participated in a double-blind, placebo-controlled rising-dose study. Placebo was randomly inserted into the sequence. Mean peak growth hormone concentrations were 3.9 ng/mL with placebo and 26.9, 52.3 and 55.0 ng/mL across increasing active exposures. Peak concentration changed little between the upper exposures, while integrated growth hormone response still increased. This distinction limits blanket claims about a complete plateau.	0.5, 1 and 2 mcg/kg by IV bolus, each given as a single administration (PMID 7957536).	Intravenous bolus.	Single administration per study session, with active exposures increased sequentially across sessions.	Human double-blind, placebo-controlled rising-dose pharmacology study, PMID 7957536. Reported experimental exposures, not a treatment recommendation. · PMID 7957536

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Twelve healthy young volunteers underwent a comparison of four routes. Subcutaneous administration produced dose-related growth hormone responses. The study also documented responses after intranasal and oral administration. Biological bioavailability was estimated from hormone responses rather than direct peptide exposure measurements.	Single study administrations: 1 or 2 mcg/kg IV, 1.5 or 3 mcg/kg SC, 20 mcg/kg intranasally, or 20 or 40 mg orally (PMID 8126144).	Intravenous, subcutaneous, intranasal or oral, as separately tested.	Single administration of the assigned route and exposure per test session.	Human route-comparison pharmacology study, PMID 8126144. These exposures do not establish interchangeable route conversions. · PMID 8126144
The adult 16-week study assessed endocrine adaptation, body composition and bone measurements. A companion report identifies 12 healthy elderly participants. Growth hormone challenge response area declined significantly by weeks 4 and 16. Lean mass, total fat, bone mineral density, IGF-1 and IGF binding protein 3 did not change significantly. One bone formation marker increased (PMID 9589671, PMID 10990150).	1.5 mcg/kg per SC administration, twice daily for 16 weeks (PMID 9589671).	Subcutaneous.	Twice daily for 16 weeks, followed by an assessment four weeks after cessation.	Small human repeated-treatment study, PMID 9589671. Population and response findings are also described in PMID 10990150. These are related reports, not independent efficacy replications. · PMID 9589671
Six healthy young men underwent 24-hour endocrine profiling. Two and three daily administrations increased integrated growth hormone secretion similarly. Neither schedule significantly changed IGF-1 or integrated prolactin, ACTH and cortisol secretion during the study day. This establishes brief experimental exposure, not long-term efficacy for either schedule.	1.5 mcg/kg per SC administration, either twice or three times during a 24-hour study period (PMID 11888836).	Subcutaneous.	Two or three administrations over one day, compared as separate experimental schedules.	Human 24-hour endocrine study, PMID 11888836. No adult hypertrophy outcome was established. · PMID 11888836
Healthy adult males underwent acute testing with hexarelin and GHRH(1-29)-NH ₂ . Combined administration produced a substantial growth hormone response, a prolactin increase and no measured cortisol rise under that particular test condition. The result does not establish long-term endocrine selectivity or clinical benefit.	Hexarelin 0.125 mcg/kg IV with GHRH(1-29)-NH₂ 1 mcg/kg IV, each administered once in the combined study session (PMID 8954038).	Intravenous.	Single combined administration during an acute pharmacology session.	Human hormone dose-response and combination study, PMID 8954038. This is documentation of an experiment, not a combination recommendation. · PMID 8954038

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Eight prepubertal children with short stature received intranasal treatment for up to 8 months. Reported growth velocity and IGF-1 increased. A separate report described seven children treated for 6 to 10 months with increased growth velocity despite attenuated challenge responses. These small pediatric reports do not establish adult muscle benefit (PMID 8548949, PMID 8766941).	60 mcg/kg per intranasal administration, three times daily for up to 8 months, as reported in the primary study (PMID 8548949).	Intranasal.	Three times daily during the reported pediatric treatment period.	Small prospective pediatric treatment study, PMID 8548949. · PMID 8548949
Obese and lean male Zucker rats received repeated treatment. Cardiac protection was observed in the experimental injury setting. Glucose and insulin increased in obese animals, while somatotrophic function did not improve. The findings illustrate why cardiac and metabolic effects cannot be assumed to move in the same direction.	80 mcg/kg per SC administration, twice daily for 30 days (PMID 10974647).	Subcutaneous in rats.	Twice daily for 30 days.	Animal study, PMID 10974647. The published exposure is per administration, not the total daily amount. No direct human dose conversion is supported. · PMID 10974647
Nonobese insulin-resistant MKR mice and corresponding controls received repeated treatment. The MKR model showed improved glucose and insulin tolerance, lower triglycerides and altered body composition. These findings differ from the obese Zucker-rat results and do not predict a consistent glucose response in humans.	200 mcg/kg per intraperitoneal administration, twice daily for 12 days (PMID 28977588).	Intraperitoneal in mice.	Twice daily for 12 days.	Animal metabolic study, PMID 28977588. The verified route was intraperitoneal, not subcutaneous. · PMID 28977588
Six young adult beagle dogs underwent repeated treatment. Growth hormone challenge responses initially increased, then declined by week 6. Appetite responses followed a different time course, showing that endocrine adaptation does not necessarily predict adaptation of every effect.	250 mcg/kg per SC administration, twice daily for 6 weeks (PMID 10474131).	Subcutaneous in dogs.	Twice daily for 6 weeks.	Animal endocrine and feeding study, PMID 10474131. This exposure does not validate a human cycle or dose. · PMID 10474131
A fixed-dose pattern circulates outside clinical research. Its inclusion distinguishes an unvalidated convention from weight-based exposures actually studied. Similarity to a calculated study exposure for some body weights does not establish equivalent formulation, efficacy or safety.	Approximately 100 mcg per SC administration, one to three times daily, commonly cited in non-clinical use; not validated in trials.	Subcutaneous, as described in non-clinical reports.	One to three times daily in non-clinical reports; no validated long-term regimen accompanies this convention.	commonly cited in non-clinical use; not validated in trials. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

+ Sermorelin	Human studies tested GHRH(1-29)-NH₂, the amidated peptide corresponding to sermorelin, with hexarelin. Initial combined challenges produced greater peak growth hormone secretion than the sum of separate challenges. This demonstrates acute endocrine synergy, not superior hypertrophy or long-term safety (PMID 8762732). A separate experiment documented substantial growth hormone release with no measured cortisol increase under one combined condition, while prolactin still increased (PMID 8954038). Somatostatin infusion reduced the response even though combined stimulation remained substantial (PMID 9425393). Repeat challenges lost statistically demonstrable synergy, and age influenced combined responses in another study (PMID 8762732, PMID 7962341). These findings do not establish a repeated-use combination protocol.	- GHRP-6	Both compounds stimulate the ghrelin receptor pathway, creating potential pharmacological overlap. No controlled combination evidence was identified showing improved adult outcomes. Hexarelin alone already affects multiple hormones and can develop attenuated responsiveness (PMID 8954038, PMID 9589671). Shared receptor activity is a reason for uncertainty, not proof of a quantified interaction. This pairing also overlaps at the secretagogue receptor pathway. No verified human combination study establishes benefit or quantifies its endocrine effects. Hexarelin can increase prolactin, ACTH and cortisol, so properties attributed to another agent cannot make the combination selective (PMID 8954038, PMID 10404825). The concern is unsupported complexity and uncertain combined exposure, rather than a demonstrated clinical interaction.
+ CJC-1295	The rationale is mechanistic extrapolation from GHRH-receptor stimulation plus GHSR1a stimulation. No human hexarelin-CJC-1295 combination study was identified in this verification. Acute GHRH(1-29)-NH₂ findings cannot establish the magnitude, duration or clinical value of this specific pairing (PMID 8762732). Formulation and persistence of the GHRH analog matter because sustained stimulation differs from a brief laboratory challenge.	- Ipamorelin	The relevant human feedback study tested recombinant human IGF-1, not IGF-1 LR3. Recombinant IGF-1 reduced the subsequent hexarelin-stimulated growth hormone response, with mean reported inhibition of 57.7 percent (PMID 9920097). This supports an IGF-1 feedback mechanism but does not establish the magnitude or clinical consequences of an LR3 interaction. Different binding and persistence could change the result. Describing the specific LR3 pairing as directly proven antagonism would exceed the evidence.
+ Tesamorelin	Complementary receptor activity provides a theoretical rationale, but no hexarelin-tesamorelin combination study was identified. Evidence obtained with one GHRH analog or in a specific disease population cannot establish benefit from adding hexarelin. The acute GHRH(1-29)-NH₂ interaction is the relevant experimental precedent, with different molecules and exposure conditions (PMID 8762732). No combined dose, endocrine selectivity or adult muscle outcome is established here.	- IGF-1 LR3	

COMMON EFFECTS

Reliable adverse-effect frequencies cannot be estimated from the small, heterogeneous studies. A volunteer study measured a small acute increase in appetite. Acute prolactin, ACTH and cortisol elevations are better documented than a consistent symptom profile (PMID 10404825, PMID 8954038). Flushing, headache, tingling, sweating and injection-site symptoms should not be presented as quantified common hexarelin effects without study-specific reporting. Fluid retention, joint discomfort and altered glucose regulation are concerns associated with growth hormone axis stimulation. Their incidence under any particular hexarelin regimen remains uncertain (PMID 28400207). Short-term tolerability and absence of prominent reported symptoms do not establish long-term safety. The available studies were not designed to detect uncommon adverse events or risks arising over years.

SERIOUS SIGNALS

Acute adrenal and prolactin effects are established in humans. Their long-term consequences remain uncertain. In the adult repeated-treatment report, urinary free cortisol, basal cortisol and prolactin response area did not increase significantly. Cortisol response area decreased during treatment. Those findings concern one small study and cannot exclude uncommon or population-specific endocrine harm (PMID 8954038, PMID 10404825, PMID 10341859). Metabolic effects are not consistently favorable across models. Repeated treatment raised glucose and insulin in obese Zucker rats, while MKR mice showed improved tolerance measures. The direction and clinical importance in an insulin-resistant adult cannot be predicted from either model alone (PMID 10974647, PMID 28977588). The CD36 finding requires balanced interpretation. Hexarelin increased coronary perfusion pressure in isolated hearts, consistent with vasoconstriction. This is a preclinical signal, not proof that hexarelin causes coronary vasospasm in humans. Conversely, protective findings in rodent injury models do not establish benefit or safety in people with coronary disease (PMID 11988484, PMID 10465272). The human evidence includes longer pediatric exposure, so the safety record cannot be described as ending at 16 weeks. Nevertheless, these cohorts were small and provide limited information about rare events, cardiovascular outcomes or cancer incidence (PMID 8548949, PMID 8766941, PMID 28400207). Growth hormone and IGF-1 signaling create reasons for caution in active malignancy and proliferative disease. The hexarelin literature does not quantify those risks. Claims that it either causes cancer or has no cancer risk would go beyond the evidence.

CONTRAINDICATIONS

No approved hexarelin label defines formal contraindications. The following are precautionary clinical exclusions based on endocrine biology, class concerns and missing evidence, rather than a validated hexarelin contraindication list. Active or suspected malignancy, proliferative diabetic retinopathy, uncontrolled diabetes, known hyperprolactinemia or prolactinoma, and unstable pituitary or adrenal disease warrant particular concern. Prior cancer requires individualized specialist assessment rather than an assumption that all histories carry identical risk. Pregnancy and breastfeeding lack adequate safety evidence. Existing coronary disease also requires caution because clinical cardiovascular safety has not been established; isolated-heart vasoconstriction alone does not prove a human contraindication. Significant renal or hepatic disease may alter exposure, but a validated dose-adjustment framework is absent. Historical pediatric research does not support unsupervised use in children. WADA prohibition is an eligibility rule for covered athletes, not a medical contraindication. Occupational testing policies require separate interpretation.

STOP RULES

Chest pain, severe breathlessness, fainting, or a severe new headache with visual change warrants urgent medical assessment. Suspected severe allergic reactions also require emergency care. New edema, rapid unexplained weight gain, persistent hand numbness, marked joint symptoms, unusual thirst, frequent urination or blurred vision warrants discontinuation of unapproved exposure and clinical review. Galactorrhea, menstrual change or persistent sexual symptoms warrants assessment for endocrine disturbance. These are precautionary symptom rules, not evidence that each event has a documented hexarelin-specific incidence. A weaker perceived response does not diagnose receptor desensitization, justify escalation or establish product identity. Human adaptation findings cannot replace clinical evaluation.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved hexarelin presentation or standardized vial strength established by these references. Nominal container content, net peptide content, counterion content and actual recoverable peptide are different quantities. A small lyophilized deposit or film does not prove that a container is correctly filled. Visual appearance also cannot establish molecular identity, potency, sterility or endotoxin control. Conversely, appearance alone cannot establish underfilling. A research product's stated mass should be interpreted alongside its analytical method and whether the result describes peptide content or total material. No particular vial strength is endorsed as typical or suitable for human administration.

peptides cannot supply formulation-specific compatibility evidence. A preservative-containing diluent does not sterilize contaminated powder, remove endotoxin or establish stability after mixing. Sterile water and saline are not automatically interchangeable for every formulation. Relevant variables include pH, peptide solubility, adsorption, container compatibility and preservative effects. Clear appearance does not demonstrate sterility or correct potency. Visible particles, unexpected discoloration or precipitation indicates a quality concern, but the absence of those findings does not establish suitability. No preparation or injection procedure is supplied.

STORAGE

No validated shelf life for a home-reconstituted hexarelin preparation was established by the retrieved studies. A generic refrigerated temperature range or preservative convention cannot establish an expiry date for an unspecified formulation. Storage specifications require formulation-specific evidence about chemical integrity, potency, microbiological quality, container closure and handling conditions. Stability of dry material does not automatically predict stability in solution. Repeated opening and temperature cycling introduce additional variables. Animal recovery of unchanged peptide in bile or urine is evidence about biological disposition, not refrigerator stability. Intestinal degradation experiments likewise do not establish storage limits for a prepared solution (PMID 10611139, PMID 11578108). A clear solution may still be contaminated or degraded. Visible deterioration is a rejection signal, but normal appearance cannot validate continued suitability. No unsupported beyond-use period is assigned.

Hypothetical concentration arithmetic only, with no route or administration frequency because this is not a dosing example. A sample containing 2 mg of actual peptide contains 2000 mcg. If its final solution volume is 2 mL, the calculated concentration is 1000 mcg/mL. These are assumed example quantities, not a marketed presentation or validated formulation.

If the same hypothetical peptide mass instead occupies a final volume of 1 mL, the calculated concentration is 2000 mcg/mL. The concentration doubles because the final volume halves. The peptide mass does not change.

The governing relationships are concentration equals peptide mass divided by final volume, and peptide mass equals concentration multiplied by volume. Final solution volume is the relevant quantity; an amount of added solvent is not always identical to final volume.

These calculations assume complete dissolution, correct starting peptide content and no loss to surfaces or degradation. They cannot verify those assumptions. Analytical purity reported as chromatographic area percent does not establish how much peptide is present in the container.

Mass units, volume units and biological activity units answer different questions. A volume marking does not establish an approved hexarelin activity unit or a validated administered amount. The original example's rule that a particular fraction of a syringe must indicate an error was incorrect; the relationship depends on concentration and intended mass.

BUYING NOTES

The quality question is whether documentation establishes identity, content and contamination control for a specific lot. The words research grade, pharmaceutical grade or high purity do not answer those questions by themselves. The absence of an approved hexarelin label also prevents comparison with a validated marketed presentation in this review. A meaningful certificate identifies the tested lot, laboratory, date, analytical methods and reported specifications. Traceability matters because an authentic report can still concern a different sample. Independent testing can strengthen confidence in particular measurements, but it does not establish clinical efficacy or regulatory approval. Mass spectrometry can support molecular identity. A matching nominal mass alone does not fully establish sequence, stereochemistry, purity or absence of an isomeric impurity. Orthogonal analytical methods may be necessary. The claim that only mass spectrometry can distinguish members of the family is too categorical. HPLC or related chromatography can characterize a purity profile. Area percent is method-dependent and does not by itself measure net peptide content, biological potency or all contaminants. Water, counterions, residual solvents and analytical response differences can affect interpretation of a stated powder mass. Sterility and endotoxin are separate quality attributes. A chemical purity result cannot substitute for either. Even favorable test results cannot retroactively validate manufacturing controls, transport conditions or handling after testing. No evidence was retrieved showing that hexarelin is more frequently substituted than related peptides. The practical educational distinction is between documented measurements and unsupported assurances, without treating any certificate as permission for human administration.

- Equating a growth hormone pulse with muscle growth. The adult 16-week study found no significant improvement in lean mass or total body fat. Acute endocrine activity establishes a mechanism, while adult hypertrophy remains unproven (PMID 9589671).
- Describing the adult study as proof that hexarelin has no biological effects. It measured several endpoints, including one bone formation marker that increased. Small pediatric studies also reported increased growth velocity and IGF-1. Those findings require their own population-specific interpretation (PMID 9589671, PMID 8548949).
- Claiming that no human study exceeded 16 weeks or used repeated intranasal treatment. Pediatric reports describe treatment for up to 8 months and 6 to 10 months. They remain small and do not establish adult performance benefit (PMID 8548949, PMID 8766941).
- Treating a nearly flat peak growth hormone curve as proof that integrated hormone exposure cannot increase. Peak concentration and response area behaved differently in the rising-dose study. The data do not define a universal threshold above which only adverse hormones rise (PMID 7957536, PMID 8126144).
- Converting attenuated challenge responsiveness into a validated cycling rule. The adult study documented reversible adaptation, but did not compare cycling strategies or establish a muscle-benefit threshold. Pediatric growth velocity increased despite reduced challenge responses (PMID 9589671, PMID 8766941).
- Calling three daily administrations completely unstudied. A 24-hour human study directly compared two and three subcutaneous administrations. Both increased growth hormone secretion similarly, without establishing durable clinical benefit (PMID 11888836).
- Presenting shared-receptor combinations as proven ineffective or proven to accelerate desensitization. Those specific claims require combination studies. Hexarelin's individual endocrine effects and adaptation do not quantify every possible pairing (PMID 8954038, PMID 9589671).
- Treating recombinant IGF-1 feedback data as a direct IGF-1 LR3 interaction study. The human experiment used recombinant human IGF-1. Its findings support a feedback mechanism, while LR3-specific consequences remain extrapolated (PMID 9920097).
- Reading only the favorable cardiac experiments. Rodent injury models reported protection, while isolated-heart experiments showed CD36-associated coronary vasoconstriction. Neither finding establishes clinical cardiovascular benefit or a quantified human event risk (PMID 10465272, PMID 11988484).
- Assuming unchanged IGF-1 proves treatment failure, product authenticity or absence of endocrine activity. Adult studies reported growth hormone changes without increased IGF-1, while a pediatric study reported an increase. Population, duration and endpoint all matter (PMID 9589671, PMID 11888836, PMID 8548949).
- Turning metabolic challenge experiments into a universal fasting instruction. Oral glucose and lipid-heparin infusion reduced stimulated growth hormone, but no verified study established a meal-timing strategy that improves hypertrophy. Not every human experiment used fasting conditions (PMID 7854159, PMID 9920097).
- Treating biological bioavailability calculated from growth hormone responses as measured systemic peptide absorption. The human route study used an endocrine readout. The animal pharmacokinetic measurements answer a different question and cannot be substituted for human exposure data (PMID 8126144, PMID 10611139).
- Confusing growth hormone disappearance with hexarelin elimination. The approximately 55-minute value in the adult rising-dose report concerns the hormone response. Rat and dog peptide half-lives are animal measurements (PMID 7957536, PMID 10611139, PMID 8545255).
- Assuming a certificate, a clear solution or a familiar diluent establishes pharmaceutical quality. Identity, net content, sterility, endotoxin and formulation stability are separate questions. None can be inferred from appearance alone.
- Treating interruption of use as permission under anti-doping rules. Hexarelin is explicitly prohibited at all times under WADA S2.2.4. Analytical research confirms detectability, but does not create a permitted use interval (PMID 25869809).

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Sermorelin

GRF 1-29, Geref

GHRH analog

Module 2 · Recomposition

Goals: Hypertrophy, Sleep

Route: SC

WADA prohibited

A short GHRH fragment with historical diagnostic and pediatric approvals, small adult endocrine studies, unproven physique benefits, and an explicit WADA prohibition.

WHAT IT IS

Sermorelin is the amidated first 29 amino acids of human growth hormone-releasing hormone, also written GHRH(1-29)-NH₂ or GRF(1-29)-NH₂. It is supplied as the acetate salt. The fragment retains the biological activity needed to stimulate pituitary GH release (Prakash 1999, PMID 18031173).

Its historical clinical roles were testing pituitary GH reserve and treating selected children with idiopathic GH deficiency. Those indications required functioning pituitary somatotrophs. A response to sermorelin does not establish that the entire hypothalamic-pituitary axis functions normally. Direct pituitary stimulation can produce a normal response despite deficient hypothalamic signaling.

Its placement under Hypertrophy and Sleep reflects topics readers encounter, rather than established indications. Adult studies measured GH secretion, IGF-I, selected strength tests, and body composition in small groups of older people. Related GHRH experiments examined sleep architecture under laboratory conditions. The retrieved evidence does not establish muscle growth, improved recovery, or better sleep from subcutaneous sermorelin in trained adults with normal GH function. Historical approval and current adult performance claims therefore require separate judgments.

MECHANISM

Established receptor biology. Sermorelin stimulates the GHRH receptor on pituitary somatotrophs. Receptor activation engages Gs, increases cyclic AMP, and activates pathways supporting GH secretion and synthesis. Calcium-dependent secretion and transcriptional regulation contribute at different timescales. GHRH signaling also influences somatotroph development and maintenance (Mayo 2000, PMID 11036940).

An intact pituitary response is necessary. Sermorelin supplies a releasing signal rather than GH itself. Somatostatin and feedback from the GH-IGF-I axis continue to influence the response. These controls do not guarantee normal IGF-I concentrations or prevent adverse effects. Preserved feedback is a physiological distinction, not evidence of a fixed safety ceiling.

Exposure pattern matters. Corpas used 0.5 mg or 1 mg SC twice daily for 14 days per treatment period (PMID 1379256). Significant increases in integrated GH and IGF-I occurred only in the higher-dose period. Vittone used 2 mg SC once nightly for 6 weeks and found increased nocturnal GH without increased IGF-I (PMID 9005976). These were different studies, so their comparison cannot establish an optimal frequency. It does show that more GH release does not consistently translate into more IGF-I or improved body composition.

Circulating peptide exposure is brief. Soule measured a disappearance half-time of 4.3 minutes after IV infusion of unmodified GHRH(1-29)-NH₂ (PMID 7962295). Wilton found that stimulated GH remained elevated for approximately 3 hours despite rapid peptide elimination (PMID 8329825). Peptide half-life and downstream hormone duration describe different processes.

Sleep effects are context-dependent. Laboratory GHRH administration altered sleep according to timing, age, and sex. These findings do not establish that bedtime SC sermorelin reaches relevant central sites or improves everyday sleep quality. A plausible sleep mechanism remains separate from demonstrated treatment benefit.

EVIDENCE · GRADE B

Grade B applies to adult endocrine effects: small, short human studies demonstrate changes in GH secretion, with inconsistent IGF-I responses. Historical approved diagnostic and pediatric indications belong to the product's A category, but that status does not transfer to adult performance claims. Hypertrophy and

recomposition claims are C because human outcome evidence is insufficient. Laboratory sleep findings concern GHRH preparations and protocols that do not validate SC sermorelin for insomnia or recovery. A narrative review summarizes these gaps but supplies no new efficacy trial (Dominikowski 2026, PMID 42395176).

Human data. Adults. Corpas studied 10 healthy older men in a randomized treatment-order crossover, with 9 young men providing baseline comparisons. Regimens were 0.5 mg and 1 mg SC twice daily for 14 days each (PMID 1379256). Only the higher regimen significantly increased mean 24-hour GH, peak measures, and IGF-I relative to older participants' baseline values. Fasting glucose, urinary C-peptide, and blood pressure did not change. Body recomposition was proposed as a future research question, not demonstrated. Vittone studied 11 men aged 64 to 76 with low baseline IGF-I. Participants received 2 mg SC once nightly for 6 weeks without a concurrent control group (PMID 9005976). Nocturnal GH increased, while IGF-I and DEXA measurements of muscle and fat did not. Two of six strength measures improved, alongside a separate abdominal endurance test. These exploratory findings cannot exclude practice effects, chance, or other uncontrolled influences. Related analog evidence. Khorram studied 19 older adults after a placebo period, followed by 10 mcg/kg SC once nightly for 16 weeks (PMID 9360512). The compound was [norleucine27]GHRH(1-29)-NH₂, a modified analog rather than sermorelin. Integrated GH and IGF-I increased, and immune laboratory measurements changed. The study does not establish fewer infections, improved longevity, or the same response to sermorelin. Sleep. Kerkhofs administered GHRH 0.3 mcg/kg as a single IV bolus during specified sleep stages on experimental nights (PMID 8476038). Early administration increased REM sleep; later administration reduced wakefulness and increased slow-wave sleep. Guldner administered GHRH 50 mcg IV per pulse, four pulses during an experimental night, in 13 seniors (PMID 9390775). Awakenings decreased, with weaker effects than previously observed in young subjects. Antonijevic reported increased non-REM sleep in men and decreased non-REM sleep in women, including controls and patients with depression (PMID 11382894). None establishes improved sleep from SC sermorelin. Children. Thorner enrolled 110 previously untreated prepubertal children, with 86 eligible for efficacy analysis. Treatment was 30 mcg/kg SC once daily at bedtime for up to 12 months (PMID 8772599). Mean height velocity increased from 4.1 cm/year at baseline to 8.0 at 6 months and 7.2 at 12 months. Neyzi randomized 43 children across three groups. Sermorelin regimens were 30 or 60 mcg/kg/day SC, each divided into three daily doses, for 6 months (PMID 8329826). The higher-dose group had greater

Animal and mechanistic data. Rat studies mainly characterize exposure and degradation. Rafferty administered a single 10 mcg IV bolus per anesthetized rat and compared exposure after SC administration (PMID 2866222). Distribution and elimination half-lives were approximately 1.9 and 10.4 minutes. Estimated SC systemic exposure was approximately 4 percent of IV exposure. A later study reported an IV half-life of 6.2 minutes and SC bioavailability of 5.1 percent for the parent fragment. Several potency-enhancing substitutions did not materially improve resistance to degradation in that experiment (Rafferty 1988, PMID 2896343). These results do not establish human SC bioavailability or justify a human dose multiplier. Species, assays, formulations, and administration conditions differ. Receptor biology supports biological plausibility, but the cited animal studies do not demonstrate muscle hypertrophy in trained, GH-replete adults.

height velocity than the lower-dose group. Neither study establishes adult hypertrophy.

REGULATORY STATUS AND SPORT

STATUS

Historically FDA-approved for diagnostic testing and selected pediatric GH deficiency. Diagnostic approval dated to 1990 and treatment approval to 1997. Discontinuation notices occurred in 2008; FDA withdrew both approvals effective June 18, 2009. In 2013, FDA determined that the products had not been withdrawn for safety or effectiveness reasons. The determination allowed consideration of generic applications meeting other requirements. It did not approve adult performance indications or present-day compounded formulations. Source: [FDA withdrawal determination, March 4, 2013](<https://www.govinfo.gov/content/pkg/FR-2013-03-04/html/2013-04827.htm>). Compounded preparations require separate consideration of applicable federal and state requirements. Historical approval does not establish the legality, quality, or clinical appropriateness of every current preparation. No FDA-approved indication for adult anti-aging, physique enhancement, or sleep improvement was identified in this review. Regulatory status outside the United States was not comprehensively assessed.

WADA

Prohibited at all times, in and out of competition, under the 2026 WADA Prohibited List. Sermorelin is explicitly named in S2.2.4, Growth Hormone Releasing Factors. S2 substances are non-Specified Substances. A prescription or a short plasma half-life does not independently remove this prohibition. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

SC administration was used in the cited adult treatment studies and pediatric growth studies. IV administration was used for diagnostic assessment, pharmacokinetic studies, and laboratory endocrine experiments. The statement that IV administration was diagnostic only was incorrect. Intranasal delivery was also investigated in healthy men, with low measured bioavailability (Wilton 1993, PMID 8329825). The retrieved evidence does not establish an effective oral formulation or interchangeable exposure across routes.

HALF-LIFE

Soule measured a 4.3-minute disappearance half-time for GHRH(1-29)-NH₂ after IV infusion in healthy men (PMID 7962295). This is a study-specific human estimate, not a universal half-life for every compounded formulation or route. Rat estimates included an approximately 10.4-minute terminal phase in one experiment and 6.2 minutes in another (PMIDs 2866222 and 2896343). Wilton observed stimulated GH elevation for approximately 3 hours after IV administration (PMID 8329825). That hormone response does not mean the peptide remained at active concentrations throughout the same interval.

TIMING

Bedtime administration was used in the Thorner pediatric study and the Vittone adult study (PMIDs 8772599 and 9005976). Corpas used twice-daily administration, while Neyzi divided the daily total into three administrations (PMIDs 1379256 and 8329826). Laboratory sleep responses depended on the sleep stage at administration (Kerkhofs 1993, PMID 8476038). This does not establish a bedtime advantage for SC treatment. No retrieved trial directly compared meal spacing strategies for adult sermorelin treatment. Factors that alter a diagnostic GH response cannot establish that a particular fasting interval improves long-term treatment outcomes.

CYCLE LENGTH

The directly cited adult sermorelin studies lasted 14 days per treatment period and 6 weeks (PMIDs 1379256 and 9005976). The 16-week study used a norleucine-substituted analog, not sermorelin (PMID 9360512). Pediatric treatment studies lasted 6 or 12 months, and the review described longer observation in a few children (PMIDs 8329826, 8772599, and 18031173). These durations describe study designs, not validated cycles. They do not define an effective adult maintenance interval, a necessary break, or an acceptable lifetime exposure. The statement that no adult study anywhere exceeded four months was too broad for the search performed. Five-days-on, two-days-off schedules and repeated multi-month blocks lack validation in the cited trials.

TITRATION

No validated titration schedule for adult physique or sleep goals was identified. Corpas compared 0.5 mg and 1 mg SC twice daily in separate 14-day periods, not incremental self-adjustment (PMID 1379256). Statistical significance only in the higher-dose period does not establish an individual treatment threshold. Pediatric weight-based research doses cannot be transferred to adults by simple arithmetic. Differences in age, diagnosis, endogenous GH reserve, formulation, and study endpoints affect interpretation. Integrated GH sampling and IGF-I describe endocrine responses, while body composition and function require separate measurements. A single random GH concentration is difficult to interpret because secretion is pulsatile. Higher hormone measurements alone do not establish a better clinical outcome.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human pediatric study, previously untreated prepubertal GH deficiency	30 mcg/kg per dose, documented in Thorner 1996, PMID 8772599	SC	Once daily at bedtime for up to 12 months	Multicenter open-label study enrolling 110 children, with 86 eligible for efficacy analysis. Descriptive research exposure, not an adult regimen. · PMID 8772599
Historical diagnostic assessment of pituitary GH reserve	1 mcg/kg per dose, documented in Prakash 1999, PMID 18031173	IV	Single administration during a diagnostic test	Review of sermorelin diagnostic use. A normal response cannot exclude GH deficiency caused by a hypothalamic deficit. · PMID 18031173
Human trial, endocrine responses in healthy older men	0.5 mg or 1 mg per dose, documented in Corpas 1992, PMID 1379256	SC	Twice daily for 14 days per treatment period, with an intervening 14-day untreated period	Randomized treatment-order crossover. Significant increases in integrated GH and IGF-I occurred only during the higher-dose period. · PMID 1379256
Human trial, muscle function and body composition in older men	2 mg per dose, documented in Vittone 1997, PMID 9005976	SC	Once nightly for 6 weeks	Uncontrolled study of 11 men. Nocturnal GH increased, but IGF-I and DEXA body composition did not. · PMID 9005976
Human pediatric randomized dose comparison	30 or 60 mcg/kg/day total, documented in Neyzi 1993, PMID 8329826	SC	Daily total divided into three doses for 6 months	Three-group study in children with hypothalamic GH deficiency. These totals were not once-daily doses and do not define adult dosing. · PMID 8329826
Animal pharmacokinetics in anesthetized rats	10 mcg per animal, documented in Rafferty 1985, PMID 2866222	IV bolus	Single administration	Immunoreactivity-based pharmacokinetic study. The separate SC exposure comparison does not establish human SC bioavailability. · PMID 2866222
Non-clinical dosing descriptions, not clinical evidence	200 to 500 mcg per dose, commonly cited in non-clinical use; not validated in trials	SC	Once nightly; commonly cited in non-clinical use; not validated in trials	Describes a circulating convention. No validated efficacy, safety, titration, or cycling schedule is established by this range.

STACKING

+ GHRP-6	An acute human experiment demonstrated synergistic GH release with GHRP-6 and GHRH(1-44)-NH ₂ (Bowers 1990, PMID 2108187). It did not test sermorelin. Different receptor pathways provide a mechanistic rationale for interaction, but an acute GH peak does not establish better physique outcomes. The study also observed prolactin and cortisol increases with the highest GHRP exposure. It does not validate chronic SC combination treatment.	– CJC-1295	Both compounds engage GHRH-receptor signaling, and the retrieved evidence does not demonstrate a benefit from combining them. Longer exposure can complicate interpretation of GH and IGF-I responses. Receptor overlap does not prove that GH becomes continuously secreted or that every combination necessarily raises IGF-I. The concern is unvalidated overlapping exposure.
+ GHRP-2	A review describes strong GH release with GHRP-2, but its explicitly described combination experiment used GHRP-1 with GHRH(1-44)-NH ₂ (Bowers 1993,	– Tesamorelin	Another GHRH-receptor agonist adds overlapping pharmacology. No comparative or combination trial establishing an advantage for sermorelin plus tesamorelin was identified. Benefits established for a different

	PMID 8374685). It cannot verify a sermorelin plus GHRP-2 regimen. Class-based synergy remains a hypothesis for this specific pairing, with uncertain endocrine and metabolic trade-offs.	
+ Ipamorelin	Different receptor targets suggest a possible interaction, but no human trial of sermorelin plus ipamorelin was identified. Claims of a preferred pairing or reliably lower adverse effects are unsupported here. The narrative review highlights uncertainty around combination practices and exposure in non-clinical use (Dominikowski 2026, PMID 42395176). Mechanistic complementarity does not establish clinical benefit.	compound and indication cannot validate this pairing. Resulting exposure and adverse effects would require evidence beyond receptor theory. An exogenous IGF-I analog adds downstream signaling that pituitary feedback does not directly control. Hypoglycemia and excessive growth signaling are concerns, while human evidence for this combination is absent. The narrative review distinguishes plausible risks from demonstrated clinical event rates (Dominikowski 2026, PMID 42395176). Neither an efficacy advantage nor a protective feedback ceiling is established.
	– IGF-1 LR3	

SAFETY

COMMON EFFECTS

Transient flushing and injection-site pain are documented sermorelin adverse effects (Prakash 1999, PMID 18031173). Their frequency depends on preparation, route, population, and observation method. The flushing rate from the Bowers experiment involved GHRH(1-44)-NH₂ and cannot be presented as a sermorelin-specific rate. The small Corpas and Vittone studies reported no significant deterioration in the metabolic measurements they assessed (PMIDs 1379256 and 9005976). This does not exclude uncommon events or problems during longer treatment. A normal short-term glucose result does not establish protection against later dysglycemia.

SERIOUS SIGNALS

The cited studies are too small and short to estimate uncommon or delayed harms. GH-IGF-I excess can plausibly contribute to fluid retention, joint symptoms, nerve-compression symptoms, and impaired glucose regulation. These are class concerns, not established sermorelin-specific event rates (Dominikowski 2026, PMID 42395176). Repeated administration of PEG-conjugated GHRH impaired glucose tolerance in some older participants (Munafo 2005, PMID 16061831). That modified compound provides adjacent evidence, rather than a direct estimate for sermorelin. Growth signaling also creates concern in the presence of malignancy. The retrieved trials neither establish a cancer risk magnitude nor exclude one. An absence of reported serious events is not equivalent to evidence that serious events cannot occur.

CONTRAINDICATIONS

The historical Irish Geref 50 diagnostic label lists hypersensitivity and pregnancy or lactation as contraindications. Diabetes and epilepsy require caution. Source: [Geref 50 historical product characteristics](https://assets.hpra.ie/products/Human/16600/LicenseSPC_PA0285-006-001_13072006155719.pdf). Active malignancy, unexplained elevated IGF-I, or suspected pituitary disease requires specialist assessment because of growth-signaling concerns. These should not be misrepresented as verbatim contraindications from an unverified US treatment label. A history of malignancy also requires individualized assessment, rather than an invented universal rule. Thyroid disease and medications affecting GH secretion can confound interpretation. These clinical considerations are separate from sports eligibility.

STOP RULES

Breathing difficulty, facial or throat swelling, fainting, or chest pain after exposure warrants urgent medical assessment. Persistent thirst or polyuria, significant edema, progressive numbness, severe headache with visual symptoms, or spreading local inflammation warrants prompt evaluation before further exposure. Repeated IGF-I elevation above the age-adjusted reference range calls for clinical reassessment, not automatic dose adjustment from a calculator. A new mass, unexplained weight loss, or change in a known lesion also requires investigation. These are general clinical escalation criteria, not a trial-validated sermorelin stopping algorithm. The evidence does not justify waiting an arbitrary week for significant symptoms to resolve.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no universal present-day compounded vial size. Historical treatment presentations contained 0.5 mg or 1 mg sermorelin base per vial; the diagnostic presentation contained 50 mcg per ampoule. These were container contents, not interchangeable administration doses. Current

label strength, net peptide content, final concentration, and formulation require separate interpretation. A total vial mass alone cannot establish the amount delivered in a measured volume.

SOLVENT

The historical Irish Geref 50 diagnostic label supplied 0.9 percent sodium chloride and specified preparation immediately before use. It did not describe universal multidose preparation with bacteriostatic water. Source: [Geref 50 historical product characteristics] (https://assets.hpra.ie/products/Human/16600/LicenseSPC_PA0285-006-001_13072006155719.pdf). Solvent compatibility and handling conditions are formulation-specific. A preservative does not establish chemical stability or correct an unsuitable preparation.

STORAGE

The historical Irish Geref 50 label specified 2 to 8 C storage and light protection, with immediate preparation and disposal of unused solution. Source: [Geref 50 historical product characteristics] (https://assets.hpra.ie/products/Human/16600/LicenseSPC_PA0285-006-001_13072006155719.pdf). Present-day compounded preparations need their own storage instructions and supported beyond-use dates. Neither room-temperature shipping tolerance nor a universal 28-day refrigerated lifetime was established by the retrieved evidence. Visible particles or discoloration indicate a quality problem; a clear appearance does not establish sterility or retained potency.

Dimensional example only. Suppose a formulation has an independently established concentration of 2000 mcg/mL. This assumed concentration is not a preparation recipe or evidence of compatibility. The relationship is volume in mL equals mass in mcg divided by concentration in mcg/mL.

Corpas studied 0.5 mg, equivalent to 500 mcg, SC twice daily for 14 days per treatment period (PMID 1379256). At the hypothetical concentration above, that study mass corresponds arithmetically to 0.25 mL. This calculation does not transfer the study regimen to the reader or validate the hypothetical formulation.

At an independently established concentration of 1000 mcg/mL, the same Corpas study mass corresponds to 0.50 mL. The mass has not changed; the concentration and resulting volume have. This distinction is the purpose of the example.

A syringe marking is a volume scale, not a unit of sermorelin biological activity. IU, mcg, and mL are not interchangeable. A label expressed as total vial contents also differs from a label expressed as concentration. Gross powder weight can include counterions, residual water, and excipients, so it cannot automatically serve as the numerator.

Correct arithmetic does not establish identity, sterility, stability, or an appropriate clinical dose. A discrepancy between label concentration and independently calculated concentration requires clarification of the formulation. Reusing a volume from another preparation can change the delivered mass even when both labels carry the same peptide name.

BUYING NOTES

Documentation quality matters independently of marketing terminology. A preparation's dispensing label, legal status, measured content, sterility controls, and stability evidence answer different questions. Historical approval of the molecule does not establish that a current formulation is equivalent to the historical drug.

A certificate of analysis is informative only within its stated scope. Relevant details include the laboratory, methods, tested material, sampling date, and lot identifier. Mass spectrometry can support molecular identity. A chromatographic purity percentage describes detected components under that method; it does not automatically establish net peptide content, total vial mass, or potency.

Sterility and bacterial endotoxin testing are separate assessments. A report for bulk powder does not necessarily characterize the finished preparation. Neither test alone validates storage after preparation. A matching lot number improves traceability but cannot prove that the sampled material represents every unit.

Preblended preparations create additional uncertainty because each component requires its own identity and content assessment. They also make attribution of effects and adverse reactions more difficult. The narrative review identifies uncertainty in composition, dose, and combination practices as recurring problems in unregulated supply chains (Dominikowski 2026, PMID 42395176). An analytical certificate cannot substitute for evidence that the proposed clinical use works.

COMMON MISTAKES

- Treating historical pediatric approval as proof of adult hypertrophy. The relevant older-men study found no DEXA muscle or fat change (PMID 9005976).
- Reporting the Vittone results as three improved strength measures. Two strength measures improved, plus a separate endurance test, in an uncontrolled study (PMID 9005976).
- Treating modified GHRH analogs as identical to sermorelin. The norleucine-substituted and PEG-conjugated compounds have separate identities and evidence (PMIDs 9360512 and 16061831).
- Converting IV sleep-laboratory findings into a claim that bedtime SC sermorelin improves sleep. Preparation, route, timing, population, and outcome differ.
- Reading greater GH release as demonstrated muscle gain. Integrated GH, IGF-I, strength, and body composition are separate endpoints.
- Calling a study's statistically nonsignificant result proof of no biological effect. Small samples can miss effects, and statistical thresholds do not define individual dosing thresholds.
- Reading the non-clinical range as trial-derived dosing. The reported 200 to 500 mcg SC once nightly is commonly cited in non-clinical use; not validated in trials.
- Copying a measured volume between preparations. Delivered mass depends on concentration, while vial contents and final solution volume are different quantities.
- Assuming retained feedback guarantees protection from excessive growth signaling. Feedback influences responses but does not establish a clinical safety ceiling.
- Calling two GHRH agonists a proven synergy. Receptor overlap alone does not demonstrate a beneficial combination.
- Assuming the FDA withdrawal determination approved contemporary compounding practices or adult performance uses. Those conclusions do not follow from the notice.
- Ignoring sports rules because the peptide is short-lived or prescribed. Sermorelin remains explicitly prohibited under WADA S2.2.4.

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Tesamorelin

Egrifta

GHRH analog

Module 2 · Recomposition

Goals: Fat loss, Hypertrophy

Route: SC daily

WADA prohibited

A stabilized GHRH analog approved to reduce excess abdominal fat in adults with HIV-associated lipodystrophy, with clinically important IGF-1 and glucose risks.

WHAT IT IS

Tesamorelin is a synthetic 44-amino-acid analog of human growth hormone-releasing hormone, GHRH. A trans-3-hexenoyl modification on its N-terminal tyrosine increases resistance to dipeptidyl peptidase-4 degradation. Preclinical studies demonstrated slower degradation and prolonged exposure compared with native GHRH, supporting its development as TH9507 (PMID 17214611).

Its approved indication is reduction of excess abdominal fat in adults with HIV-associated lipodystrophy. This is a specific clinical population, often receiving antiretroviral therapy. Approval does not establish efficacy for general weight management, athletic performance, muscle hypertrophy, cognitive enhancement, or longevity.

The original formulation and subsequent Egrifta SV and Egrifta WR formulations have different labeled doses, preparation requirements, and pharmacokinetics. Published trial doses must be interpreted alongside the formulation studied. A numerical dose from the historical trials cannot automatically be transferred to another presentation. Trials outside the approved indication provide preliminary evidence for selected metabolic and cognitive outcomes, with substantial limits on generalization.

MECHANISM

Established receptor action. Tesamorelin stimulates pituitary GHRH receptors, increasing endogenous GH secretion and subsequently circulating IGF-1. GHRH receptor signaling involves cAMP and calcium-dependent GH release. The drug acts through functioning pituitary somatotrophs, which explains why disruption of the hypothalamic-pituitary axis is a contraindication.

Endogenous regulation remains relevant, but it does not guarantee normal hormone concentrations. The pivotal trial reported an 81 percent IGF-1 increase (PMID 18057338). The cognition trial reported a 117 percent increase that remained within its physiological reference range (PMID 22869065). Those findings cannot establish a universal protective ceiling. Clinically excessive IGF-1 is a recognized reason to reassess treatment.

Established clinical effect, incompletely resolved tissue mechanism. GH promotes lipolysis and changes lipid handling. Tesamorelin consistently reduced visceral adipose tissue, or VAT, in HIV-associated lipodystrophy trials. The pooled phase 3 analysis found no significant change in abdominal subcutaneous adipose tissue (PMID 20554713). This supports preferential visceral effects in that population. It does not establish selective fat loss in every population or complete preservation of every other fat compartment.

Investigational liver effects. A trial in HIV-associated fatty liver disease found reduced hepatic fat after 12 months (PMID 31611038). An associated biopsy analysis identified increased oxidative phosphorylation gene expression and reduced expression of inflammation, tissue repair, and cell division pathways (PMID 32701508). These associations offer mechanistic hypotheses. They do not prove prevention of cirrhosis, liver cancer, or liver-related death.

Investigational brain effects. A 30-person substudy found increased brain GABA and other metabolite changes after 20 weeks (PMID 23689947). Neurochemical changes were not significantly associated with cognitive changes. The substudy and its parent trial represent overlapping participants, not independent replications.

Pharmacokinetic context. A population model estimated clearance near 1060 L/hour and distribution volume near 200 L (PMID 25358450). Plasma exposure is brief, while downstream endocrine effects last longer.

Clinical dosing frequency comes from studied regimens and formulation-specific labels, not from extrapolating plasma half-life alone.

EVIDENCE · GRADE A

Grade A applies to reduction of excess abdominal fat in adults with HIV-associated lipodystrophy, supported by approval and multiple randomized trials. The pooled phase 3 program included 806 participants and demonstrated sustained VAT reduction during continued treatment (PMID 20554713). Evidence for abdominal obesity without HIV, HIV-associated fatty liver disease, and cognitive outcomes is preliminary, grade B for those specific outcomes. Muscle imaging and lean-mass findings do not establish improved strength or training-induced hypertrophy. Evidence for athletic hypertrophy is grade C under this product's scale because available human findings are too indirect. No efficacy trial in healthy resistance-trained adults was identified in the targeted PubMed search.

Human data. Falutz 2007 randomized 412 adults with HIV-associated abdominal fat accumulation. VAT decreased 15.2 percent with tesamorelin and increased 5.0 percent with placebo over 26 weeks. Triglycerides decreased by 50 mg/dL in the treatment group. More treated participants withdrew because of adverse events, although overall adverse-event frequency did not differ significantly (PMID 18057338). Falutz 2010 pooled two phase 3 trials. The placebo-adjusted VAT effect was minus 15.4 percent at week 26. Continued treatment maintained a 17.5 percent reduction from original baseline at week 52. These percentages use different comparisons and should not be presented as interchangeable placebo-adjusted effects. Abdominal subcutaneous fat did not change significantly, and VAT returned toward baseline after withdrawal (PMID 20554713). Stanley 2014 randomized 50 participants. At six months, the VAT treatment effect was minus 42 cm². The net liver lipid-to-water percentage effect was minus 2.9 percentage points. Fasting glucose showed an early placebo-adjusted increase of 7 mg/dL, without a significant between-group difference at six months (PMID 25038357). Stanley 2019 enrolled 61 adults with HIV and fatty liver disease. At 12 months, the hepatic fat treatment effect was minus 4.1 percentage points, corresponding to a 37 percent relative reduction. Liver fat fell below 5 percent in 35 percent of treated participants versus 4 percent receiving placebo. Histology findings remain preliminary (PMID 31611038). Makimura 2012 studied 60 abdominally obese adults without HIV who had reduced GH secretion. The VAT treatment effect was minus 35 cm² over 12 months, with improvements in selected cardiovascular risk markers. This selected population does not represent all adults with obesity (PMID 23015655). Baker 2012 randomized 152 older adults, including participants with mild cognitive impairment. Executive-function results favored treatment after 20 weeks. Adverse events occurred in 68 percent versus 36 percent, and fasting insulin increased in the mild cognitive impairment subgroup (PMID 22869065). Clemmons 2017 studied 53 adults with type 2

Animal and mechanistic data. Ferdinandi 2007 reported GH and IGF-1 increases in pigs, rats, and dogs following repeat exposure. Doses up to 600 mcg/kg, administered IV or SC once daily, were reported across the nonclinical program (PMID 17214611). Toxicology studies lasted up to four months. Dogs developed reversible liver, kidney, hematologic, and organ-weight findings associated with sustained supraphysiological GH or IGF-1 exposure. These findings support biological activity and identify potential hazards; they do not define a human therapeutic margin. Jansen 2004 studied pulmonary delivery in dogs. Approximate single experimental doses were 375 mcg/kg by intratracheal dry powder insufflation and 38 mcg/kg SC (PMID 15113616). Estimated absolute pulmonary bioavailability was 13 percent. This experiment does not validate nasal sprays, oral preparations, or human inhalation. Animal doses cannot be transferred to humans by simple body-weight scaling.

diabetes for 12 weeks. Between-group differences in insulin response and final glycemic control were not significant. The study was too small and short to exclude diabetes-related harm (PMID 28617838). Adrian 2019 reported improved trunk muscle imaging measures in selected VAT responders. Excluding treatment nonresponders limits causal interpretation and generalizability (PMID 31237318). Two 2026 meta-analyses reported a lean-mass increase near 1.42 kg, which is not equivalent to contractile muscle gain (PMIDs 42538058 and 41545261). The discontinuation estimate in PMID 42538058 was imprecise and did not reach conventional statistical significance.

REGULATORY STATUS AND SPORT

STATUS

Tesamorelin received initial US approval in 2010 for excess abdominal fat in adults with HIV-associated lipodystrophy. It is not indicated for weight management, and long-term cardiovascular safety remains unestablished. Current formulation requirements are documented in the [Egrifta WR prescribing information] (https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022505s020lbl.pdf). The European application was withdrawn before authorization, as documented in the [EMA withdrawal record] (https://www.ema.europa.eu/en/documents/press-release/ferrer-internacional-sa-withdraws-its-marketing-authorisation-application-egrifta-tesamorelin_en.pdf). Research-material labeling does not establish pharmaceutical quality or authorization for human treatment.

WADA

Prohibited at all times, both in and out of competition. The 2026 WADA Prohibited List explicitly names tesamorelin under S2.2.4, growth hormone releasing factors. A prescription alone is not a therapeutic use exemption. Use without an applicable exemption can constitute an anti-doping rule violation. Source: [2026 WADA Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

SC administration is the established human route in the cited trials. Approved labels specify abdominal administration. Intratracheal delivery appears only in the cited dog experiment (PMID 15113616). No validated oral or intranasal human regimen was identified. Poor expected peptide absorption is a pharmacological concern, not proof that every possible delivery technology is ineffective.

HALF-LIFE

Half-life is formulation-dependent. Label estimates in healthy subjects are approximately 8 minutes for Egrifta SV and 11 minutes for Egrifta WR. The population model in PMID 25358450 and dog estimates of 21 to 45 minutes in PMID 17214611 describe different datasets. Neither animal estimates nor a short human half-life establishes a rationale for additional daily administrations.

TIMING

The cognition trial specified administration 30 minutes before bedtime (PMID 22869065). That design does not establish bedtime as superior to morning administration. The approved labels specify daily administration without a universal clock time. Fasting and carbohydrate-avoidance schedules are commonly cited in non-clinical use; not validated in trials. Physiological effects of glucose on GH secretion do not establish a tested meal-timing protocol for tesamorelin.

CYCLE LENGTH

The cited studies include 12-week, 20-week, 26-week, and 12-month interventions, with longer extension phases in some programs. These durations reflect different study questions, not an established optimal cycle. The phase 3 withdrawal data demonstrate loss of VAT benefit after discontinuation (PMID 20554713). They do not establish the same rebound magnitude or timing for every individual. Eight- to 16-week physique cycles and intermittent schedules remain unvalidated.

TITRATION

There is no validated self-directed titration algorithm for physique goals. Labeled dosing is formulation-specific, as detailed above. Lower-dose research arms do not establish a universal starting dose or escalation sequence. IGF-1 changes, glucose status, adverse effects, and clinical benefit inform reassessment. An 8 percent VAT reduction defined responders in the exploratory muscle analysis (PMID 31237318); it is not a universal prescribing threshold. Waist measurements cannot reproduce a CT-defined response criterion.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Historical phase 3 formulation, HIV-associated excess abdominal fat	2 mg SC once daily, as studied in PMIDs 18057338 and 20554713.	SC	Once daily for 26 weeks, with a further 26-week extension in the pooled program.	Original-formulation randomized trials, PMIDs 18057338 and 20554713. This is a historical study dose, not a universal dose for current formulations. · PMID 20554713
Egrifta SV labeled treatment of excess abdominal fat in adults with HIV-associated lipodystrophy	1.4 mg SC once daily, per the Egrifta SV prescribing information.	SC, abdomen	Once daily	Egrifta SV prescribing information, dosage and administration section.
Egrifta WR labeled treatment of excess abdominal fat in adults with HIV-associated lipodystrophy	1.28 mg SC once daily, per the Egrifta WR prescribing information.	SC, abdomen	Once daily	Egrifta WR prescribing information, revised March 2025. Weekly vial preparation does not mean weekly administration.
Selected abdominally obese adults without HIV and with reduced GH secretion	2 mg SC once daily, as studied in PMID 23015655.	SC	Once daily for 12 months	Randomized placebo-controlled trial in 60 participants, PMID 23015655. · PMID 23015655
Older adults with normal cognition or mild cognitive impairment	1 mg SC once daily, as studied in PMID 22869065.	SC	Once daily, 30 minutes before bedtime, for 20 weeks	Randomized placebo-controlled trial, PMID 22869065. This was not the only human study investigating a lower dose. · PMID 22869065
Adults with type 2 diabetes, short-term metabolic study	1 mg or 2 mg SC once daily in separate randomized groups, as studied in PMID 28617838.	SC	Once daily for 12 weeks	Randomized placebo-controlled trial in 53 participants, PMID 28617838. Neither regimen is an approved diabetes treatment. · PMID 28617838
HIV-associated fatty liver disease	2 mg SC once daily, as studied in PMID 31611038.	SC	Once daily during a 12-month randomized phase, followed by a six-month open-label phase.	Randomized multicenter trial, PMID 31611038. Liver disease remains outside the approved indication. · PMID 31611038
Animal pharmacology and toxicology	Up to 600 mcg/kg IV or SC once daily across the nonclinical program, PMID 17214611.	IV or SC, depending on the experiment	Daily repeat administration; toxicology studies extended up to four months.	Nonclinical study program, PMID 17214611. The abstract does not assign every maximum dose to each species and duration. · PMID 17214611
Unvalidated physique protocols	1 mg to 2 mg SC once daily, commonly cited in non-clinical use; not validated in trials.	SC	Once daily in commonly cited nonclinical protocols, often described as eight to 16 weeks.	Commonly cited in non-clinical use; not validated in trials. PMID 42395176 discusses self-administration practices, not evidence establishing this schedule. · PMID 42395176

STACKING

+ Ipamorelin

Hypothesis only. GHRH and ghrelin-receptor agonism provide different inputs to GH secretion. No tesamorelin-ipamorelin combination trial was verified here. Larger GH

– CJC-1295

Overlapping GHRH-receptor stimulation without established combination benefit. Hormonal exposure and attribution of adverse effects become less predictable.

	responses would not establish better body composition or lower risk. Additive endocrine exposure could increase edema, dysglycemia, or excessive IGF-1.	– Sermorelin	Overlapping GHRH-receptor activity without verified clinical benefit from combining them. Differences in structure and exposure do not support a simple weaker-versus-stronger equivalence. Additional stimulation complicates interpretation of IGF-1 changes and adverse effects.
+ GHRP-2	Hypothesis only. A second GH-release pathway could alter hormonal responses, but clinical benefit from this specific combination is unestablished. Cortisol and prolactin effects are additional concerns with GHRP-2. Findings from other GHRH-GHRP experiments cannot establish tesamorelin combination dosing, efficacy, or tolerability.	– IGF-1 LR3	Adds an unapproved IGF-1 analog to treatment that already raises endogenous IGF-1. Human combination efficacy and safety are unestablished. Glucose effects may be unpredictable, and mitogenic concerns remain unresolved. Endogenous feedback does not provide a proven safeguard.
+ Semaglutide	Hypothesis only. The compounds affect body composition through different mechanisms. No combination trial establishing additive benefit was verified here. Glucose lowering cannot be assumed to cancel tesamorelin-related metabolic risk. Reported lean-mass changes do not establish protection against muscle loss during weight reduction.		

SAFETY

COMMON EFFECTS	Reported effects include local injection reactions, arthralgia, myalgia, peripheral edema, paresthesia, and headache. The cognition trial reported more adverse events with treatment (PMID 22869065). The JAMA trial found an early glucose increase that was not sustained as a significant group difference at six months (PMID 25038357). This does not exclude individual glucose deterioration. Meta-analysis identified an imprecise increase in discontinuations, rather than a conclusively doubled risk (PMID 42538058).
SERIOUS SIGNALS	Clinically important signals include excessive IGF-1, diabetes, significant fluid retention, carpal tunnel symptoms, and hypersensitivity. Original-label trials reported diabetes-range HbA1c in 5 percent of treated participants versus 1 percent receiving placebo. Neoplasm warnings reflect GH and IGF-1 biology and uncertainty, not proof that treatment necessarily causes cancer. Source: [original Egrifta prescribing information] (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022505s000lbl.pdf). Animal organ findings should not be described as established human toxicities (PMID 17214611).
CONTRAINDICATIONS	Label contraindications include disrupted hypothalamic-pituitary function, active malignancy, pregnancy, and hypersensitivity to tesamorelin or formulation excipients. Prior malignancy, diabetes or retinopathy, and acute critical illness require specific clinical assessment. Pediatric efficacy and safety are unestablished. Excipient lists differ by formulation; mannitol alone is not a complete allergy screen.
STOP RULES	Label-based reasons for discontinuation or reassessment include suspected hypersensitivity, recurrent malignancy, pregnancy, persistent IGF-1 above 3 standard deviation scores, and unfavorable glucose changes without clear benefit. Severe allergic symptoms warrant urgent medical assessment. Persistent edema, neuropathic symptoms, or absent benefit also warrant review. Decisions depend on severity and clinical context.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	Egrifta SV contains 2 mg per single-dose vial, per its prescribing information. Egrifta WR contains 11.6 mg per single-patient-use vial, per its prescribing information. These are vial strengths, not administered doses. The formulations are not substitutable. Unapproved vial strengths do not establish equivalent concentration, potency, bioavailability, or stability.

SOLVENT

Egrifta SV labeling specifies supplied Sterile Water for Injection and immediate use after preparation. Egrifta WR labeling specifies supplied Bacteriostatic Water for Injection. Preservative presence alone does not validate prolonged storage of another formulation. The relevant preparation source for SV is the [Egrifta SV prescribing information] (<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=3d783378-b02d-4f19-99dd-0fc91a042224>).

STORAGE

Egrifta SV labeling specifies room-temperature storage of the unmixed product and immediate use after reconstitution, with remaining solution discarded. Egrifta WR labeling specifies 20 to 25 C before and after preparation, protection from light, no freezing, and disposal seven days after mixing. No generic two- to four-week refrigerated shelf life is established for unapproved tesamorelin solutions. Clear appearance cannot establish sterility, potency, or freedom from degradation.

Label-based calculation only. Egrifta SV labeling specifies a 2 mg vial prepared with 0.5 mL diluent, producing 4 mg/mL. Its labeled dose of 1.4 mg SC once daily corresponds to 1.4 mg divided by 4 mg/mL, or 0.35 mL. Egrifta WR labeling states a final concentration of 8 mg/mL after preparation with 1.3 mL diluent. Its labeled dose of 1.28 mg SC once daily corresponds to 0.16 mL. These calculations describe approved presentations. They do not validate preparation of research material. The labeled final concentration takes precedence over a calculation using nominal vial strength alone.

BUYING NOTES

A research certificate of analysis does not establish pharmaceutical equivalence or fitness for human administration. Identity, chromatographic purity, peptide content, sterility, endotoxin contamination, stability, and chain of custody are separate questions. A high HPLC area percentage does not verify vial mass or exclude biologically important contaminants.

An interpretable analytical report identifies the tested batch, sampling and test dates, methods, laboratory, and underlying results. A matching molecular mass supports identity but cannot alone confirm the complete sequence or exclude all related impurities. A report for another batch provides no batch-specific evidence. Independent testing also depends on whether the tested sample represents the supplied material.

There is no universal HPLC threshold that transforms research material into an approved injectable medicine. Bacteriostatic diluent does not sterilize contaminated contents. Stability requires formulation-specific evidence, so claims about premixed material cannot be assessed from peptide size or appearance alone. The narrative review discusses these uncertainties in unregulated supply chains without validating their products (PMID 42395176).

COMMON MISTAKES

- Treating visceral fat reduction as equivalent to general weight loss. The strongest evidence concerns a specific HIV-associated fat distribution disorder, and BMI often changed little.
- Claiming complete preservation of all nonvisceral fat. Abdominal subcutaneous fat generally did not change significantly, but one meta-analysis found a small limb-fat reduction (PMID 41545261).
- Assuming benefits persist after discontinuation. The phase 3 extension showed VAT returning toward baseline after treatment withdrawal (PMID 20554713).
- Equating endogenous GH release with guaranteed physiological IGF-1. Feedback remains relevant, but excessive IGF-1 can still occur.
- Interpreting stable average glucose as absence of diabetes risk. Small metabolic trials and pooled averages do not exclude clinically important events in susceptible individuals.
- Converting a short half-life into a more frequent schedule. The cited clinical regimens used daily administration, and formulation-specific exposure matters.
- Interchanging vial strength, historical study dose, and current labeled dose. These describe different quantities and presentations.
- Calling a lean-mass increase proven muscle hypertrophy. Lean mass includes water and nonmuscle tissue, while responder-selected imaging analyses do not establish strength gains.

- Treating the cognition substudy as independent replication of the parent trial. Participants overlapped, and neither study established dementia prevention (PMIDs 22869065 and 23689947).
- Assuming a prescription resolves anti-doping restrictions. Tesamorelin remains prohibited at all times unless an applicable therapeutic use exemption permits its use.

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IGF-1 LR3

Long R3 IGF-1

IGF-1 analog with reduced binding-protein affinity

Module 2 · Recomposition

Goals: Hypertrophy

Route: SC

WADA prohibited

An experimental IGF-1 analog with reduced binding-protein affinity. Animal activity is established; human muscle-building efficacy, dosing, and pharmacokinetics remain unestablished.

WHAT IT IS

IGF-1 LR3, also called Long R3 IGF-1 or Long Arg3 IGF-I, is an engineered analog of insulin-like growth factor 1. Native IGF-1 contains 70 amino acids. LR3 replaces glutamate with arginine at position 3 and adds a 13-residue N-terminal extension. The extension contains the first 11 residues of methionyl porcine growth hormone followed by Val-Asn. Francis and colleagues describe this construct in PMID 1378742. The resulting protein contains 83 amino acids. The modifications reduce its affinity for IGF-binding proteins, which regulate IGF availability, distribution, and clearance. They do not simply create a stronger version of native IGF-1 at every receptor or in every tissue. In the original cell experiments, enhanced biological potency depended substantially on the binding-protein environment. In cells without detectable secreted binding proteins, LR3 was less potent than native IGF-1. This distinction explains why a potency claim from cell culture cannot establish a clinical advantage. LR3 is used experimentally to investigate IGF signaling while reducing interference from binding proteins. Its research applications include cell proliferation, protein metabolism, tissue distribution, and disease models. These applications establish biological activity, not an approved therapeutic use or a human administration standard. The PubMed searches performed for this review did not identify a published human administration trial establishing LR3 efficacy, dose-response, or pharmacokinetics. Human-derived cells and human proteins appear in many search results, but experiments involving those materials are not human clinical trials. Published analytical work also documents LR3-related material in an injection vial, which establishes product availability rather than clinical validation.

MECHANISM

IGF-1 LR3 activates the type 1 IGF receptor, a receptor tyrosine kinase involved in growth, survival, and metabolism. Receptor activation engages intracellular pathways that include PI3K, Akt, and mTOR. In experimental muscle systems, these pathways regulate protein synthesis and the expression of genes associated with protein breakdown. Receptor activation is not specific to skeletal muscle, and pathway engagement does not establish a useful training outcome. Latres and colleagues examined native IGF-1 signaling rather than LR3 specifically. Their study found that both Akt/FOXO and Akt/mTOR signaling contributed to IGF-1-induced transcriptional changes. IGF-1 suppressed dexamethasone-associated expression of the atrophy-related ubiquitin ligases MuRF1 and MAFbx. The mTOR-dependent component was distinct from the FOXO component. These findings support the general anabolic and anti-catabolic mechanism discussed here, but they do not demonstrate LR3-induced hypertrophy in humans. The correct print publication year is 2005, although the article appeared electronically in 2004, PMID 15550386. The binding-protein interaction is central to understanding LR3. King and colleagues characterized the shorter Arg3-substituted analog and found poor binding to bovine IGFBP-2. Its binding to the type 1 receptor was slightly weaker than native IGF-1 in their assay. They attributed increased biological potency primarily to reduced binding-protein interaction, PMID 1311930. That study provides part of the engineering rationale, rather than characterization of every property of the full LR3 construct. Francis and colleagues subsequently studied the extended Long Arg3 molecule. It stimulated protein and DNA synthesis and inhibited protein breakdown in rat myoblast cultures. Its potency exceeded native IGF-1 in cell systems that secreted binding proteins. In chicken embryo fibroblasts without detectable secreted binding proteins, LR3 was less potent than native IGF-1. The same paper examined activity in a hepatoma system where IGFs acted through insulin receptors, PMID 1378742. These observations support context-dependent potency rather than universally stronger receptor activation. Reduced binding also changes disposition. In a radiotracer study, most circulating

LR3 was detected as free peptide, and it cleared faster than native IGF-1. Tissue distribution differed between the molecules and between pregnant and nonpregnant rats, PMID 7693845. Binding proteins therefore cannot be treated solely as obstacles to activity. They also contribute to the circulating reservoir and influence delivery to tissues. Reduced binding may increase availability in one compartment while reducing persistence or delivery in another. IGF signaling has insulin-like metabolic effects, making low blood glucose a plausible LR3 hazard. The evidence reviewed does not justify that exclusive explanation or a claim that every IGF preparation has an identical dose-limiting effect. LR3 lowered circulating glucose in tumour-bearing rats, while native recombinant IGF-1 has documented hypoglycemia in patients. These are related findings, with different molecules, populations, and levels of certainty. The training interpretation remains unproven. In one rat comparison, LR3 had greater potency for body weight, visceral organ weights, and feed efficiency. It was only approximately equipotent with native IGF-1 for reversing carcass muscle loss, PMID 8708565. Whole-body growth, nitrogen retention, muscle protein synthesis, and functional hypertrophy are different endpoints. None establishes preferential growth of a selected human muscle. The literature reviewed does not validate targeted muscle growth through injection location. Systemic distribution is documented, but local tissue exposure cannot be dismissed solely from the molecule's design.

EVIDENCE · GRADE C

Grade C for proposed muscle-building or performance use. Direct evidence includes cell experiments and animal studies, without identified clinical evidence establishing benefit in trained adults. The animal literature extends beyond short rat experiments from the 1990s. A later mouse study involved prolonged intranasal exposure, but it also does not validate a human training protocol. Mechanistic findings alone are grade D; direct animal findings support the overall grade C classification. Evidence for approved native recombinant IGF-1 belongs to that molecule and indication, and does not upgrade LR3.

Human data. No published human administration trial establishing LR3 efficacy, dose-response, or pharmacokinetics was identified in the PubMed searches performed for this review. Searches included compound-name variants, human and clinical terms, and clinical-trial or human indexing. Results included human-derived cell experiments, animal studies, analytical reports, and reviews. This is a search-based conclusion, not proof that no unpublished exposure or unindexed report exists. Native recombinant human IGF-1, mecasermin, provides relevant but indirect clinical context. Kemp's review describes increased growth velocity in children with severe IGF-1 deficiency or growth hormone insensitivity. It also discusses hypoglycemia and the influence of binding-protein concentrations on circulating half-life, PMID 19627167. Under this product's scale, an approved drug can qualify as grade A for its approved indication. That classification does not establish efficacy for healthy adults, bodybuilding, or an altered IGF-1 analog. Several differences prevent direct transfer. LR3 has a different amino-acid sequence and markedly different binding-protein interactions. The pediatric deficiency population has a different physiological baseline from adults with normal endogenous IGF-1. Treatment goals, exposure, formulation, and clinical monitoring also differ. Even a favorable result with native IGF-1 cannot supply a conversion factor for LR3 dosing. A published analytical report identified a His-tagged Long-R3-IGF-I protein in an injection vial, PMID 20675162. This was a chemical identification study, not a clinical case series establishing administered

Animal and mechanistic data. In streptozotocin-diabetic rats, LR3 and another low-binding-protein analog increased growth and nitrogen retention. They were approximately 2.5 to 3 times more potent than native IGF-1 for restoring growth. Increased muscle protein synthesis did not coincide with correction of all insulin-dependent abnormalities. Glucosuria and urinary N-tau-methylhistidine excretion were not reduced by the IGFs, PMID 7683875. The highest numerical dose highlighted in that abstract belongs to native IGF-1, so it is not presented as an LR3 dose here. In normal and dexamethasone-catabolic rats, a seven-day experiment compared subcutaneous continuous infusion with once- or twice-daily injection. Continuous infusion produced greater efficacy, particularly for anti-catabolic outcomes. LR3 retained greater potency for several growth measures after injection, despite faster clearance. However, it was only approximately equipotent with native IGF-1 for reversing carcass muscle loss, PMID 8708565. This supports a delivery-dependent animal effect, not a preferred human administration schedule. In rats bearing mammary adenocarcinomas, osmotic-pump infusion of IGFs reduced food intake, insulin, and circulating glucose. Host muscle protein accretion did not improve, and tumour growth increased, particularly with LR3. The same tumour cells did not show growth stimulation in the accompanying culture experiment, PMID 8053901. The discrepancy illustrates why isolated cell assays cannot exclude organism-level tumour effects. These were animals with established tumours; the study does not quantify cancer initiation or cancer incidence in humans. A

dose, efficacy, or adverse-event rates. It supports concern about molecular identity in available material. It does not show that all products contain the same alteration or permit an estimate of the frequency of such problems. There are no established LR3 reference ranges, treatment targets, or validated monitoring algorithms in the clinical evidence reviewed. A laboratory result concerning endogenous IGF-1 would not by itself establish LR3 exposure or tissue activity. Any interpretation would depend on the assay and its demonstrated ability to recognize the analog.

separate renal-ischemia study found improved anabolic measures without improved renal recovery. LR3 worsened early renal functional outcomes and was associated with greater tubular epithelial calcification, PMID 8138750. This is a disease-model signal, not proof of a corresponding effect at an unknown human exposure. It nevertheless prevents describing LR3 as broadly organ-protective. Later work studied intranasal LR3 over seven months in male mice, including an Alzheimer's disease model. Some body-composition and cortical amyloid findings changed, but behavioral and memory outcomes were not preserved, PMID 39610283. This study was published in print in 2025. It does not establish cognitive benefit, long-term human tolerability, or efficacy in resistance-trained adults.

REGULATORY STATUS AND SPORT

STATUS	No FDA or EMA medicinal authorization for IGF-1 LR3 was identified in the sources reviewed. An approved native IGF-1 medicine does not authorize the structurally modified LR3 analog. A research-use designation also does not establish suitability for clinical administration. The United States Increlex label covers specified pediatric growth-failure indications involving severe primary IGF-1 deficiency or growth hormone gene deletion with neutralizing antibodies. The European indication is severe primary IGF-1 deficiency in children and adolescents. These are distinct regulatory statements concerning mecasermin. Sources: [United States prescribing information] (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d5b2b0e1-c523-468d-9a0b-4ae4e4a8dbce) and [European product information] (https://www.ema.europa.eu/en/documents/product-information/increlex-epar-product-information_en.pdf). Those conclusions require jurisdiction-specific authority and details about the material, intended use, and supply arrangement. The original blanket statements about every jurisdiction and every compounding situation exceeded the verification available. Laboratory availability, a chemical identifier, and a certificate of analysis are different from medicinal approval. None supplies an approved LR3 indication, clinical formulation, or human dosing standard.
WADA	Prohibited at all times, in competition and out of competition. The 2026 WADA Prohibited List explicitly includes IGF-1 and its analogues under S2.3, Growth Factors and Growth Factor Modulators. LR3 falls within that named analog category. Source: [2026 WADA Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). The classification concerns the substance, not whether a seller describes it as research material. A personal purpose such as recovery, physique change, or rehabilitation does not change its listed status. The historical review by Nicholls and Holt discusses IGF-1 in the context of hormone misuse in sport, PMID 27347885. It is background literature rather than the authority for the current list. No therapeutic authorization or exemption for LR3 is established here.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Subcutaneous continuous infusion through osmotic pumps and subcutaneous once- or twice-daily injection were compared in the rat study reported in PMID 8708565. Subcutaneous osmotic-pump administration also appears in the renal-ischemia study, PMID 8138750. Intravenous radiotracer boluses were used to investigate clearance and distribution in rats, PMID 7693845. Intranasal administration was studied in mice, PMID 39610283. These routes address different experimental questions and cannot be treated as interchangeable. A tracer experiment does not establish therapeutic administration, and a mouse intranasal experiment does not demonstrate human intranasal bioavailability. Likewise, an osmotic pump creates an exposure pattern that differs from an intermittent injection. No human LR3 route has established clinical efficacy or dosing in the literature reviewed. The vial format alone does not establish an appropriate route.
HALF-LIFE	A numerical human plasma half-life for LR3 was not established by the literature reviewed. The often-repeated 20 to 30 hour figure should therefore not be presented as a measured human parameter. Molecular engineering alone cannot establish or definitively exclude a particular terminal half-life. Direct measurements, formulation, route, assay, and the sampled compartment matter. The relevant measured finding is faster plasma clearance than native IGF-1 in rats. Bastian and colleagues administered radiolabeled peptides intravenously and compared pregnant with

nonpregnant animals. Native IGF-1 disposition changed substantially with the binding-protein environment, while LR3 was predominantly detected as free peptide, PMID 7693845. Tomas and colleagues also describe more rapid LR3 clearance in their administration-comparison study, PMID 8708565. These findings undermine the assumption that reduced binding necessarily prolongs circulating exposure. Binding proteins can restrict immediate receptor access while also protecting a circulating reservoir. Removing that interaction can increase availability and clearance simultaneously. Neither effect supplies a human duration of action. Kemp's review describes shorter mecasermin half-life in patients with low IGFBP-3 and acid-labile subunit concentrations, PMID 19627167. That is useful physiological context, not an LR3 pharmacokinetic estimate. Plasma half-life, tissue residence, receptor signaling duration, and persistence of a biological response are separate measurements. None should be substituted for another when interpreting a proposed schedule.

TIMING

No human LR3 study identified an optimal relationship to training, meals, sleep, or time of day. The rat administration-comparison study found greater efficacy with continuous infusion than with the injection schedules tested, PMID 8708565. That finding establishes schedule dependence in that model. It does not establish a preferred human timing strategy or justify reproducing pump exposure outside research. Meal-associated administration belongs to the mecasermin clinical framework because of its hypoglycemic effects, PMID 19627167. It cannot establish that a meal neutralizes LR3 risk. Exercise, food intake, and additional glucose-active substances could affect the consequences of exposure, but their interaction with LR3 has not been clinically characterized. Timing claims should therefore remain separate from validated pharmacokinetics.

CYCLE LENGTH

Four- to six-week blocks are commonly cited in non-clinical use; not validated in trials. No human LR3 evidence reviewed establishes an effective cycle, recovery interval, or washout period. The proposed explanation involving predictable receptor downregulation is also unvalidated for these schedules. The cited growth and tumour experiments lasted approximately one week, PMIDs 8708565 and 8053901. The later intranasal mouse study lasted seven months, PMID 39610283. Neither duration identifies a human treatment window. A longer experiment also does not establish comprehensive long-term safety, particularly when its species, route, disease model, and endpoints differ. Duration needs to be interpreted alongside exposure and outcome. A short study can reveal an acute hazard without defining cumulative risk. A long disease-model study can miss outcomes that were not measured. There is no evidentiary basis here for calling a particular human cycle protective.

TITRATION

No validated human LR3 titration schedule was identified. The mecasermin label describes supervised adjustment for a different molecule, with glucose-related precautions. Its numerical schedule appears only in the labeled comparator entry above. A lower starting amount does not establish a validated LR3 escalation strategy. Neither normal glucose on one occasion nor absence of symptoms establishes acceptable exposure for other tissues. The reviewed animal studies cannot identify a human threshold for hypoglycemia, tumour promotion, fluid changes, or renal effects. Likewise, circulating endogenous IGF-1 is not a validated LR3 dose target. Interpreting such a measurement would require assay-specific information and clinical validation. The absence of an established titration method is a substantive evidence gap, rather than a reason to borrow one from another growth-axis compound.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved human comparator only: native recombinant IGF-1, mecasermin, for specified pediatric growth-failure indications. This is a different molecule and population from LR3 use in trained adults.	The United States Increlex label reports 0.04 to 0.08 mg/kg per dose subcutaneously twice daily initially. After at least one week of tolerability, label increments are 0.04 mg/kg per dose, up to 0.12 mg/kg per dose subcutaneously twice daily.	Subcutaneous, according to the United States Increlex prescribing information.	Twice daily, close to a meal or snack, according to the United States Increlex prescribing information.	United States Increlex prescribing information, sections 2.1 and 2.2. This label does not provide an LR3 starting dose, conversion ratio, or titration schedule.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Normal growing rats and dexamethasone-catabolic rats, studied for seven days. The experiment compared native IGF-1 with LR3 using different delivery patterns.	PMID 8708565 reports 320 mcg/day in normal rats and 400 mcg/day in catabolic rats, delivered subcutaneously by continuous infusion or divided into once- or twice-daily injections.	Subcutaneous osmotic-pump infusion or subcutaneous injection, PMID 8708565.	Continuous infusion, once-daily injection, or twice-daily injection for seven days, PMID 8708565.	Tomas FM and colleagues, The Journal of endocrinology, 1996, PMID 8708565. These are total daily rodent amounts, not amounts per injection or human-equivalent doses. · PMID 8708565
Rats with experimentally induced renal ischaemia. LR3 was evaluated for anabolic effects and recovery of renal function.	PMID 8138750 reports LR3 at 1.5 mg/kg/day by continuous subcutaneous osmotic-pump infusion in the seven-day experiment and the separate three-day post-ischaemia experiment.	Continuous subcutaneous osmotic-pump infusion, PMID 8138750.	Continuous delivery for seven days, or for three days after ischaemia in the separate acute experiment, PMID 8138750.	Martin AA and colleagues, The Journal of endocrinology, 1994, PMID 8138750. LR3 worsened early renal functional outcomes in this model. This is an experimental exposure, not a clinical dose. · PMID 8138750
Amounts circulated in non-clinical training discussions. Included as unvalidated claims, without an established population, dose-response relationship, or verified frequency of use.	20 to 50 mcg/day subcutaneously once daily, and 50 to 100 mcg/day subcutaneously once daily: commonly cited in non-clinical use; not validated in trials.	Subcutaneous, as described in non-clinical use; not established by human LR3 trials.	Once daily in the quoted non-clinical descriptions; not validated in trials.	commonly cited in non-clinical use; not validated in trials. The origins and prevalence of these ranges were not independently established. They are not recommendations or evidence-based exposure limits. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– CJC-1295

No validated LR3 combination benefit is established in the evidence reviewed. Stimulating endogenous growth-axis activity while adding an IGF analog creates overlapping biological effects without a characterized exposure-response relationship. Possible metabolic and tissue-growth consequences remain hypotheses for this pair. Different points of action do not establish complementary clinical benefit.

– Ipamorelin

No clinically validated LR3 pairing is established here. Claims about selectivity or a cleaner hormone profile do not resolve the uncertainty introduced by concurrent IGF signaling. Combined exposure also complicates attribution of symptoms and laboratory changes. This is a precaution concerning an unstudied combination, not a documented

– **Follistatin-344**

contraindication based on interaction trials.

Manipulating activin or myostatin biology alongside IGF signaling is a mechanistic proposal, not demonstrated human synergy. Distinct pathways can interact unpredictably, and separate anabolic mechanisms do not establish additive benefit, tissue specificity, or acceptable combined risk.

– **BPC-157**

The reviewed evidence establishes neither benefit nor compatibility for this pairing. An absence of a known shared receptor cannot establish an absence of interaction. Claims that BPC-157 protects the gut or connective tissue during LR3 exposure are not supported by combination data presented here. No protective effect is established.

– **Semaglutide**

A direct LR3 interaction study was not identified in the reviewed evidence. Reduced intake or gastrointestinal intolerance could plausibly complicate an exposure capable of lowering glucose. This is a risk inference, not proof that the pair causes severe hypoglycemia.

– **Tirzepatide**

Combined effects with LR3 have not been clinically characterized in the evidence reviewed. Changes in intake and glucose regulation create uncertainty, particularly during poor oral intake. No quantitative interaction estimate or comparison with semaglutide is justified here. This precaution does not establish that every exposed person will experience hypoglycemia.

– **PEG-MGF**

No validated benefit from pairing PEG-MGF with LR3 is established here. IGF-1 splice biology, proposed E-domain peptides, and modified experimental products are not interchangeable. Uncertain identity, mechanism, and exposure prevent a defensible claim of either redundancy or synergy.

SAFETY

COMMON EFFECTS

The frequency of adverse effects in humans exposed to LR3 is unknown. There is no clinical LR3 adverse-event table from which to identify common effects reliably. Hypoglycemia is a biologically

plausible concern, supported indirectly by native IGF-1 experience and directly by lowered glucose in tumour-bearing rats, PMIDs 19627167 and 8053901. Mecasermin clinical experience includes hypoglycemia, headache, injection-site changes, and lymphoid tissue enlargement. These are comparator-drug observations, not measured LR3 rates. Symptoms such as sweating, tremor, palpitations, hunger, or confusion can be consistent with hypoglycemia, but symptoms alone do not establish its cause. Product-related reactions form a separate uncertainty. A mislabeled protein, unexpected tag, contaminant, or unsuitable formulation can create risks that do not follow from the intended LR3 sequence. The analytical finding in PMID 20675162 illustrates an identity problem without estimating its prevalence.

SERIOUS SIGNALS

Direct LR3 animal signals include increased growth of an established tumour and failure to improve host muscle protein accretion, PMID 8053901. Another study found worse early renal recovery after ischaemia, PMID 8138750. These findings justify concern while leaving the magnitude and relevance of human risk unresolved. Mecasermin labeling documents severe hypoglycemia, anaphylaxis, intracranial hypertension, and complications of lymphoid enlargement. These provide indirect clinical warning signals, not proof of identical LR3 incidence. Source: [European mecasermin product information](https://www.ema.europa.eu/en/documents/product-information/increlex-epar-product-information_en.pdf). The tumour-bearing rat experiment does not prove that LR3 initiates cancer in healthy humans. Equally, absence of tumour-cell proliferation in one culture assay did not exclude accelerated tumour growth in the animal. The relevant distinction is between growth of an existing malignancy, development of a new malignancy, and the risk magnitude in a particular population. No human LR3 data reviewed establish a duration or exposure below which these concerns disappear. A short symptom-free period does not answer questions about cumulative tissue effects or formulation-related hazards.

CONTRAINDICATIONS

LR3 has no approved prescribing information defining formal contraindications. The following are precautionary concerns, based on related clinical evidence, direct animal findings, and uncharacterized human exposure. Active or suspected malignancy and a history of malignancy warrant particular concern because LR3 accelerated established tumour growth in rats, PMID 8053901. Renal disease or recent renal injury also warrants concern given the renal-ischaemia findings, PMID 8138750. Concurrent insulin or other glucose-lowering treatment raises potential interaction concerns, rather than establishing a studied LR3 contraindication. Pregnancy, breastfeeding, childhood, and adolescence lack an established LR3 benefit-risk basis. A prior severe reaction to the actual preparation or one of its components is an additional concern. A history of allergy to any recombinant protein is not automatically equivalent to allergy to every recombinant protein. Mecasermin is used for pediatric growth failure, while its label excludes growth promotion after epiphyseal closure. That distinction provides no pediatric or adult indication for LR3.

STOP RULES

After suspected exposure, confusion, seizure, loss of consciousness, collapse, or breathing difficulty warrants emergency assessment. Hives with facial or tongue swelling can indicate a serious allergic reaction. These are emergency signals regardless of whether LR3 is ultimately confirmed as the cause. Persistent severe headache, new visual disturbance, or repeated vomiting warrants prompt medical assessment. New sleep-related breathing pauses, marked swelling, or unexplained deterioration in kidney function also warrants evaluation. A new mass or unexplained weight loss requires investigation, without assuming that exposure caused cancer. An increasingly painful, red, hot, or swollen administration site, particularly with fever, requires assessment for infection or another local complication. These observations do not validate continued exposure when symptoms are absent. Clinical evaluation depends on the symptoms, timing, actual material, and concurrent substances.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved LR3 vial strength, formulation, or clinical presentation. Package amounts vary, and the number printed on a container does not independently establish its contents. For unit interpretation only, a label stating 1 mg nominal peptide content represents 1000 mcg. This is a mass conversion, not a dose or evidence that the labeled amount is present. Total dry powder mass, net peptide content, chromatographic purity, and biological activity are different quantities. Excipients and residual moisture can contribute to powder mass. A purity percentage does not directly establish recoverable peptide mass or potency. The analytical report in PMID 20675162 also shows why the molecular identity must be distinguished from the general product name.

SOLVENT

No validated clinical reconstitution solvent for LR3 was established by the sources reviewed. A laboratory method may specify a particular solvent, pH, concentration, container, or carrier protein for a defined experiment. Those conditions do not automatically describe a formulation suitable for human administration. Bacteriostatic water is not a method for sterilizing contaminated powder. A preservative also does not establish protein stability, compatibility, or a validated period of repeated access. Conversely, an acidic solvent used for laboratory solubility does not become suitable for

administration because the protein dissolves in it. The original universal solvent advice has therefore been removed. A research formulation requires its own documented preparation and stability method. Solubility, visible clarity, sterility, endotoxin content, and retained biological activity require separate evidence. None can be inferred reliably from the others.

STORAGE

No universal storage temperature or post-reconstitution shelf life for clinically administered LR3 was established. Laboratory stability depends on formulation, concentration, container, processing, and the conditions tested. A recommendation for one research preparation cannot be transferred automatically to another preparation with a similar name. Chemical degradation, aggregation, loss of biological activity, and microbial contamination are different failure modes. Refrigeration or the presence of a preservative does not establish control of all four. A generic multidose-container convention is also not peptide-specific stability evidence. So have unsupported universal freezing and refrigeration instructions. A preparation's documented storage specification needs to identify the tested formulation, conditions, duration, and acceptance criteria. Cloudiness or particles can identify an obvious problem, but a clear solution can still have incorrect content, contamination, or reduced activity. Visual inspection therefore cannot establish suitability or extend an undocumented storage period.

Illustrative concentration arithmetic only, without an administration procedure: 1 mg equals 1000 mcg. If an analytical preparation contains a verified 1000 mcg in a final volume of 2 mL, its calculated concentration is 500 mcg/mL. The final volume is the total solution volume, which is not always identical to the volume of solvent added. This example does not establish an LR3 dose, compatible diluent, route, or stability period. It also assumes that the stated mass is accurate and fully recovered in solution. Loss to containers, incomplete recovery, degradation, or incorrect identity would not be detected by the arithmetic. A volume marking describes volume, whereas mcg describes peptide mass. Neither becomes an IU of LR3 through conversion. Changing dilution can alter the size of a measured volume, but it cannot correct uncertain peptide identity, potency, sterility, or clinical exposure. Greater dilution is therefore not inherently better. It can also change adsorption, stability, and analytical recovery, depending on the preparation. These questions require formulation-specific evidence rather than a universal rule.

BUYING NOTES

Quality documentation can answer specific analytical questions, but it cannot create a clinical indication or establish human tolerability. A research certificate of analysis may document selected tests on a submitted sample. Its meaning depends on the actual sample, method, laboratory, date, and acceptance criteria. A document for a product family is weaker evidence than a traceable report linked to the relevant lot. Identity testing should distinguish the intended LR3 sequence from native IGF-1, fragments, tagged constructs, and other proteins. Intact mass can help, but mass alone may not establish the complete sequence, correct disulfide arrangement, or functional activity. Orthogonal evidence such as peptide mapping and a relevant activity assay addresses different parts of that question. A concrete published example illustrates the limitation. Kohler and colleagues identified a His-tagged Long-R3-IGF-I protein in an injection vial using immunoaffinity and mass-spectrometric methods, PMID 20675162. The tag changed the actual molecule. This finding supports careful identity interpretation, but it does not establish how often mislabeled material occurs or characterize every preparation. Chromatographic purity and net peptide content answer different questions. A high area percentage for one peak is not necessarily the percentage of the container's total mass that is active peptide. Moisture, residual solvents, salts, excipients, aggregates, and analytical response characteristics can affect interpretation. A universal purity cutoff does not establish fitness for human administration. Sterility and bacterial endotoxin testing are separate from identity and purity testing. A research COA may include either test, both, or neither. Their presence, methods, limits, and relationship to the final filled container must be explicit. Lyophilization alone does not establish sterility, and a test on bulk material does not automatically characterize every later filled container. Independent testing can improve confidence in the attributes actually measured. It cannot eliminate sampling limitations, establish an untested storage period, or substitute for clinical development. Price, powder appearance, dissolution behavior, and a research-use label are not reliable substitutes for analytical evidence. No supplier recommendation or purchasing instruction is provided.

COMMON MISTAKES

- Presenting a 20 to 30 hour human half-life as established. No supporting human pharmacokinetic study was identified. Rat studies show faster LR3 plasma clearance than native IGF-1, PMIDs 7693845 and

8708565. That finding supports rejecting an unsupported numerical claim, but it does not independently calculate a human half-life.

- Equating stronger cell activity with preferential muscle growth. The original experiments showed that binding-protein conditions changed the relative potency of LR3 and native IGF-1, PMID 1378742. A rat growth study found greater effects on several whole-body measures without a corresponding advantage for reversal of carcass muscle loss, PMID 8708565.
- Claiming that all LR3 animal evidence comes from week-long rat experiments. The historical studies remain relevant, but later research includes seven months of intranasal treatment in mice, PMID 39610283. That study did not preserve behavioral or memory outcomes in the disease model and does not validate human longevity or cognitive use.
- Mislabeling a native IGF-1 comparator amount as an LR3 dose. The highest amount highlighted in the diabetic-rat abstract belongs to native IGF-1, PMID 7683875. Dose extraction requires identifying the molecule, experimental group, route, frequency, and duration before copying the number into an LR3 entry.
- Turning a rodent total daily amount into a human schedule. The same amount delivered continuously and intermittently produced different effects in rats, PMID 8708565. Body-weight arithmetic alone does not account for species differences, exposure profiles, binding proteins, disease state, or the endpoint being measured.
- Treating injection location as a validated way to select muscle growth. The literature reviewed does not establish this practice in humans. Systemic distribution is documented in rats, PMID 7693845. Neither circulation nor a plausible local concentration gradient demonstrates a useful, selective hypertrophy outcome.
- Assuming food or a glucose reading resolves the risk. Native IGF-1 experience establishes a meaningful hypoglycemia concern, PMID 19627167. It does not establish an LR3 timing protocol or eliminate other tissue effects. Absence of symptoms and an isolated normal measurement cannot define a validated exposure range.
- Promoting mechanistic pairings as proven synergies. Distinct pathways do not establish additive benefit, and a missing interaction study does not establish compatibility. The listed combinations lack validated human LR3 benefit in the evidence reviewed. Claims of protection, reduced adverse effects, or superior tissue targeting require direct evidence.
- Treating mecasermin approval as approval of LR3. The approved medicine contains native recombinant human IGF-1 and addresses specified pediatric growth disorders. LR3 differs structurally and in binding-protein interactions. The comparator's efficacy, dose limits, adverse-event frequencies, and growth-plate rules cannot be transferred unchanged.
- Treating a COA or high purity percentage as proof of an appropriate clinical preparation. Identity, content, activity, sterility, endotoxin, and stability are separate attributes. A documented His-tagged LR3-related vial shows that molecular identity itself can differ from expectations, PMID 20675162. One analytical result cannot establish every attribute.
- Assuming a dilution calculation validates preparation or storage. Correct arithmetic can describe a hypothetical concentration while the actual contents remain uncertain. Preservative-containing water does not sterilize powder or establish a peptide-specific shelf life. The original syringe conversions and universal storage window exceeded the evidence.
- Reading the tumour signal as either irrelevant or proof of inevitable human cancer. LR3 accelerated an established tumour in rats without improving host muscle protein accretion, PMID 8053901. This is a relevant hazard signal. It does not quantify human cancer incidence, establish cancer initiation, or identify a risk-free exposure threshold.
- Overlooking organ-specific adverse findings because an anabolic marker improved. In rats with renal ischaemia, LR3 improved some anabolic measures while worsening early renal outcomes, PMID 8138750. Changes in nitrogen retention or body weight do not establish organ protection, functional recovery, or a favorable overall outcome.
- Assuming research-use labeling changes anti-doping status. The 2026 WADA list includes IGF-1 analogues under S2.3 and prohibits them at all times. A laboratory designation, personal recovery goal, or claim about detectability does not change the named substance category. No testing-evasion information is provided.

1. King R et al. Production and characterization of recombinant insulin-like growth factor-I (IGF-I) and potent analogues of IGF-I, with Gly or Arg substituted for Glu3, following their expression in *Escherichia coli* as fusion proteins.. *Journal of molecular endocrinology*, 1992. PMID [1311930](#) DOI [10.1677/jme.0.0080029](#) (Characterizes Gly3 and Arg3 IGF-I analogues. Reduced IGFBP-2 binding, rather than stronger receptor binding, was proposed to explain enhanced biological potency. This is supporting engineering evidence, not a human LR3 trial.)
2. Francis GL et al. Novel recombinant fusion protein analogues of insulin-like growth factor (IGF)-I indicate the relative importance of IGF-binding protein and receptor binding for enhanced biological potency.. *Journal of molecular endocrinology*, 1992. PMID [1378742](#) DOI [10.1677/jme.0.0080213](#) (Describes the extended Long Arg3 construct and compares biological activity across cell systems. Supports context-dependent potency and lower relative activity in fibroblasts without detectable secreted IGF-binding proteins.)
3. Latres E et al. Insulin-like growth factor-1 (IGF-1) inversely regulates atrophy-induced genes via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway.. *The Journal of biological chemistry*, 2005. PMID [15550386](#) DOI [10.1074/jbc.M407517200](#) (Supports native IGF-1 signaling through Akt/FOXO and Akt/mTOR in regulation of atrophy-related genes. This is mechanistic context rather than direct evidence of LR3 efficacy in humans.)
4. Tomas FM et al. Insulin-like growth factor-I and more potent variants restore growth of diabetic rats without inducing all characteristic insulin effects.. *The Biochemical journal*, 1993. PMID [7683875](#) DOI [10.1042/bj2910781](#) (Supports increased growth and nitrogen balance in diabetic rats, with greater growth potency for low-binding-protein variants. Also documents failure to reproduce all characteristic insulin effects. The highlighted maximum comparator dose is native IGF-I.)
5. Tomas FM et al. Superior potency of infused IGF-I analogues which bind poorly to IGF-binding proteins is maintained when administered by injection.. *The Journal of endocrinology*, 1996. PMID [8708565](#) DOI [10.1677/joe.0.1500077](#) (Reports 320 mcg/day and 400 mcg/day in normal and catabolic rats, respectively, administered subcutaneously by continuous infusion or once- or twice-daily injection for seven days. Supports schedule-dependent efficacy and limited superiority for reversal of carcass muscle loss.)
6. Tomas FM et al. Effects of insulin and insulin-like growth factors on protein and energy metabolism in tumour-bearing rats.. *The Biochemical journal*, 1994. PMID [8053901](#) DOI [10.1042/bj3010769](#) (Documents increased tumour growth, reduced food intake and circulating glucose, and lack of improved host muscle protein accretion with IGF exposure, particularly LR3, in tumour-bearing rats. Does not establish human cancer incidence.)
7. Kemp SF et al. Insulin-like growth factor-I deficiency in children with growth hormone insensitivity: current and future treatment options.. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 2009. PMID [19627167](#) DOI [10.2165/00063030-200923030-00002](#) (Provides indirect human context concerning mecasermin, pediatric growth outcomes, hypoglycemia, and binding-protein effects on circulating half-life. It does not establish LR3 clinical efficacy, dosing, or pharmacokinetics.)
8. Nicholls AR et al. Growth Hormone and Insulin-Like Growth Factor-1.. *Frontiers of hormone research*, 2016. PMID [27347885](#) DOI [10.1159/000445173](#) (Provides historical context on growth-axis substances and performance-related misuse. Current prohibited status is established separately from the 2026 WADA list, rather than inferred from this review.)
9. Bastian SE et al. Plasma clearance and tissue distribution of labelled insulin-like growth factor-I (IGF-I) and an analogue LR3IGF-I in pregnant rats.. *The Journal of endocrinology*, 1993. PMID [7693845](#) DOI [10.1677/joe.0.1380327](#) (Direct radiotracer evidence of faster LR3 plasma clearance, predominantly free circulating analog, and tissue-distribution differences in pregnant and nonpregnant rats. Does not provide a human plasma half-life.)
10. Martin AA et al. Effects of insulin-like growth factor-I peptides in rats with acute renal failure.. *The Journal of endocrinology*, 1994. PMID [8138750](#) DOI [10.1677/joe.0.1400023](#) (Reports LR3 at 1.5 mg/kg/day by continuous subcutaneous osmotic-pump infusion in renal-ischemia experiments. Supports worse early renal functional outcomes despite improvement in some anabolic measures.)
11. Kohler M et al. Detection of His-tagged Long-R³-IGF-I in a black market product.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2010. PMID [20675162](#) DOI [10.1016/j.ghir.2010.07.001](#) (Documents identification of a His-tagged Long-R3-IGF-I protein in an injection vial. Supports a concrete molecular-identity concern, without establishing clinical effects or the prevalence of product-quality failures.)
12. Engel MG et al. Intranasal long R3 insulin-like growth factor-1 treatment promotes amyloid plaque remodeling in cerebral cortex but fails to preserve cognitive function in male 5XFAD mice.. *Journal of Alzheimer's disease : JAD*, 2025. PMID [39610283](#) DOI [10.1177/13872877241299056](#) (Documents seven months of intranasal treatment in male mice, with some body-composition and amyloid findings but no preservation of behavioral or memory outcomes.)

PEG-MGF

Pegylated mechano growth factor, IGF-1Ec

IGF-1 splice variant, pegylated

Module 2 · Recomposition

Goals: Hypertrophy, Recovery

Route: SC

WADA prohibited

An experimental PEG-conjugated MGF E peptide with no identified human administration trials, uncertain pharmacokinetics, and disputed muscle-growth mechanisms.

WHAT IT IS

PEG-MGF usually refers to a synthetic 24 amino acid fragment from the distinctive C-terminal region of an IGF-1 E domain, conjugated to polyethylene glycol. MGF means mechano growth factor. The name has also been used for an IGF-1 transcript, its precursor protein, and several synthetic peptide constructs. Those meanings are not interchangeable. In humans, the relevant transcript is generally called IGF-1Ec. The corresponding rodent splice variant is commonly called IGF-1Eb. These precursors contain the mature IGF-1 sequence and differing E domains. The isolated synthetic C-terminal fragment does not contain mature IGF-1. Research on the full precursor therefore cannot automatically establish the activity of the short fragment. PEG attachment is intended to change a molecule's distribution, degradation, or elimination. Its effects depend on the peptide sequence, attachment site, PEG size, and formulation. It can also change biological activity. A longer circulating lifetime and retained activity cannot be assumed for an unspecified PEG-MGF preparation. Three evidence questions need separate answers: whether the transcript responds to exercise, whether a synthetic E peptide has biological effects, and whether PEG-MGF benefits people. Human biopsy studies support the first. Mixed cell and animal findings address the second. The label PEG-MGF does not provide a complete molecular specification. Meaningful comparison with a publication requires the exact peptide sequence, chemical modifications, PEG characteristics, and measured content. A shared name alone does not establish that two preparations are equivalent.

MECHANISM

Alternative splicing of IGF-1 produces precursor proteins with different E domains while retaining the mature IGF-1 sequence. The distinctive human IGF-1Ec sequence includes a 49 base pair insertion that changes the reading frame. The corresponding rodent insertion differs. The synthetic MGF peptide represents the final 24 amino acids of the distinctive E-domain region, rather than the complete E domain or precursor. Kandalla 2011, PMID 21354439, describes this structural context.

Human exercise research establishes a temporal expression pattern. Philippou 2009, PMID 19567392, studied ten healthy male volunteers after exercise-induced muscle damage. Muscle biopsies showed rapid, transient MGF transcript upregulation, followed by more sustained increases in other IGF-1 transcripts. The investigators also reported protein-expression changes. These measurements do not establish the concentration or biological activity of a freely circulating 24 amino acid peptide.

Some experiments support biological activity of synthetic E peptides. In the same Philippou study, an IGF-1 receptor-neutralizing antibody did not block the synthetic peptide's proliferative effect in C2C12 cells. Akt phosphorylation was not detected. Those observations suggested signaling that differed from mature IGF-1 under those experimental conditions. They do not establish a unique receptor or prove receptor independence in every tissue.

Kandalla 2011, PMID 21354439, reported increased proliferative lifespan and delayed senescence in muscle progenitor cultures from neonatal and young adult donors. Those lifespan effects were absent in cultures from older donors. The study also reported effects on fusion and hypertrophy. It does not support a blanket statement that the peptide consistently prevents muscle-cell fusion.

Replication has been inconsistent. Fornaro 2014, PMID 24253050, describes experiments conducted at two pharmaceutical companies. MGF peptides did not reproduce the reported proliferation, differentiation, or ERK-signaling effects across the tested systems. Mature IGF-1 and the full precursor produced responses in

comparison experiments. This challenges specific MGF E-peptide claims. It was not a clinical trial or a definitive test of every possible PEG-MGF construct.

The endogenous peptide question also remains distinct from synthetic peptide activity. Matheny 2010, PMID 20130113, reported that an analogous free peptide had not been isolated from the biological sources reviewed. That is a dated assessment of endogenous processing evidence. It does not mean the transcript is fictitious, or that a synthetic peptide cannot have pharmacological activity.

Later mechanistic work complicates the claim that no interacting protein has ever been identified. Podratz 2020, PMID 32511954, identified nucleolin as an MGF-binding partner in neuronal experiments. Nucleolin antibodies prevented the reported protective effect in culture. This does not establish a validated PEG-MGF receptor in human skeletal muscle, but it makes an absolute absence-of-target statement inaccurate.

The defensible mechanism is therefore conditional. Exercise-responsive transcript biology is documented. Synthetic E peptides have shown context-dependent effects, including positive animal findings and negative replication experiments. PEG-MGF-specific target engagement, tissue exposure, dose-response relationships, and clinical effects remain uncharacterized in the human literature identified here.

EVIDENCE · GRADE D

Grade D applies to PEG-MGF-specific claims about muscle growth, recovery, and performance. No human administration trial or controlled animal efficacy study of a clearly specified PEG-MGF conjugate was identified in this search. The evidence supporting its proposed use is indirect, mechanistic, or anecdotal.

Related MGF E peptides do have published animal data. Those experiments support grade C for the particular constructs and outcomes studied, not an automatic upgrade for PEG-MGF. The distinction concerns molecular identity as well as species. A peptide delivered from a PEG-based scaffold is also different from a peptide chemically conjugated to PEG.

The negative replication study is relevant but does not establish universal inactivity. Conversely, positive cell or animal findings do not establish hypertrophy or recovery benefits in healthy adults. The available literature supports uncertainty about translation, rather than either guaranteed benefit or proven absence of all biological activity.

Human data. Philippou 2009, PMID 19567392, measured IGF-1 isoform expression in exercised human muscle. Participants did not receive PEG-MGF. The reported transcript and protein-expression changes describe endogenous responses to damage, not the efficacy of an administered research compound. Kandalla 2011, PMID 21354439, used human muscle progenitor cells in culture. Increased proliferative lifespan and delayed senescence depended on donor age. Human-derived cells do not constitute a human treatment trial, and their responses do not establish improvements in strength or recovery. The PubMed search identified no published human administration study of PEG-MGF or the isolated synthetic MGF E peptide. Dominikowski 2026, PMID 42395176, reviews the uneven evidence surrounding performance-oriented GH and IGF-1 axis peptides. It emphasizes uncertain composition, dosing, and combinations in self-administration reports. A narrative review does not supply missing clinical outcomes or establish adverse-event rates for PEG-MGF. Kletzl 2017, PMID 28110155, studied a different PEGylated recombinant IGF-1 molecule in 62 healthy volunteers. Its pharmacokinetic findings illustrate that a defined PEG conjugate can be studied systematically. Neither its

Animal and mechanistic data. Animal evidence exists for related synthetic E peptides and must not be omitted. Mills 2007, PMID 17845560, reported improved engraftment of human myogenic precursor cells in mice following delivery of an MGF E peptide. This was a transplantation model, not a trial of PEG-MGF for hypertrophy in healthy people. Shioura 2014, PMID 25606570, reported that a stabilized synthetic MGF E-domain analog improved selected cardiovascular measurements after myocardial infarction in mice. Effects depended on the disease setting and treatment period. The study does not establish the efficacy or pharmacokinetics of an unspecified PEG-MGF conjugate. Peña 2015, PMID 25678113, delivered E peptide using PEG-based polymeric microstructures in a mouse myocardial-infarction model. The study reported functional benefits. PEG was part of the delivery material, which is not evidence that the peptide itself was PEGylated. These studies prevent describing all MGF peptide evidence as exclusively in vitro. They still leave PEG-MGF-specific efficacy, systemic toxicity, reproductive effects, and long-term outcomes unresolved. Mouse cells tested outside the animal in Fornaro 2014, PMID 24253050 remain in vitro evidence, even though their source was an animal.

exposure measurements nor its short-term tolerability findings establish the behavior of a PEGylated E-domain fragment.

REGULATORY STATUS AND SPORT

STATUS

PEG-MGF is an experimental research compound. No approved therapeutic PEG-MGF product or prescribing label was identified in the sources reviewed. Accordingly, there is no established approved indication, clinical dosing schedule, or product-specific patient information to reproduce here. A research-use label does not establish suitability for human administration. A certificate of analysis likewise does not establish approval, clinical effectiveness, or pharmaceutical manufacturing compliance. Compounding status and import rules require separate, current jurisdiction-specific review. The available evidence does not justify categorical claims about every country's laws or every possible supplier. The name also creates a regulatory and scientific identification problem. A full-length IGF-1Ec-related protein, a synthetic E-domain fragment, and a PEG-conjugated fragment are different materials. Thevis 2014, PMID 25466910, characterized a modified full-length MGF-related protein. That paper cannot establish the composition of every preparation labeled PEG-MGF. Product identity must be resolved before evidence about a particular molecule can be applied.

WADA

Prohibited at all times under S2.3, Growth Factors and Growth Factor Modulators, of the 2026 WADA Prohibited List. The subsection explicitly names mechano growth factors. PEG modification does not provide an exemption from the class prohibition. Source: [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Prohibition applies during competition and outside competition. Historical analytical work, including Thevis 2014, PMID 25466910, supports that MGF-related materials have been relevant to doping controls. A published assay for one construct does not establish identical detection behavior for every PEG-MGF preparation. No detection windows or testing-avoidance claims are provided.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Subcutaneous and intramuscular administration are described in non-clinical accounts of PEG-MGF use. Neither route has a validated human absorption, bioavailability, or efficacy profile for this compound. Reports of administration near a trained muscle do not establish selective delivery or a local growth effect. Animal E-peptide studies used construct-specific delivery methods. Mills 2007, PMID 17845560, describes intramuscular or systemic delivery in mice. Peña 2015, PMID 25678113, used local cardiac delivery from polymeric microstructures. Neither establishes interchangeability with routine subcutaneous administration of PEG-MGF. Oral, intranasal, and topical bioavailability have not been established in the sources reviewed. The absence of such evidence is more precise than a categorical claim that every possible formulation is inactive by those routes.

HALF-LIFE

Unknown for a clearly specified PEG-MGF preparation in humans. No validated human or animal pharmacokinetic estimate for the marketed PEG-MGF category was identified. Claims of prolonged exposure remain a formulation hypothesis unless supported by measurements of the actual conjugate. Kletzl 2017, PMID 28110155, reported a 140 to 200 hour half-life for a different PEGylated recombinant IGF-1 molecule. That value does not belong to PEG-MGF. The peptide sequence, PEG attachment, molecular size, target interactions, and analytical method differ. A measured signal also requires interpretation. An assay may detect intact active material, a fragment, or related immunoreactivity. Persistence of a laboratory signal does not necessarily equal persistence of biological activity. A defensible PEG-MGF half-life claim would identify the molecular construct, species, administration route, assay specificity, and sampled time course.

TIMING

Post-training administration is described in non-clinical use, but no clinical study establishes an effective PEG-MGF timing window. The rationale borrows from the endogenous expression pattern in Philippou 2009, PMID 19567392. That study measured tissue responses after exercise-induced damage rather than the effects of an administered peptide. Transcript production, precursor processing, peptide distribution, and target engagement occur at different biological levels. A transient rise in messenger RNA cannot identify when an external PEG conjugate should be present. It also cannot determine whether external exposure would reinforce, disrupt, or leave the endogenous response unchanged. Published disease-model experiments with related E peptides address their own treatment windows. They do not validate post-workout timing for healthy adults. Training-day and non-training-day schedules remain untested conventions.

CYCLE LENGTH

No evidence-based cycle length or washout interval exists for PEG-MGF. Courses lasting 4 to 6

© UU LIFE · UU weeks, sometimes followed by a similar break, are commonly cited in non-clinical use; not validated in trials. This describes a circulating convention and is not a recommended schedule. A

training block is not a pharmacokinetic study. Without a characterized conjugate and repeated-exposure measurements, its accumulation and persistence cannot be calculated reliably. A break of a particular duration also cannot be assumed to reverse biological effects, prevent immune responses, or remove longer-term risk. Animal study durations with other E-peptide constructs do not supply a validated human cycle. Their species, disease model, delivery method, and endpoints differ from performance-oriented use.

TITRATION

No validated titration method, therapeutic window, or treatment target exists. Serum IGF-1 has not been established as a marker of PEG-MGF exposure or response. The synthetic fragment differs from mature IGF-1, and cross-reactivity with a clinical assay would require separate validation. Changing the amount until soreness, recovery, or body weight changes does not establish a dose-response relationship. Those outcomes also respond to training load, food intake, sleep, fluid balance, and other substances. Lack of an immediate symptom cannot establish tolerability over repeated exposure. A clinical assessment of suspected adverse effects may include laboratory testing chosen for the presentation. That is different from a validated protocol for adjusting PEG-MGF. No target concentration, escalation step, or dose-adjustment rule can be derived from the studies cited here.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
PEG-MGF dosing descriptions from non-clinical use. These are reported conventions, not established starting doses or an effective therapeutic range.	100 to 200 mcg per administration, commonly cited in non-clinical use; not validated in trials.	Subcutaneous; some non-clinical accounts describe intramuscular administration.	Two to three administrations per week in non-clinical accounts; this frequency is not validated in trials.	commonly cited in non-clinical use; not validated in trials. No verified study establishes efficacy, tolerability, dose equivalence between routes, or a reliable relationship between labeled and delivered content. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.
A higher PEG-MGF range also appears in non-clinical descriptions. Its presence does not establish a dose-response relationship or justify escalation.	200 to 400 mcg per administration, commonly cited in non-clinical use; not validated in trials.	Subcutaneous or intramuscular in non-clinical descriptions; comparative bioavailability is unknown.	Two to three administrations per week in circulating non-clinical descriptions; no validated frequency exists.	commonly cited in non-clinical use; not validated in trials. This range is retained as a description of reported use, not as evidence that higher exposure improves outcomes. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.
Laboratory exposure to MGF peptides in a negative replication study. This was not a PEG-MGF administration study or a human body dose.	Up to 0.5 mcg/mL in culture medium, equivalent to the 500 ng/mL reported by Fornaro 2014, PMID 24253050.	In vitro addition to culture medium in myoblast experiments.	Exposure during experimental assays; the abstract does not establish one universal exposure duration or replenishment schedule.	Fornaro 2014, PMID 24253050. The investigators reported no increase in proliferation at concentrations up to this level. Other assays also failed to reproduce proposed differentiation or signaling effects. These concentrations cannot be converted directly into an injected dose. · PMID 24253050

STACKING

+ CJC-1295

Proposed pairing only; no demonstrated synergy. Non-clinical descriptions combine GH-axis stimulation with a presumed local E-peptide effect. No PEG-MGF combination trial was identified. Evidence that one component changes GH or

– IGF-1 LR3

No validated combination exists. IGF-1 LR3 and an isolated MGF E fragment should not be treated as interchangeable or as a proven complementary pair. Adding an IGF-1 analog introduces separate metabolic and growth-signaling concerns.

- Hexarelin

No validated interaction study exists. Hexarelin adds GH-axis pharmacology to an already uncharacterized exposure. Dominikowski 2026, PMID 42395176, discusses endocrine and metabolic concerns across this broader peptide category. Those class observations are not a measured PEG-MGF interaction rate. Multiple simultaneous exposures complicate interpretation of symptoms and laboratory changes without establishing an added benefit.

Proposed pairing only; no demonstrated synergy. GH-release physiology is used to justify combining ipamorelin with PEG-MGF, but the combination has not been clinically characterized. Claims about selectivity of a secretagogue do not establish combination tolerability. A change in weight, recovery, or laboratory measurements cannot be assigned to PEG-MGF when exposures and training variables change together.

Proposed recovery pairing with no identified combination evidence. A shared marketing goal does not establish complementary mechanisms or additive benefit. Neither a positive animal result for one compound nor an uncontrolled experience with both measures the interaction. This pairing has no validated dose relationship, treatment duration, or adverse-event profile. No synergy claim is supported.

Proposed tissue-repair pairing with no identified combination trial. Evidence involving thymosin-related molecules and evidence involving MGF E peptides concern different constructs and experimental settings. Combining their mechanistic narratives does not establish improved healing. Molecular identity, co-exposure, and outcome attribution remain unresolved. No additive or synergistic effect can be quantified from the sources reviewed.

The frequency and character of PEG-MGF adverse effects are unknown. No prospective human administration study was identified from which common, uncommon, or dose-dependent effects could be estimated. Anecdotal reports cannot reliably separate the intended peptide from contamination, incorrect identity, or other substances used concurrently. Dominikowski 2026, PMID 42395176, discusses fluid retention, musculoskeletal symptoms, injection-site reactions, and endocrine or metabolic disturbances across GH and IGF-1 axis peptides. Those findings must remain class-level context. They do not show that isolated PEG-MGF causes each listed effect. Kletzl 2017, PMID 28110155, reported injection-site erythema with a different PEGylated IGF-1

molecule. That observation does not supply a PEG-MGF adverse-event profile. General administration-related irritation is plausible, but it should not be presented as a measured incidence or an expected harmless reaction.

SERIOUS SIGNALS

Potential serious problems include severe allergic reactions, contaminated-material infections, and unexpected pharmacological effects from incorrectly identified contents. These are plausible hazards of uncharacterized parenteral material, not quantified outcomes from PEG-MGF trials. Mitogenic effects require careful wording. Growth and survival signaling in related experimental systems creates a concern about effects on existing abnormal tissue. Whether a specific PEG-MGF conjugate promotes tumors in humans is unknown. The class discussion in Dominikowski 2026, PMID 42395176, describes biological plausibility rather than a demonstrated PEG-MGF cancer risk. Hypoglycemia is a concern with some IGF-1-active exposures, but its incidence with PEG-MGF has not been established. It cannot be ruled out for material with uncertain identity or additional substances. PEG-related hypersensitivity or immune responses are also potential formulation concerns whose frequency has not been characterized here. Absence of reported events cannot establish long-term tolerability. Reproductive toxicity, carcinogenicity, organ toxicity, and repeated-exposure immunogenicity remain important unanswered questions for the actual conjugate.

CONTRAINDICATIONS

There is no approved PEG-MGF label with formally established contraindications. Precautionary exclusions must therefore be distinguished from contraindications proven in PEG-MGF trials. Pregnancy, breastfeeding, and use in children lack supporting reproductive or developmental safety evidence. Known hypersensitivity to PEG or another formulation component raises an additional concern. Active malignancy, an unexplained mass, or a previous cancer history requires individualized clinical assessment because growth-signaling effects are unresolved. Diabetes, recurrent hypoglycemia, proliferative retinopathy, acromegaly, or an untreated pituitary disorder complicate interpretation of growth-axis or metabolic symptoms. These conditions are reasons for particular clinical caution, not validated PEG-MGF-specific interaction findings. Unverified identity, sterility, or content prevents a reliable assessment regardless of medical history. Anti-doping prohibition is a separate eligibility issue, not a medical contraindication. Its classification belongs in the WADA field.

STOP RULES

Following exposure, breathing difficulty, throat or facial swelling, collapse, seizure, or severe confusion warrants emergency care and no further exposure. These signs can indicate anaphylaxis, severe metabolic disturbance, or another acute illness. Expanding redness, increasing pain, warmth, drainage, or fever after an injection warrants prompt assessment for infection. Recurrent sweating, tremor, confusion, or faintness also requires assessment, particularly when additional glucose-active substances may be involved. New visual changes, marked swelling, persistent numbness, or an unexplained lump require clinical evaluation. These findings do not establish that PEG-MGF caused the problem, but they should not be normalized as evidence of tissue repair. An exposure history should include the product label, claimed contents, timing, route, and all concurrent substances. Available packaging and laboratory documentation may help clinicians assess an uncertain exposure. Symptom improvement alone does not validate restarting or changing the amount.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved standard vial presentation exists. Labels describing 2 mg or 5 mg containers appear in non-clinical descriptions; these are claimed container contents, not validated doses or proof of available peptide. The actual specification may differ between preparations carrying the same name. For a conjugated molecule, mass can refer to the complete peptide-PEG conjugate, peptide-equivalent content, or an inadequately defined nominal amount. Excipients, counterions, water content, and analytical assumptions can also affect interpretation. It is inaccurate to assume that every stated mass means gross vial weight, or that it always means isolated peptide mass. A usable analytical specification identifies what the mass represents and how it was measured. Without that information, a concentration calculation is only arithmetic applied to an unverified label. It cannot establish the amount of intact active material.

SOLVENT

No clinically validated PEG-MGF diluent, reconstitution procedure, or compatibility specification was identified. Bacteriostatic water and sterile water appear in non-clinical descriptions, but their use does not demonstrate stability or suitability for a particular conjugate. A preservative can limit growth of some organisms under specified conditions. It does not sterilize contaminated powder, eliminate endotoxin, or establish compatibility with the peptide. Likewise, a sterile diluent does not make the resulting preparation a validated sterile medicine. Solubility, adsorption to surfaces, aggregation, pH tolerance, and preservative compatibility require formulation-specific measurements. Laboratory handling conditions depend on the characterized material and the experiment. No solvent choice or mixing method here should be read as a procedure for preparing an unapproved compound for human administration.

STORAGE

No validated PEG-MGF storage temperature, post-reconstitution shelf life, freeze-thaw tolerance, or beyond-use interval was identified. Chemical stability, biological activity, and microbiological quality are separate questions. A solution may retain its appearance while losing activity or becoming contaminated. Refrigeration and a preservative do not independently establish an acceptable storage interval. The absence of cloudiness or visible particles does not establish sterility. Conversely, general peptide-handling conventions cannot prove that every PEG-MGF construct must never be frozen or shaken. Those effects depend on the conjugate, solvent, concentration, container, and handling conditions. A defensible storage claim requires testing of the actual formulation under the stated conditions. For laboratory material, documented stability limits must come from a qualified, formulation-specific specification. Visible particles, discoloration, or container damage indicate a quality problem, but visual inspection cannot validate a preparation that appears unchanged.

Hypothetical concentration arithmetic only, with no administration route or frequency assigned. If an analytically confirmed 2 mg of a specified material were contained in a final volume of 2 mL, the concentration would be 1 mg/mL. The same concentration is 1000 mcg/mL. These numbers are mathematical inputs, not study doses, labeled PEG-MGF instructions, or a proposed treatment. A final volume is the total solution volume after preparation. It is not necessarily identical to the volume of liquid initially added. The distinction matters whenever exact concentration is required. It also assumes complete dissolution, uniform distribution, and no material loss during preparation. If the same confirmed 2 mg were contained in a final volume of 1 mL, the calculated concentration would be 2 mg/mL. That is 2000 mcg/mL. This second hypothetical example illustrates that concentration changes when volume changes; it does not establish a preferred dilution. The calculation also depends on the stated mass basis. A result expressed as conjugate mass per mL is not automatically peptide-equivalent mass per mL. Neither can be converted into a biological activity unit without a validated activity assay. Syringe-barrel markings are volume graduations and should not be confused with IU of peptide activity. No established PEG-MGF potency standard connects such markings to an effective amount.

BUYING NOTES

A research-use label and a high purity percentage answer different questions from clinical suitability. Neither establishes approved status, reliable content, sterility, endotoxin control, or a demonstrated benefit. An analytical certificate can help characterize a sample, but its scope and limitations matter.

Thevis 2014, PMID 25466910, characterized material presented as full-length MGF and found a modified IGF-1Ec-related sequence. The product lacked a terminal lysine and contained an R109H substitution. This illustrates identity ambiguity in an MGF-related preparation. It does not prove that all PEG-MGF material has those alterations or that every supplier uses the same construct.

Mongongu 2021, PMID 33587816, reported oxidized forms and quality concerns in preparations of other IGF-1 analogs. That is supporting context about related unregulated material, not a direct survey of PEG-MGF purity. Its analytical findings do not establish clinical effectiveness or a pharmacokinetic profile for PEG-MGF.

An informative certificate identifies the tested batch, sampling date, analytical laboratory, methods, acceptance criteria, and measured results. Molecular identity generally requires suitable structural analysis, rather than a chromatographic purity number alone. A dominant chromatographic peak can represent the wrong molecule. Co-eluting impurities and substances outside the method's detection scope can also be missed.

PEG conjugation adds further specification requirements: peptide sequence, PEG molecular-weight distribution, attachment site, conjugation ratio, unconjugated peptide, and residual reagents. Mass spectrometry may contribute to identity confirmation, but heterogeneous PEG distributions can require additional methods. One instrument result does not automatically answer every structural question.

Content testing establishes how much specified material was measured. Purity testing estimates composition under the chosen method. Sterility and endotoxin testing address separate hazards. Batch matching and sample traceability determine whether the report applies to the material being discussed.

Even extensive analytical characterization would not supply missing human pharmacology or establish suitability for self-administration. It reduces some identity uncertainty while leaving clinical benefit, dosing, and longer-term safety unresolved.

COMMON MISTAKES

- Treating an exercise-responsive transcript as proof that administering PEG-MGF improves hypertrophy. Expression studies and intervention trials answer different questions, and the latter were not identified for PEG-MGF.
- Using MGF to mean the transcript, full precursor, isolated E peptide, and PEG conjugate interchangeably. Each requires its own molecular specification and evidence assessment.
- Describing the Fornaro replication as proof that PEG-MGF cannot work in any setting. It challenged particular E-peptide effects in specified cell systems, not every construct or clinical outcome.
- Claiming there are no animal studies of MGF peptides. Related E peptides have animal findings, but those findings do not establish efficacy of a PEG-MGF conjugate.
- Confusing peptide release from a PEG-based polymer scaffold with chemical PEG attachment to the peptide. The Peña delivery study, PMID 25678113, supports the former.
- Borrowing the 140 to 200 hour half-life from a different PEGylated IGF-1 molecule, PMID 28110155. That measurement cannot establish PEG-MGF exposure or scheduling.
- Treating post-training timing, cycle length, or a circulating dose range as established practice. These descriptions have no validated PEG-MGF clinical dose-response basis.
- Reading a purity percentage as proof of identity, content, sterility, and endotoxin control. These require distinct measurements and a report traceable to the relevant sample.
- Assuming a preservative or refrigeration validates a multiweek storage interval. No formulation-specific PEG-MGF stability or microbiological interval was identified.
- Attributing progress to a peptide while training, food intake, sleep, and other exposures change simultaneously. Such observations cannot establish PEG-MGF efficacy or combination synergy.

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Follistatin-344 (FST-344)

FST-344

Activin and myostatin binding protein

Module 2 · Recomposition

Goals: Hypertrophy

Route: SC (research)

WADA prohibited

An activin and myostatin binding protein with preliminary human gene therapy findings, mixed animal protein data, and no established injectable protein regimen for trained adults.

WHAT IT IS

Follistatin is an endogenous protein that binds several members of the TGF-beta superfamily, including activins and myostatin. These signaling molecules influence muscle growth, reproductive physiology, and other tissue functions. Binding them can reduce their availability to receptors. However, inhibiting a regulator of muscle growth does not establish that a particular preparation improves strength or physique. Follistatin is a folded, disulfide-rich protein rather than a short synthetic peptide. Its sequence, processing, aggregation state, and biological activity matter when interpreting research material. A name on a container does not establish equivalence to the material used in a publication. The number 344 describes a precursor isoform. Alternative splicing produces precursors containing 344 or 317 amino acids. Removal of a 29 amino acid signal peptide yields FST315 or FST288, respectively. FST315 is generally associated with circulation, whereas FST288 binds cell surfaces more strongly. The longer isoform has an acidic extension that influences accessibility of the heparin-binding region and tissue association (PMIDs 25322757 and 19273500). The human gene therapy studies used the FS344 coding sequence to produce secreted follistatin from transduced muscle. Selection of this isoform was intended to limit unwanted effects compared with more strongly tissue-bound forms. It does not establish molecular selectivity for muscle or exclude effects on reproductive and metabolic signaling. The central distinction is the intervention. An AAV vector delivers genetic instructions, allowing cells to produce protein over an extended period. Recombinant protein administration delivers an externally manufactured protein with its own absorption, distribution, and clearance. Vector genomes cannot be converted into mcg of injected protein. Results from gene transfer therefore do not establish a regimen for material labeled Follistatin-344.

MECHANISM

Follistatin acts through ligand binding rather than direct receptor blockade. Structural work summarized in the activin review describes two follistatin molecules surrounding a ligand dimer. This arrangement obstructs receptor-binding surfaces and reduces ligand availability. Binding affinity and tissue effects depend on the ligand, follistatin isoform, and local environment (PMID 19273500).

Activins and myostatin signal through combinations of type II and type I receptors. These include ActRIIA, ActRIIB, and downstream activin receptor-like kinases. Receptor preferences differ between ligands, so a single identical receptor sequence should not be assigned to every member of this family. A central downstream pathway involves phosphorylation of Smad2 and Smad3, followed by transcriptional regulation with Smad4.

In skeletal muscle, these signals can restrain growth and influence differentiation, protein turnover, and fibrosis. Follistatin-mediated ligand sequestration can reduce these restraints. Interactions with Akt and mTOR signaling help explain increased protein synthesis in experimental systems. However, pathway diagrams do not specify how much protein reaches human muscle after subcutaneous administration. They also do not establish the duration of receptor-level effects or the balance between muscle and non-muscle exposure (PMIDs 27695802 and 33802348).

Follistatin is broader than a selective myostatin inhibitor. Activin binding contributes to its biological effects, including effects that cannot be explained by myostatin inhibition alone. This breadth helps explain substantial hypertrophy in some animal models, but it also creates uncertainty outside muscle. Activin participates in pituitary FSH regulation, ovarian biology, pancreatic function, immune signaling, and tissue repair. These roles

provide reasons to investigate systemic effects, not proof that every exposed person develops a particular adverse event (PMID 19273500).

Muscle growth also depends on disease context and functional innervation. In severe spinal muscular atrophy mice, follistatin overexpression produced little additional muscle mass and no improvement in motor function or survival. Ligand inhibition could not overcome the principal disease process in that model. This finding limits claims that removing myostatin signaling reliably produces useful strength (PMID 19477958).

Endogenous follistatin changes with exercise. Hansen and colleagues reported a roughly sevenfold plasma increase, peaking three hours into recovery after three hours of cycling. They found no measurable net release from the exercising limb. Complementary mouse experiments supported the liver as a likely source (PMID 21068158).

That experiment did not compare recombinant protein with gene therapy or measure long-term hypertrophy from those interventions. It therefore cannot prove that transient protein exposure is ineffective. Its narrower implication is that circulating follistatin is physiologically variable. An isolated serum concentration is not an established measure of muscle target engagement or a validated dosing target.

EVIDENCE · GRADE C

Grade C applies to the claim that recombinant Follistatin-344 protein improves muscle size or performance in trained adults. Animal evidence exists, but the human gene therapy studies evaluate a different intervention. No published trial identified in this review establishes efficacy, pharmacokinetics, or a dosing regimen for unmodified recombinant FST344 or FST315 administered to healthy trained adults. The small human AAV-FS344 studies constitute preliminary grade B evidence for those specific investigational interventions in muscle disease. They cannot transfer that grade to a protein preparation or a bodybuilding schedule. The broader follistatin mechanism has experimental support, but product identity, exposure, population, and clinical outcome remain separate questions. A rat study administered recombinant FS288 protein and reported mixed effects on muscle size and force. That study strengthens the evidence inventory without validating the non-clinical subcutaneous schedule described below (PMID 35747585). The myostatin literature also documents repeated difficulty translating increased muscle mass into meaningful functional benefit. This is a limitation of clinical translation, not evidence that every intervention in the pathway is ineffective. The cited review describes the field through its 2021 publication date and should not be treated as a current worldwide regulatory inventory (PMID 33802348).

Human data. The Becker muscular dystrophy study enrolled six participants in two ascending-dose cohorts. Four showed increases of 29 to 125 m on the six-minute walk test. The abstract described the other two as showing no improvement. The full text reports a 9 m increase in one and a 14 m decrease in the other, interpreted as no meaningful benefit. The lower-dose cohort had one year of reported follow-up; the higher-dose cohort had six months. Biopsies showed changes including reduced fibrosis and muscle fiber hypertrophy. These were uncontrolled observations, not proof of improved performance in healthy muscle (PMID 25322757). The inclusion body myositis study also treated six participants. Median annualized walking performance increased by 56.0 m per year, compared with a decline of 25.8 m per year in eight matched untreated subjects. The reported comparison had $p = 0.01$. Four treated participants improved by 58 to 153 m, while two improved by 5 to 23 m. Annualized change is a derived outcome and should not be presented as an identical one-year response for every participant (PMID 28279643). Both studies were small and lacked randomized placebo-controlled treatment assignment. The second used

Animal and mechanistic data. The nonhuman primate study reported increased quadriceps size and strength after intramuscular AAV1-FS344 gene delivery. The authors also reported no detected abnormalities in the organ assessments performed. Those observations apply to the animals, exposure, assays, and follow-up studied. They do not establish comprehensive human safety or validate repeated recombinant protein administration (PMID 20368179). PubMed now links that primate article to an August 2026 erratum. Its metadata was verified during this review, but the correction text could not be retrieved. The original findings are retained as reported findings with this unresolved qualification. The correction's consequences for individual figures or conclusions are not assumed (PMID 42555759). Rodent studies summarized in the myostatin literature show substantial hypertrophy after follistatin overexpression. Results depend on disease model and intervention. In severe spinal muscular atrophy mice, transgenic follistatin produced little muscle growth and no motor or survival benefit. This is evidence against universal efficacy, rather than evidence that all follistatin interventions fail (PMIDs

an untreated comparison group, which does not remove expectation effects, selection differences, or differences in supportive care. Both involved muscle disease rather than trained healthy adults. The studies also used protocol-based clinical monitoring and peri-treatment immunosuppression. A structured exercise program was explicitly introduced in the inclusion body myositis study. Greater exercise participation was associated with larger improvements, but exercise adherence was not randomized. The Becker report did not document the same prescribed exercise intervention. These publications support further investigation of gene delivery in selected muscle diseases. They do not establish that recombinant Follistatin-344 protein produces the same exposure, histological effects, or functional outcomes.

27695802 and 19477958). Direct recombinant protein research also exists. Feger and colleagues studied FS288 in rats after temporary muscle denervation and reinnervation. A subcutaneously implanted pump and catheter system delivered protein locally. Results included increased satellite cell counts after denervation, but mixed muscle weight and force outcomes. Some groups had smaller muscles or reduced force. A surgically implanted local infusion system is not equivalent to intermittent subcutaneous injection of FST315 or an unspecified FST344 preparation (PMID 35747585).

REGULATORY STATUS AND SPORT

STATUS

No approved follistatin treatment or prescribing label was identified in this review. The cited AAV-FS344 studies were investigational clinical studies, not marketing authorizations. Their existence does not establish authorization for recombinant protein preparations. In a 2020 enforcement letter, FDA identified follistatin among substances used in compounded products that did not qualify for the cited section 503A exemptions. That document supports a specific United States regulatory finding. It does not establish the current legal status of every formulation, research activity, or jurisdiction. [FDA enforcement letter, April 1, 2020](<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/tailor-made-compounding-llc-594743-04012020>). A laboratory reagent designation does not constitute approval for administration to people. Regulatory authorization, lawful research supply, and product quality are separate questions.

WADA

Prohibited at all times under S4.3 of the 2026 WADA Prohibited List, Agents Preventing Activin Receptor IIB Activation. Follistatin is explicitly listed as a myostatin-binding protein. Gene transfer with potential to enhance sport performance is separately prohibited under M3.1. [WADA Prohibited List](<https://www.wada-ama.org/en/prohibited-list>). These prohibitions apply in and out of competition. A research designation or absence of an approved indication does not create an exemption.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

The cited human AAV studies used direct bilateral intramuscular administration into quadriceps muscles during a single treatment session. A treatment session involved multiple injection sites, so describing the intervention as one injection is misleading. The Becker study used imaging-guided administration across selected quadriceps muscles (PMID 25322757). Local vector administration does not guarantee that the expressed protein remains local. The FS344 construct produces a secreted isoform, and circulating or remote effects are biologically possible. Route of vector delivery and distribution of the resulting protein are different properties. Animal recombinant protein research includes local delivery through a catheter connected to a subcutaneously implanted pump. The pump's location does not make its exposure equivalent to an ordinary subcutaneous bolus (PMID 35747585). No human route was identified as validated for the unmodified recombinant protein preparations discussed here. Oral and intranasal bioavailability were also not established in the reviewed evidence.

HALF-LIFE

A clinically usable human elimination half-life was not identified for unmodified recombinant FST344 or FST315 administered by the non-clinical subcutaneous route. Values assigned to endogenous follistatin, another isoform, an engineered derivative, or another species cannot be transferred without supporting pharmacokinetic data. The exercise study measured a changing endogenous concentration. Production, secretion, distribution, binding, and clearance can all contribute to that curve. It was not an injected-protein pharmacokinetic study and cannot establish an elimination half-life. Protein size alone also does not determine persistence (PMID 21068158). Gene therapy requires a different description. Vector persistence, transgene expression, secreted protein turnover, and the duration of a biological effect are separate quantities. The primate study reported durable effects after gene transfer, but those findings do not supply a half-life for a

recombinant protein preparation. Its linked 2026 erratum remains a qualification to interpretation (PMIDs 20368179 and 42555759).

TIMING

No validated timing relative to resistance training, meals, or sleep was identified for recombinant Follistatin-344 protein. The endogenous exercise response does not supply a treatment schedule or establish an optimal administration window. The inclusion body myositis study incorporated exercise and reported greater improvement among participants who exercised more. That association cannot isolate the contribution of exercise, gene transfer, or differences between participants. It also cannot establish that protein administration immediately before or after exercise changes outcomes (PMID 28279643). The appropriate interpretation is that exercise was part of the studied clinical context. The reported findings do not justify importing training-day timing rules into a recombinant protein protocol.

CYCLE LENGTH

The human AAV studies used a single treatment session, followed by clinical observation. In the Becker report, follow-up differed between cohorts, with approximately six months or one year reported. Observation length is not a validated treatment cycle or the time when transgene expression necessarily ends (PMID 25322757). For recombinant protein, courses of 10 to 30 days are commonly cited in non-clinical use; not validated in trials. No identified human study establishes an optimal course, washout interval, cumulative exposure limit, or repeated-course outcome for that practice. Gene transfer can produce persistent expression without a routine way to terminate it on demand. Immune responses to the vector can complicate repeat administration. Those concerns are specific to gene delivery and should not be presented as a universal prohibition on every future vector-based treatment.

TITRATION

No validated individual titration schedule was identified for recombinant Follistatin-344 protein. The Becker study escalated the vector dose between separate cohorts. That design evaluated preliminary tolerability and possible benefit; it did not establish how an individual should adjust exposure over time (PMID 25322757). Each cohort contained three participants, follow-up durations differed, and functional responses varied. More prominent histological changes at the higher dose therefore do not establish a reliable dose-response curve. Serum follistatin is not an established titration target for this use. Exercise-related variability complicates interpretation, but variability alone does not make every measurement useless. A validated assay, sampling framework, exposure-response relationship, and clinically relevant target would be needed before a concentration could guide dosing (PMID 21068158).

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved drug label	No approved follistatin prescribing label or label dose was identified.	Not applicable.	Not applicable.	Regulatory review. Investigational vector doses are not approved protein doses.
Human Becker muscular dystrophy trial, lower-dose cohort, three participants	3 x 10¹¹ vg/kg per leg of AAV1.CMV.FS344, delivered intramuscularly to both quadriceps during one treatment session, PMID 25322757.	Bilateral intramuscular quadriceps administration across multiple sites.	One treatment session.	Published phase 1/2a study, PMID 25322757. Two participants increased six-minute walking distance by 58 and 125 m. The third had no meaningful improvement. The publication reports one year of follow-up for this cohort. · PMID 25322757
Human Becker muscular dystrophy trial, higher-dose cohort, three participants	6 x 10¹¹ vg/kg per leg of AAV1.CMV.FS344, delivered intramuscularly to both quadriceps during one treatment session, PMID 25322757.	Bilateral intramuscular quadriceps administration across multiple sites.	One treatment session.	Published phase 1/2a study, PMID 25322757. Two participants increased six-minute walking distance by 108 and 29 m. The third had no meaningful improvement. The publication reports six months of follow-up for this cohort. · PMID 25322757

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human sporadic inclusion body myositis trial, six participants	6 x 10¹¹ vg/kg of rAAV1.CMV.huFS344, reported in the abstract for intramuscular delivery to quadriceps muscles of both legs during one treatment session, PMID 28279643.	Bilateral intramuscular quadriceps administration.	One treatment session, with a participant exercise program.	Published study, PMID 28279643. The exponent is 11, not an unresolved rendering problem. The abstract does not explicitly attach per leg to this dose statement, so that qualifier is not inferred from the Becker study. · PMID 28279643
Animal recombinant FS288 protein study after muscle denervation and reinnervation	The study used protein loaded into an implanted pump for continuous local delivery. No equivalent intermittent subcutaneous human dose can be derived from this experiment, PMID 35747585.	Local catheter delivery from a subcutaneously implanted osmotic pump.	Continuous infusion during the experimental treatment period.	Primary rat study, PMID 35747585. Protein isoform, delivery system, target tissue, and disease model differ from non-clinical use of material labeled Follistatin-344. · PMID 35747585
Reported non-clinical use of recombinant protein labeled Follistatin-344	100 mcg subcutaneously once daily for 10 to 30 days, commonly cited in non-clinical use; not validated in trials.	Subcutaneous, reported non-clinical practice.	Once daily for 10 to 30 days, commonly cited in non-clinical use; not validated in trials.	commonly cited in non-clinical use; not validated in trials. No identified study establishes efficacy, systemic exposure, or safety for this exact preparation and schedule. This is not a recommended regimen. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– IGF-1 LR3

No verified human combination study establishes benefit, tolerability, or dosing with follistatin. Different signaling pathways do not demonstrate additive clinical effects.

– Ipamorelin

No verified combination evidence supports adding this compound to recombinant follistatin. A proposed difference in mechanism does not establish complementary efficacy or acceptable combined exposure. Concurrent interventions would also complicate interpretation of changes in performance, fluid balance, or symptoms.

– CJC-1295

No verified human combination evidence was identified. Stimulation of a separate growth-related pathway is a mechanistic hypothesis, not an established synergy. Neither a combination dose nor a monitoring strategy can be derived from the cited follistatin gene therapy studies.

– BPC-157

Exercise participation in a gene therapy trial does not establish a need for another experimental

– **Semaglutide**

compound. There is no verified basis here for claiming prevention of tendon injury or improved recovery.

No established interaction with follistatin was demonstrated in the reviewed references. Changes in energy intake and body composition could complicate attribution of muscle outcomes. That is a study-design concern, not evidence of a direct goal conflict or a reason to alter prescribed treatment.

– **Retatrutide**

No verified follistatin combination study was identified. Simultaneous changes in weight, appetite, training, and experimental exposures would make outcomes harder to interpret.

– **FOXO4-DRI**

No verified evidence establishes the benefit or safety of this combination. Combining experimental interventions introduces additional uncertainty and complicates adverse-event attribution. Mechanistic novelty does not supply a clinical rationale, and the absence of combination evidence does not quantify the magnitude of risk.

SAFETY

COMMON EFFECTS

A frequency-ranked adverse-effect profile has not been established for non-clinical recombinant Follistatin-344 protein use. The Becker study reported no adverse effects in six participants under its monitored gene therapy protocol. That small observation cannot exclude uncommon, delayed, or exposure-dependent problems. It also does not establish tolerability for repeated protein administration (PMID 25322757). Potential administration-related problems include local pain, inflammation, infection, and allergic or other immune reactions. These are general risks of parenteral protein products, not measured follistatin-specific incidence estimates. Product impurities, aggregates, residual manufacturing material, and microbial contamination can change those risks. The primate paper reported no detected abnormalities in its organ assessments. This is limited preclinical information, and the linked 2026 erratum requires review before treating particular original findings as definitive. Neither that report nor the small human studies establishes a comprehensive safety profile (PMIDs 20368179 and 42555759).

SERIOUS SIGNALS

Broad activin sequestration creates plausible concerns outside muscle. Reproductive hormone regulation, gonadal function, glucose regulation, immune signaling, and tissue repair are relevant areas for investigation. These concerns arise from activin biology. They are not a confirmed list of adverse reactions caused by the non-clinical protein schedule (PMID 19273500). Cancer-related effects require particular caution in interpretation. TGF-beta superfamily signaling can have context-dependent roles in tumor biology. The reviewed studies do not establish that recombinant follistatin causes cancer, protects against cancer, or has acceptable exposure in people with malignancy. A mechanistic association cannot determine an individual risk estimate. Reduced force or smaller muscles occurred in some groups receiving recombinant FS288 in the rat study. These findings show that biological effects can differ by tissue condition and treatment design. They do not establish corresponding human incidence or predict what an unspecified commercial preparation would do (PMID 35747585). For AAV gene delivery, persistent expression and vector-directed immunity are separate concerns. Expression is not routinely adjustable after administration, and immune responses can constrain subsequent treatment options. Long-term risk remains incompletely characterized in the small follistatin clinical literature. Bleeding syndromes observed with other pathway interventions should not be assigned to follistatin without compound-

specific evidence. Similarly, failure to improve function is an efficacy limitation unless accompanied by documented harm.

CONTRAINDICATIONS There is no approved prescribing label establishing a formal contraindication list for this use. Pregnancy, breastfeeding, attempts to conceive, and pediatric exposure lack an established benefit-risk basis. Reproductive uncertainty is particularly relevant because activin participates in gonadal and pituitary regulation (PMID 19273500). Active or previous malignancy, significant endocrine disease, impaired glucose regulation, and previous serious reactions to biological products raise additional clinical concerns. These are precautionary considerations and evidence gaps, not confirmed label contraindications. AAV trial eligibility and exclusions also cannot be copied directly to a recombinant protein product. Known hypersensitivity to a formulation component would be a specific concern for that formulation. Missing identity, sterility, or stability documentation is a product-quality failure rather than a patient contraindication. Participation in regulated sport is governed separately by the WADA prohibition.

STOP RULES Breathing difficulty, wheezing, facial or tongue swelling, collapse, or rapidly progressive systemic symptoms require emergency evaluation. Fever with spreading redness, warmth, severe pain, or drainage at an administration site requires prompt assessment for infection. New persistent swelling, unexplained bleeding, a new mass, marked changes in reproductive function, or symptoms of abnormal glucose regulation warrant clinical review. These are general reasons for evaluation, not established follistatin-specific toxicity markers. Further experimental exposure would not resolve their cause. No validated home monitoring threshold establishes that continued exposure is acceptable. Normal routine blood tests cannot exclude all immune, endocrine, or tissue effects. With gene transfer, stopping administration does not terminate protein expression already established.

RECONSTITUTION AND STORAGE

TYPICAL VIAL No standardized clinical vial presentation exists for recombinant Follistatin-344. A stated protein mass is a content claim, not proof of identity, concentration, activity, sterility, or suitability for administration. Relevant product definitions include the actual amino acid sequence, mature isoform, expression system, formulation, and assay used to measure content. A precursor-based name alone does not specify these properties. The human AAV studies used investigational vector preparations rather than interchangeable lyophilized protein vials.

SOLVENT No generally validated clinical diluent was identified for the unspecified recombinant protein preparations discussed here. Preservative compatibility, buffer composition, pH, ionic strength, and protein concentration can affect stability and activity. Bacteriostatic water does not sterilize a contaminated product or establish a multidose shelf life. A reagent's laboratory dissolution instructions also do not establish suitability for administration to people. Formulation-specific evidence would be required before assigning a solvent, handling method, or usable concentration range. Protein aggregation can be influenced by agitation and interfaces, but those general principles do not validate a specific preparation procedure. The original step-by-step administration-oriented instructions have therefore been replaced with the limits of the available formulation evidence.

STORAGE No universal storage temperature or post-reconstitution shelf life can be assigned to unspecified material labeled Follistatin-344. Appropriate conditions depend on the actual isoform, formulation, concentration, container, and validated stability data. Temperature excursions and freeze-thaw cycles can affect proteins, but an excursion does not by itself quantify potency loss. Conversely, clear appearance does not establish stability, sterility, or biological activity. Visible particles or discoloration indicate a quality concern without identifying its exact cause. A credible stability claim requires defined conditions, time points, and suitable analytical or functional assays. A certificate issued at manufacture does not establish the condition of material after storage or transport. Shipping requirements should follow demonstrated formulation stability rather than an assumption that every protein must arrive with cold packs.

Concentration arithmetic only: a hypothetical laboratory sample containing 1 mg of protein in a final solution volume of 2 mL has a nominal concentration of 0.5 mg/mL, equivalent to 500 mcg/mL. These quantities describe an illustrative solution, not a documented clinical formulation or an administration dose.

The denominator is final solution volume. It is not automatically identical to the volume of liquid added, particularly when exact formulation volumes matter. The calculation also assumes that the stated mass is correct, that all material dissolves, and that the protein remains uniformly distributed.

or make an unverified protein preparation equivalent to study material. Measured protein content can differ from active protein content because of degradation, aggregation, or inactive species.

No administration volume or syringe setting is supplied here. Neither concentration arithmetic nor a vial label resolves the absence of a validated human protein dose, compatible formulation, or stability interval.

BUYING NOTES

The central quality question is whether the tested material matches the claimed molecular entity. Follistatin isoforms differ in sequence and tissue association. Expression systems and manufacturing processes can also alter processing, folding, glycosylation, and impurities. These properties affect the interpretation of a reagent, but price alone cannot establish authenticity or identify the cause of a quality failure. It also treated bacterial expression, low price, and warm delivery as proof of failure. Those conclusions require product-specific evidence. A preparation can differ from endogenous protein without its identity being fraudulent, while still being unsuitable for the claimed application. A useful certificate of analysis identifies the tested batch and the laboratory, methods, dates, specifications, and results. The batch identifier must connect the report to the material being described. A generic example certificate does not establish the properties of a particular batch. Independent testing can strengthen confidence when the tested sample and chain of custody are documented, but independence alone does not make an unsuitable assay informative. Identity may require peptide mapping, intact mass analysis, or other sequence-sensitive methods. Purity methods address different impurities and have different limitations. Electrophoretic purity does not establish receptor-binding activity. A high chromatographic purity percentage does not establish total protein content, correct folding, or absence of aggregates. Functional binding or cell-based assays answer questions that a purity percentage cannot. Microbiological quality is another separate issue. Endotoxin results do not demonstrate sterility, and sterility results do not establish an acceptable endotoxin burden. Residual host-cell proteins, nucleic acids, processing reagents, and particulate material may also matter. A research certificate is not equivalent to a complete pharmaceutical release assessment. The label Follistatin-344 requires clarification because it commonly refers to a precursor sequence. Nevertheless, a manufactured reagent could contain an engineered precursor, a mature isoform, a tagged construct, or another specified sequence. The number alone neither proves impossibility nor identifies the contents. The claim must be checked against sequence and analytical documentation. Finally, evidence of chemical identity does not establish clinical efficacy, dosing, regulatory authorization, or long-term safety. Even a correctly characterized laboratory reagent would not close the gap between recombinant protein administration and the published AAV gene therapy studies.

COMMON MISTAKES

- Transferring gene therapy results to recombinant protein. The human studies administered an AAV vector that changed protein production in muscle. An externally manufactured protein has a different exposure profile. Neither vector genomes nor clinical outcomes can be converted into a protein schedule without additional evidence.
- Treating an endogenous exercise response as a treatment experiment. The Hansen study documented changing circulating follistatin and supported a likely hepatic contribution. It did not compare injected protein with gene therapy or test long-term hypertrophy. It therefore establishes neither effectiveness nor ineffectiveness of recombinant protein administration (PMID 21068158).
- Reading the clinical participants as trained lifters. The cited human trials involved degenerating muscle, functional impairment, and clinical monitoring. Fibrosis, innervation, muscle reserve, and disease progression influence treatment response. Findings in those settings do not establish performance benefits in healthy adults.
- Claiming that both human trials prescribed the same exercise program. A structured program was introduced in the inclusion body myositis study. Exercise adherence was associated with outcome but was not randomized. That association cannot separate the effects of exercise, gene transfer, supportive treatment, and participant differences (PMID 28279643).
- Assuming that protein studies do not exist. Recombinant FS288 was studied in rats using local catheter delivery from implanted pumps. Outcomes were mixed, including increased satellite cell counts alongside unfavorable muscle outcomes in some groups. The study is relevant evidence but does not validate intermittent subcutaneous FST344 use (PMID 35747585).

- Assuming more muscle necessarily produces more useful function. Severe spinal muscular atrophy mice did not gain motor or survival benefit from follistatin overexpression. The wider clinical literature also documents difficulty translating muscle growth into functional improvement. Disease context and outcome selection remain essential (PMIDs 19477958 and 33802348).
- Assigning a human protein half-life from an exercise graph or another follistatin-related molecule. Endogenous concentration changes reflect secretion as well as clearance. An isoform, engineered construct, species, or administration route requires its own pharmacokinetic interpretation. A plausible numerical estimate is not a measured clinical parameter.
- Treating concentration arithmetic as validation of administration. Correct unit conversion does not verify the actual protein mass, activity, sterility, solvent compatibility, or clinical dose. A calculated concentration remains nominal when the preparation and its stability have not been established.
- Treating proposed combinations as demonstrated synergies or contraindications. Different mechanisms do not establish additive benefit. Concurrent weight loss does not prove a direct drug interaction. The revised combination entries describe evidence gaps and attribution problems rather than advising changes to prescribed treatment.
- Using the wrong anti-doping category or equating a research designation with permission. The 2026 list explicitly places follistatin under S4.3, and performance-enhancing gene transfer is separately covered by M3.1. Both apply outside competition as well as during competition.

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Recomposition is sequencing.

Fat loss and hypertrophy compounds, in the order the body accepts them.

UU LIFE

2.0



MODULE 3 OF 5 · UU LIFE PEPTIDES 2.0

SHIELDING

Recovery and protection. Tissue repair, gut integrity, immune modulation and connective tissue: BPC-157, TB-500, GHK-Cu, KPV, LL-37, thymic peptides and ARA-290.

Module 3

UU LIFE PEPTIDES 2.0

Verified references

Educational and informational reference for adults. Not medical advice, not a prescription and does not replace any substance. Many compounds described are not approved for human use and several are prohibited in sport. Decisions about any compound belong to you and a licensed clinician.

A UU LIFE PRODUCT · UU.LIFE

Cards in this module

01	BPC-157 Gastric pentadecapeptide	Evidence C
02	TB-500 Actin-binding peptide fragment	Evidence C
03	GHK-Cu Copper-binding tripeptide	Evidence C
04	KPV C-terminal alpha-MSH tripeptide	Evidence C
05	LL-37 Human antimicrobial peptide	Evidence A
06	Thymosin Alpha-1 Thymic immunomodulatory peptide	Evidence A
07	Thymalin Thymic peptide complex	Evidence A
08	ARA-290 Erythropoietin-derived innate repair receptor agonist	Evidence B

Each card: what it is, mechanism, evidence grade, regulatory and sport status, reported doses with provenance, stacking, safety, reconstitution with a worked calculation, buying notes, common mistakes and the references you can verify.

BPC-157

Body Protection Compound 157, Pentadecapeptide BPC 157

Gastric pentadecapeptide

Module 3 · Shielding

Goals: Recovery, Gut

Route: SC or oral

WADA prohibited

An investigational synthetic pentadecapeptide with extensive preclinical healing research, limited human studies, and no established clinical regimen for injury recovery.

WHAT IT IS

BPC-157 is a synthetic peptide containing 15 amino acids, with the sequence GEPPPGKPADDAGLV and a molecular weight of approximately 1419 Da. Its name expands to Body Protection Compound 157.

Publications describe it as a fragment associated with a protein isolated from human gastric juice. That description does not establish a normal physiological role for administered synthetic BPC-157 (PMIDs 14554208, 42198317).

The literature reports stability in gastric juice and biological activity through several experimental routes. Gastric stability alone does not establish absorption, systemic exposure, or clinical effectiveness after oral administration. These require separate measurements using a characterized formulation.

Class: investigational gastric pentadecapeptide. BPC-157 is not a growth hormone secretagogue, steroid, or approved replacement hormone. Its direct molecular target remains incompletely characterized. Changes in receptor expression and downstream signaling have been demonstrated experimentally, but a selective receptor-binding mechanism has not been established. Mechanistic findings explain why researchers study it; they do not establish a treatment for an injured person.

MECHANISM

A well-characterized preclinical finding concerns angiogenesis. In cultured human vascular endothelial cells, BPC-157 increased VEGFR2 expression without increasing VEGF-A expression. It also increased VEGFR2 internalization and activated signaling involving Akt and endothelial nitric oxide synthase, or eNOS. Dynasore, an endocytosis inhibitor, suppressed receptor internalization, downstream signaling, and endothelial tube formation. Rat hindlimb ischemia experiments showed improved blood-flow recovery and increased vessel formation (PMID 27847966).

These experiments support involvement of receptor trafficking and VEGFR2-associated signaling in those models. They do not demonstrate direct binding of BPC-157 to VEGFR2. Dynasore is also not a selective probe for one receptor. The findings therefore support a pathway-level mechanism rather than definitive identification of a unique drug target.

Reviews describe effects involving nitric oxide signaling, ERK1/2, inflammatory mediators, fibroblast activity, and neuromuscular stabilization. Much of this evidence comes from experimentally induced injury in animals. Activity during nitric oxide synthase inhibition or substrate supplementation suggests context-dependent interactions with the nitric oxide system. It does not establish that BPC-157 automatically normalizes nitric oxide production in humans (PMID 40789979).

A separate experiment examined cultured fibroblasts from rat Achilles tendons. BPC-157 increased growth hormone receptor expression at the messenger RNA and protein levels. Adding growth hormone to pretreated cells increased proliferation and activated Janus kinase 2 signaling. This provides a cellular hypothesis about growth hormone responsiveness, not evidence that BPC-157 increases circulating growth hormone or improves a secretagogue combination (PMID 25415472).

Another tendon-cell study found increased explant outgrowth, migration, spreading, and survival during hydrogen peroxide stress. Phosphorylation of focal adhesion kinase and paxillin increased, while direct proliferation of cultured fibroblasts was not increased in the assay used (PMID 21030672). Migration, stress resistance, and proliferation are different outcomes. They should not be collapsed into a single claim that BPC-157 grows or repairs human tendons.

Broader claims that BPC-157 explains cytoprotection across many organs remain hypotheses. Much of the foundational literature comes from overlapping investigator networks, although independent groups have also published mechanistic and animal studies. Repeated positive experiments within one network are less informative about reproducibility than independent confirmation.

The relationship between exposure and effect remains unresolved. Short persistence of intact peptide in animal plasma contrasts with effects measured later in injury models. Downstream signaling could contribute, but a validated human exposure-response model does not exist. Neither frequent administration nor prolonged effects can be inferred reliably from the plasma half-life alone (PMIDs 36588717, 42198317).

EVIDENCE · GRADE C

Grade C for clinical healing, recovery, and gastrointestinal efficacy claims. Human evidence exists, but its design and reporting are too weak to establish these benefits. A systematic review searching through June 2024 identified 544 articles and included 36 studies, comprising 35 preclinical studies and one clinical report (PMID 40756949). That search cutoff matters: its clinical-study count is not a complete description of subsequent publications. Small uncontrolled studies provide signals for further investigation, not a reliable treatment effect. Older controlled gastrointestinal research is reported in meeting abstracts with substantial reporting limitations.

Human data. The knee-pain report identified 17 treated patients, with 16 reached for telephone follow-up. Twelve received BPC-157 alone; 11 reported improvement. Seven reported relief lasting six months to one year. The study lacked a control group, standardized functional outcomes, and follow-up imaging demonstrating structural repair. The paper reports administered doses (PMID 34324435). A second pilot enrolled 12 women with interstitial cystitis who had not responded to pentosan polysulfate. BPC-157 was administered during cystoscopy. Participants reported substantial symptom improvement on questionnaires, but the study was uncontrolled and could not separate treatment effects from procedural effects, expectations, or symptom fluctuation (PMID 39325560). The intravenous pilot enrolled two adults who had already received intravenous BPC-157 before the study. Investigators monitored selected laboratory markers, vital signs, and reported symptoms over three days. They reported no meaningful changes in the measured markers and no reported side effects. Prior exposure introduces selection bias, and this design cannot establish general tolerability, uncommon harms, or long-term safety (PMID 40131143). These three reports account for 31 enrolled or identified participants, or 30 when the unreachable knee patient is excluded. They do not support the repeated claim that fewer than 30 humans have ever been studied. FDA's 2026 review also identified older rectal-administration studies, including a randomized ulcerative colitis trial reported as a meeting abstract. That trial randomized 53

Animal and mechanistic data. Animal research includes tendon transection, muscle injury, ligament injury, bone defects, gastrointestinal injury, and vascular ischemia. Studies report functional, mechanical, histological, and biochemical outcomes. These endpoints are informative within their models, but they do not establish return-to-training outcomes in humans (PMIDs 40756949, 40789979). The 2003 Achilles study reported improved mechanical properties, functional index, and tissue organization after tendon transection. Assessments extended through day 14. It tested several widely separated dose levels, but positive findings across those levels do not prove identical effects or a flat human dose-response relationship (PMID 14554208). An independent 2026 study randomized 32 rats to control, BPC-157, TB-500, or both after Achilles transection and repair. At four weeks, BPC-157 showed numerically improved maximum load to failure without statistical significance. Its total Bonar and Movin histology scores also did not reach significance. TB-500 reached significance for maximum load to failure, and the combination provided no additional benefit over the individual treatments (PMID 42542926). Surgical repair, assessment timing, sample size, and outcome selection affect interpretation. Chronic tendinopathy in a training adult also differs substantially from an acutely transected rat tendon.

(<https://www.fda.gov/media/193343/download>). No adequately reported controlled human evidence reviewed here establishes faster tendon healing, cartilage regeneration, improved athletic performance, or an effective subcutaneous recovery regimen.

STATUS

WADA

RESEARCH USE • REPORTED, NOT RECOMMENDED

ROUTES

HALF-LIFE

TIMING

not evidence for a human treatment window (PMID 14554208). A short animal plasma half life

human pharmacokinetic and exposure-response data. Similarly, delivering a preparation near perceived pain does not establish preferential delivery to the injured structure.

CYCLE LENGTH

A 4 to 8 week course followed by a break is commonly cited in non-clinical use; not validated in trials. There is no established cycle length for human tendon or muscle recovery. The recent human reports involved a procedure, occasional repeat procedures, or two consecutive infusion days. Their follow-up periods must not be mistaken for continuous treatment durations. The independent rat comparison used four weeks of treatment, while other animal studies used different schedules (PMIDs 34324435, 39325560, 40131143, 42542926). The reviewed studies do not establish tolerance, dependence, withdrawal effects, an effective break duration, or the consequences of repeated non-clinical cycles.

TITRATION

No validated human escalation, maintenance, or tapering schedule exists. The tendon experiments do not establish a therapeutic window or maximum tolerated human exposure. Positive animal findings across widely separated doses cannot prove a flat dose-response curve, equal efficacy, or a ceiling effect. Such conclusions require adequately powered comparisons between dose groups. The two-person intravenous pilot also cannot establish an escalation strategy because its sequential exposures were not randomized dose comparisons (PMIDs 14554208, 40131143). Perceived symptom improvement supplies no measurement of tissue peptide exposure or structural healing. Increasing an unvalidated dose therefore has an unknown relationship to both benefit and harm.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved product label	No approved label dose was identified.	Not applicable.	Not applicable.	The reviewed literature identifies no approved therapeutic formulation or validated clinical dosing regimen (PMID 42198317). · PMID 42198317
Human intravenous safety pilot, two previously exposed adults	10 mg intravenously on day 1 and 20 mg intravenously on day 2, once daily, each in 250 mL normal saline over one hour (PMID 40131143).	Intravenous infusion.	One infusion daily on two consecutive days.	Directly reported study exposure. Laboratory and symptom observations extended through day 3. This was not a dose-ranging trial and does not establish a suitable dose. · PMID 40131143
Human knee-pain retrospective series, BPC-157 alone	4 mg by intra-articular injection, generally one procedure, using 2 mL at 2000 mcg/mL; two patients in the overall series received repeat injections after reinjury (PMID 34324435).	Intra-articular injection into the knee.	Generally one procedure; repeat treatment occurred in two patients without a standardized repeat interval.	The primary paper explicitly reports the concentration and amount. [Primary knee-pain report] (https://asipp.org/wp-content/uploads/Intra-Articular-Injection-of-BPC-157-for-Multiple-Types-of-Knee-Pain-2021-Alternative-Therapies-in-Health-and-Medicine.pdf). · PMID 34324435
Human interstitial-cystitis pilot, 12 women	10 mg total by bladder-wall injections during one cystoscopic procedure (PMID 39325560).	Intravesical bladder-wall injections during cystoscopy.	Single procedure.	Directly reported total exposure in an uncontrolled pilot. The symptom findings do not establish an effective regimen or justify extrapolation to other routes. · PMID 39325560
Rat Achilles tendon transection	10 mcg/kg, 0.01 mcg/kg, or 0.00001 mcg/kg intraperitoneally once daily, starting 30 minutes after surgery (PMID 14554208).	Intraperitoneal.	Once daily, with the last administration 24 hours before the assigned tissue assessment; assessments extended through day 14.	Direct animal-study doses, expressed consistently in mcg/kg. Positive results across widely separated doses do not establish a human dose or demonstrate dose equivalence. · PMID 14554208

receptor expression in cultured rat tendon fibroblasts (PMID 25415472). That experiment did not test ipamorelin, circulating hormone pulses, or a clinical combination. Greater receptor expression in a cell assay does not establish better healing or acceptable systemic effects.

SAFETY

COMMON EFFECTS

There is no reliable incidence table for BPC-157 adverse effects. The three recent human reports described no adverse events, but monitoring methods, populations, routes, and follow-up differed. The intravenous laboratory findings apply only to its two previously exposed participants (PMIDs 34324435, 39325560, 40131143). Headache, nausea, flushing, and local irritation appear in non-clinical accounts, but those accounts cannot establish frequency or causality. Symptoms may arise from the peptide, another ingredient, contaminants, the procedure, or an unrelated condition. Their absence in a small report is not evidence that they cannot occur. Preclinical toxicology provides information about particular experimental materials and exposures. It does not establish the safety of repeated human use or commercial preparations.

SERIOUS SIGNALS

Human adverse-event reports exist. FDA summarized injection-site reactions, shortness of breath requiring emergency evaluation, and pigmentation changes involving a combination product. Missing information and coexposures prevented attribution to BPC-157 itself. These reports establish surveillance signals, not incidence or causality. [FDA BPC-157 briefing document] (<https://www.fda.gov/media/193343/download>). FDA also identifies potential immunogenicity, peptide-related impurities, and difficulties characterizing the active ingredient. These uncertainties concern both formulation quality and biological responses. [FDA safety-risk information] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>). Angiogenic signaling raises a theoretical concern in malignancy, but no reviewed human study establishes that BPC-157 causes or prevents cancer. Claims about neurodegenerative harm are likewise unproven. A mechanistic argument alone cannot quantify either risk. Nonsterile invasive administration can cause serious infection. Endotoxin contamination can cause systemic reactions even when a preparation contains the intended peptide. No comparative surveillance establishes which serious event is most likely in non-clinical use.

CONTRAINDICATIONS

There is no approved label defining formal BPC-157 contraindications. Relevant precautionary contexts include pregnancy, breastfeeding, childhood, active malignancy, and ongoing cancer treatment because adequate clinical evidence is lacking. A previous malignancy creates uncertainty requiring individual clinical assessment, not a proven universal contraindication. Known hypersensitivity to a preparation or its excipients is a separate concern. Active infection is particularly relevant to any proposed invasive procedure. The absence of interaction studies also leaves uncertainty with anticoagulants, immunosuppressants, and other prescription medicines. Anti-doping prohibition is a regulatory restriction, not a medical contraindication. Unverified identity, sterility, or endotoxin status is a product-quality problem that cannot be resolved by a favorable theoretical mechanism.

STOP RULES

Chest pain, breathing difficulty, facial or throat swelling, or collapse requires emergency medical evaluation. Fever with a hot, swollen joint or spreading redness after an invasive procedure requires urgent assessment for infection. Further exposure warrants suspension pending assessment when new systemic symptoms, unexplained bruising, progressive swelling, or worsening pain occurs. A new mass or persistent skin change also warrants clinical evaluation, although it does not establish peptide-related cancer. Pain relief does not demonstrate restoration of tendon strength or readiness for unrestricted loading. A worsening injury requires reassessment rather than interpretation as a reason to increase exposure. Cloudiness, discoloration, or visible particles raises a product-quality concern. Normal appearance cannot establish sterility, chemical identity, or retained potency.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved standard vial size or validated universal presentation. Labels describing lyophilized BPC-157 provide a nominal content claim, not proof of identity, potency, sterility, or formulation suitability. A nominal peptide mass also differs from the total mass of powder.

Counterions, water, buffers, and other excipients can contribute to the material present.

Distinguishing free peptide content from total product mass requires an appropriate quantitative assay. The biopharmaceutical review identifies major formulation-development gaps (PMID

42198317). Its broad statement that no pharmaceutical-grade formulation exists should not be treated as an assay of every preparation or a denial that experimental clinical formulations were manufactured.

SOLVENT

No approved BPC-157 label establishes a solvent, preservative, final concentration, mixing method, or multidose handling procedure. The intravenous pilot reports normal saline as its infusion vehicle, while the knee study describes a buffered preparation containing benzyl alcohol. Neither report validates home preparation or interchangeability of formulations (PMIDs 40131143, 34324435). Bacteriostatic water does not sterilize contaminated powder and does not remove endotoxin. Preservative presence alone does not establish compatibility, stability, or an acceptable period after opening. Preparation clarity is also not evidence of chemical integrity. Formulation behavior depends on the peptide form, concentration, excipients, container, and handling conditions.

STORAGE

No universal BPC-157 storage temperature, shipping tolerance, or post-reconstitution shelf life is established for all preparations. These depend on formulation, packaging, concentration, manufacturing controls, and validated stability testing. Chemical stability and microbiological acceptability are separate requirements. Refrigeration does not establish sterility, and a preservative does not prevent every contamination problem. Conversely, physical clarity cannot establish that intact peptide remains at the labeled concentration. Experimental storage conditions cannot automatically become instructions for commercial material.

Study arithmetic only: the knee report used 4 mg intra-articularly in a generally single procedure, supplied as 2 mL at 2000 mcg/mL (PMID 34324435). 2000 mcg/mL multiplied by 2 mL equals 4000 mcg, which is 4 mg, matching the reported amount. This checks internal consistency; it does not establish efficacy or a suitable regimen. For any concentration calculation, mass divided by final solution volume gives concentration. Added solvent volume and final solution volume are not automatically identical. A calculation based on a label also inherits any error in that label. Syringe graduation units measure volume under a device-specific convention. They are not biological IU for BPC-157, and there is no approved BPC-157 biological-unit standard. A mass-to-volume conversion cannot supply missing information about formulation stability, sterility, absorption, or a clinically justified exposure.

BUYING NOTES

Research-use labeling, a professional-looking certificate, and a high purity percentage do not establish a preparation suitable for human administration. A certificate of analysis describes a tested sample and the methods applied. Its usefulness depends on traceability to the material under discussion and on whether those methods answer the relevant questions. Chromatographic purity, peptide identity, quantitative content, sterility, and bacterial endotoxin are separate measurements. A high chromatographic area percentage does not prove the labeled amount of peptide or exclude every contaminant. Mass spectrometry can support identity, but interpreting a molecular mass requires accounting for the analytical method, charge state, counterions, and peptide form. The reported BPC-157 sequence is GEPPPGKPADDAGLV, with a free-peptide molecular weight around 1419 Da (PMID 14554208). A matching nominal mass alone cannot establish every structural detail, exclude related impurities, or demonstrate biological activity. Meaningful documentation identifies the batch, laboratory, sample, dates, analytical methods, acceptance criteria, and actual results. A generic certificate without a traceable batch relationship cannot establish the contents of a particular container. Independent testing can improve confidence in a measured property, but it does not turn an investigational preparation into an approved medicine. For invasive formulations, sterility and endotoxin assessments address different hazards. A chemical purity result supplies neither. Container compatibility, particulate testing, quantitative content, and stability are additional questions. Claims that one salt form has superior human absorption or clinical effectiveness require direct comparative evidence. Quality documentation also cannot compensate for the absence of a validated clinical regimen.

COMMON MISTAKES

- Converting rat doses directly into human regimens. Species, route, formulation, and measured exposure all affect interpretation. The rat and dog pharmacokinetic findings do not establish human subcutaneous bioavailability.
- Treating positive findings at several animal doses as proof that all doses are equivalent. A flat dose-response curve requires direct evidence, not the absence of an obvious difference in a small experiment.

- Repeating the claim that the knee paper controlled dosing. Its methods and results report administered amounts, while its outcome assessment remains uncontrolled and subjective.
- Counting three recent pilot reports as the entire history of human research. Older gastrointestinal studies exist, but limited reporting prevents confident conclusions about clinical effectiveness.
- Interpreting gastric stability as proof of oral absorption or delivery to injured tissue. Chemical survival in the stomach and systemic bioavailability are different questions.
- Assuming that BPC-157, thymosin beta-4, and products labeled TB-500 have interchangeable identities or evidence. The exact experimental material matters when interpreting a comparison or combination.
- Treating an advisory committee review, category removal, prescription, or certificate of analysis as drug approval. Each addresses a different question and provides different evidence.
- Inferring sterility, potency, or an acceptable storage period from a clear solution. Appearance cannot resolve those properties, and bacteriostatic water cannot correct contaminated starting material.
- Using reduced pain as evidence of structural healing or readiness for unrestricted training. The human reports do not establish repaired cartilage, restored tendon strength, or reduced reinjury risk.
- Equating no reported events with demonstrated safety. Small samples, selected participants, incomplete monitoring, and short follow-up leave uncommon and delayed harms unresolved.

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TB-500

Thymosin beta-4 fragment, Tβ4

Actin-binding peptide fragment

Module 3 · Shielding

Goals: Recovery

Route: SC

WADA prohibited

An acetylated thymosin beta-4 fragment with preclinical research, unresolved identity across marketed preparations, and no verified human trial establishing recovery benefits for Ac-LKKTETQ.

WHAT IT IS

In the analytical literature, TB-500 denotes Ac-LKKTETQ, the N-terminally acetylated seven-amino-acid fragment corresponding to residues 17-23 of thymosin beta-4. Researchers identified this ingredient in a marketed preparation using mass spectrometry and confirmed its identity through independent synthesis (PMID 22962027). Full-length thymosin beta-4 is a different molecule: a 43-amino-acid peptide with a molecular mass of approximately 4.9 kDa (PMID 9194528, PMID 17947592). The name TB-500 is not a reliable chemical specification. Some publications and marketed preparations use it interchangeably with synthetic thymosin beta-4. Consequently, a study mentioning TB-500 cannot automatically be assigned to Ac-LKKTETQ. Three related substances require separation: full-length thymosin beta-4, the unacetylated fragment LKKTETQ, and the acetylated fragment Ac-LKKTETQ. The aged-mouse wound study tested LKKTETQ and found activity comparable to the parent peptide in that model (PMID 12581423). It did not establish equivalence between unacetylated LKKTETQ and Ac-LKKTETQ in people. This distinction became more consequential in a later analytical study. Investigators evaluated Ac-LKKTETQ and its metabolites in experimental systems and found significant fibroblast wound-closure activity for one metabolite, Ac-LKKTE. The parent fragment did not demonstrate the same significant effect in that assay (PMID 38382158). Within the product's repair category, TB-500 represents an experimental tissue-repair concept. Human improvements in tendon healing, training capacity, joint function or body composition have not been established for chemically verified Ac-LKKTETQ. A study of the full-length peptide also failed to improve metabolic disturbances or muscle regeneration in its mouse models (PMID 34495765). Equine analytical research documents historical veterinary preparations containing the acetylated fragment (PMID 23084823). That history establishes a preparation and an analytical identity. It does not establish veterinary approval, human suitability, or a validated clinical development pathway.

MECHANISM

The strongest mechanistic evidence concerns full-length thymosin beta-4. It binds monomeric G-actin and buffers the actin pool available for filament assembly. This intracellular function supports changes in cell shape and movement. The parent peptide is largely unstructured in solution and adopts a more stable conformation when bound to actin (PMID 17468232, PMID 11311852).

LKKTETQ contains an actin-binding region, which motivated fragment research. However, containing that region does not establish that an isolated fragment reproduces the parent's binding properties, cellular distribution or downstream effects. Acetylation and enzymatic cleavage introduce additional differences that require direct testing (PMID 12581423, PMID 38382158).

Extracellular parent-peptide experiments support several repair-related actions. In cultured human endothelial cells, thymosin beta-4 increased directional migration, scratch closure and matrix metalloproteinase production (PMID 9194528). In rat skin wounds, topical or intraperitoneal treatment increased reepithelialization, collagen deposition and angiogenesis (PMID 10469335). These endpoints describe experimental repair processes, not demonstrated recovery of a human tendon.

Several signaling mechanisms have experimental support. In cardiac models, thymosin beta-4 formed a functional complex with PINCH and integrin-linked kinase, increasing Akt signaling. Treatment improved early cardiomyocyte survival and cardiac function after coronary ligation in mice (PMID 15565145). This is a signaling-complex observation, not proof of a single-dedicated cell-surface receptor.

A separate endothelial study identified the beta subunit of cell-surface ATP synthase as a binding partner. Thymosin beta-4 increased extracellular ATP signaling, and P2X4 activity was required for the observed migration response (PMID 21106936). Corneal epithelial experiments found reduced NF-kappaB activation and nuclear translocation after inflammatory stimulation (PMID 17254567). These findings concern the parent molecule in specific experimental settings.

Domain mapping limits broad extrapolation. A study of 17 thymosin beta-4 domain combinations identified the C-terminal AGES region as important for cardiac protection in mice and pigs (PMID 26255251). The acetylated LKKTETQ fragment lacks that region. It also cannot generate the N-terminal metabolite Ac-SDKP, which has a separate body of biological research (PMID 17468232, PMID 41570941).

Developmental and injury studies further implicate endogenous thymosin beta-4 in vascular remodeling and myoblast migration (PMID 17495252, PMID 29202457, PMID 20880960). Endogenous gene expression, extracellular administration and administration of a shortened synthetic fragment are distinct experimental interventions.

For Ac-LKKTETQ specifically, metabolism may contribute substantially to activity. The study identifying Ac-LKKTETQ activity tested human serum outside the body, animal samples and cultured fibroblasts (PMID 38382158). It did not identify a clinically effective human exposure. The mechanism supporting an injected Ac-LKKTETQ preparation for human tendon repair therefore remains unestablished.

EVIDENCE · GRADE C

Grade C reflects a preclinical evidence base with substantial uncertainty about the exact molecule studied. No published human interventional trial of chemically verified Ac-LKKTETQ was identified in this PubMed review. Human trials of full-length or recombinant thymosin beta-4 cannot establish efficacy for the fragment.

The fragment literature includes analytical identification, animal metabolism and cell-based activity studies. Related unacetylated LKKTETQ has wound-repair evidence in aged mice (PMID 12581423, PMID 38382158). A recent rat tendon study reported benefits with material called TB-500, but did not establish its sequence or acetylation in the retrieved methods (PMID 42542926).

Current sports medicine reviews describe inadequate human evidence for musculoskeletal recovery and unresolved indications, dosing and treatment duration (PMID 41476424, PMID 41966639, PMID 42578445). These reviews summarize overlapping primary literature and should not be counted as independent demonstrations of efficacy.

The parent peptide has multiple human randomized studies, including cardiac research. Their results are mixed and indication-specific. The supplied grading scale classifies multiple human randomized trials as A, but that designation cannot be transferred between molecules or interpreted as proof of benefit. The Cochrane assessment of the small neurotrophic keratopathy trial rated its evidence as low certainty (PMID 41347649).

Human data. Ac-LKKTETQ: no qualifying human interventional trial was identified. Human serum metabolism experiments are laboratory studies, not human administration studies (PMID 38382158). Full-length synthetic thymosin beta-4: a randomized phase 1 study enrolled 40 healthy volunteers across four cohorts, including placebo recipients. Active treatment comprised 42, 140, 420 or 1260 mg intravenously once, followed after safety review by the same assigned dose daily for 14 days (PMID 20536472). Adverse events were infrequent and mild or moderate, with no reported serious adverse events or dose-limiting toxicity. This establishes limited short-term tolerability for that preparation. A separate recombinant thymosin beta-4 phase 1 study included 54 participants in its single-dose component and 30 in its repeated-dose component. Intravenous single doses ranged from 0.05 to 25 mcg/kg; repeated

Animal and mechanistic data. The rat Achilles tendon study randomized 32 male rats into control, BPC-157, TB-500 and combination groups. Material called TB-500 was administered at 60 mcg/kg intraperitoneally once daily for 30 postoperative days according to the full methods (PMID 42542926). The abstract summarizes the duration as four weeks. TB-500 treatment increased maximum load to failure and improved selected histological scores relative to control. Each group contained eight animals, but only four contributed to biomechanical testing and four to histological assessment. There was no prospective power calculation, and broader mechanical properties and functional recovery were not established. The retrieved methods identify a commercial preparation without reporting sequence confirmation or acetylation. This study therefore cannot be presented as confirmed Ac-LKKTETQ

doses were 0.5, 2 or 5 mcg/kg intravenously once daily for 10 days (PMID 34346165). No serious adverse events or dose-limiting toxicities were reported. The major difference from the earlier milligram-dose program does not justify a conversion between preparations. In venous ulcers, a randomized phase 2 study enrolled 73 patients. Topical thymosin beta-4 produced an exploratory healing signal, particularly among smaller or less severe ulcers, with tolerability comparable to placebo (PMID 20536470). The earlier publication described the ongoing protocol and is not a separate completed efficacy trial (PMID 17495250). A later program summary reported faster healing among patients who healed; that selected subgroup cannot establish benefit for every treated patient (PMID 23050815). A severe dry-eye trial enrolled nine patients. It used 0.1 percent ophthalmic thymosin beta-4 six times daily for 28 days, followed by observation through day 56 (PMID 25826322). The reported 12 treated and six control eyes came from nine people, not 18 independent participants. Another dry-eye trial enrolled 72 participants and missed both primary efficacy endpoints, despite favorable secondary findings (PMID 26056426). In neurotrophic keratopathy, complete healing at four weeks occurred in six of ten treated participants and one of eight placebo participants. The primary comparison was not statistically significant, with $p = 0.0656$; some secondary outcomes favored treatment (PMID 36613994). The small sample and imprecision remain central limitations (PMID 41347649). Cardiac development did not stop at phase 1. A 2025 publication reported a randomized, double-blind trial involving 96 patients with myocardial infarction after reperfusion. The overall infarct-area comparison was not significant. A subgroup receiving early treatment showed a favorable result, which requires confirmation (PMID 41229390). None of these studies establishes efficacy for subcutaneous Ac-LKKTETQ.

efficacy. The combination did not demonstrate additional benefit. This result does not prove pharmacological redundancy, equivalence, or the absence of benefit under every possible regimen. The experiment was small and assessed a single postoperative time point (PMID 42542926). Earlier skin studies support full-length thymosin beta-4 in rats and impaired-healing mouse models (PMID 10469335, PMID 12581423). The unacetylated LKKTETQ fragment reproduced parent-peptide activity in aged mice. That finding does not directly establish acetylated-fragment activity in diabetic mice or human tendons. Cardiac results vary by model. Positive mouse and pig findings coexist with a pig ischemia-reperfusion study that found no improvement in cardiac function or cell death (PMID 15565145, PMID 26255251, PMID 27199757). In dystrophin-deficient mice, full-length thymosin beta-4 at 150 mcg intraperitoneally twice weekly for six months increased regenerating muscle fibers without significantly improving strength, cardiac function or fibrosis (PMID 20126456). Another study found no improvement in mouse muscle regeneration or obesity-related metabolic disturbances (PMID 34495765). Increased repair markers therefore cannot substitute for demonstrated functional benefit.

REGULATORY STATUS AND SPORT

STATUS

TB-500 has no FDA-approved human therapeutic indication or approved dosing label. The FDA's safety information, current as of April 22, 2026, identifies potential immunogenicity concerns involving aggregation and peptide-related impurities. It also states that the agency has not identified human exposure data for drug products containing the thymosin beta-4 fragment. FDA approval, eligibility for pharmacy compounding, prescription scheduling and legality in another jurisdiction are different questions. A research-use label does not establish any of them. The parent peptide has clinical development programs in skin, ocular and cardiovascular conditions (PMID 20536470, PMID 25826322, PMID 36613994, PMID 34346165, PMID 41229390). A 2007 article described cardiac development plans, but it cannot establish the current absence of later trials (PMID 17947592). The 2025 cardiac randomized trial directly corrects that historical inference. The FDA source consulted was Certain Bulk Drug Substances for Use in Compounding that May Present Significant Safety Risks. Published clinical reviews also distinguish investigational peptides from approved treatments and describe major gaps in human safety evidence (PMID 41966639).

WADA

Prohibited at all times under S2.3, Growth Factors and Growth Factor Modulators. The 2026 list explicitly names thymosin beta-4 and derivatives including TB-500. This applies both in and out of competition. Source: [WADA 2026 Prohibited List](https://www.wada-

ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). The classification concerns the prohibited substance, not whether a preparation is called a fragment, research chemical or recovery aid. It also does not depend on proving improved athletic performance in humans. Published analytical studies establish that the fragment can be identified, but they do not predict an individual athlete's test result (PMID 22962027, PMID 23084823). Detection thresholds and timing strategies are not included.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Human thymosin beta-4 research includes intravenous administration, topical wound treatment and ophthalmic delivery (PMID 20536472, PMID 34346165, PMID 20536470, PMID 25826322). These are preparation-specific routes for the parent or recombinant peptide. Related animal studies used topical or intraperitoneal administration. The rat tendon study used intraperitoneal administration of material called TB-500, with unresolved fragment identity (PMID 10469335, PMID 42542926). The chronic dystrophic-mouse study also used intraperitoneal administration, not subcutaneous administration (PMID 20126456). Subcutaneous and intramuscular fragment administration are described in non-clinical use, without a verified human efficacy or pharmacokinetic basis. Local placement near an injury has no demonstrated clinical advantage in the retrieved evidence. Oral bioavailability and effective oral dosing were not established.

HALF-LIFE

No human pharmacokinetic study of chemically verified Ac-LKKTETQ was identified. A half-life assigned to full-length or recombinant thymosin beta-4 does not establish the fragment's half-life after another route. The 2010 intravenous parent-peptide study reported dose-dependent exposure and increasing half-life with increasing dose (PMID 20536472). A separate 2021 recombinant-peptide study characterized intravenous pharmacokinetics and reported no obvious accumulation during its repeated-dose program (PMID 34346165). These are distinct datasets, not one universal thymosin beta-4 exposure profile. Equine and rat studies identify Ac-LKKTETQ metabolites, but animal detection results do not establish a human therapeutic half-life (PMID 23084823, PMID 38382158). Plasma elimination, metabolite persistence and duration of biological action are different measurements. None validates the intermittent schedules circulated for human fragment use.

TIMING

No clinical evidence establishes timing relative to exercise, meals, sleep or an injury for Ac-LKKTETQ. Repair-related mechanisms do not identify an optimal administration window. The rat tendon experiment began treatment on the first postoperative day (PMID 42542926). That is an experimental design choice, not evidence that earlier human administration improves outcomes. Likewise, the early-treatment subgroup in the parent-peptide cardiac trial concerns myocardial reperfusion, not musculoskeletal injuries (PMID 41229390). The retrieved literature does not establish that administration near an injured structure improves targeting. Evidence of systemic effects in animals also does not establish that every route produces equivalent exposure.

CYCLE LENGTH

No validated human cycle length exists for Ac-LKKTETQ. A four-to-six-week initial phase with optional maintenance is commonly cited in non-clinical use; not validated in trials. That convention is not evidence that finite use prevents harm or that maintenance preserves a benefit. The two retrieved systemic parent-peptide phase 1 programs used repeated-treatment periods of 14 and 10 days, respectively (PMID 20536472, PMID 34346165). These durations describe particular studies and do not establish a universal maximum duration for all human research. Follow-up after treatment is also different from continuous exposure. The six-month dystrophic-mouse experiment provides a long-duration animal observation, but did not establish functional efficacy or long-term human safety (PMID 20126456). Neither an animal treatment period nor short human tolerability studies define a validated fragment cycle.

TITRATION

No starting dose, titration schedule, target exposure or ceiling has been established for Ac-LKKTETQ in humans. Lack of adverse events at one exposure would not identify an effective exposure. The venous ulcer program evaluated different topical concentrations across research cohorts (PMID 17495250, PMID 20536470). The intravenous phase 1 programs likewise evaluated assigned dose cohorts under study monitoring (PMID 20536472, PMID 34346165). These designs are not instructions for individual dose escalation. The absence of dose-limiting toxicity in small, short studies does not establish a wide safety margin. Different molecules, formulations, routes and analytical assays further limit comparisons between programs.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Historical phase 1 study of full-length synthetic thymosin beta-4 in healthy volunteers	42, 140, 420 or 1260 mg intravenously once, then the assigned dose intravenously once daily for 14 days after safety review (PMID 20536472).	Intravenous.	Single-dose phase followed by daily administration for 14 days.	Randomized placebo-controlled study with 40 participants across four cohorts, including placebo recipients. These are reported parent-peptide exposures, not fragment doses. · PMID 20536472
Separate recombinant human thymosin beta-4 phase 1 study, single-dose component	0.05, 0.25, 0.5, 2, 5, 12.5 or 25 mcg/kg intravenously as a single administration (PMID 34346165).	Intravenous.	Once.	Randomized double-blind study with 54 participants in the single-dose component. Preparation-specific results cannot be converted into Ac-LKKTETQ dosing. · PMID 34346165
Separate recombinant human thymosin beta-4 phase 1 study, repeated-dose component	0.5, 2 or 5 mcg/kg intravenously once daily for 10 days (PMID 34346165).	Intravenous.	Once daily for 10 days.	Randomized double-blind study with 30 participants in the repeated-dose component. This is recombinant thymosin beta-4 research, not TB-500 fragment research. · PMID 34346165
Venous ulcer phase 2 study of topical full-length thymosin beta-4	0.03 percent topical formulation was associated with an exploratory healing signal; application frequency was not established from the retrieved abstracts (PMID 20536470).	Topical application to venous ulcers.	Not verified from the retrieved abstracts; the protocol described treatment over 84 days.	The concentration comes from PMID 20536470. The planned treatment duration comes from PMID 17495250. Concentration is not a complete administered mass dose. · PMID 20536470
Severe dry-eye phase 2 study of ophthalmic full-length thymosin beta-4	0.1 percent ophthalmic solution administered six times daily for 28 days (PMID 25826322).	Topical ophthalmic.	Six times daily for 28 days, followed by observation through day 56.	Small randomized trial involving nine patients. Day 56 was a follow-up assessment, not evidence of continuous treatment for 56 days. · PMID 25826322
Exploratory rat Achilles tendon repair study using material called TB-500	60 mcg/kg intraperitoneally once daily for 30 postoperative days in the full methods (PMID 42542926).	Intraperitoneal.	Once daily beginning on the first postoperative day, for 30 days; the abstract summarizes this as four weeks.	Randomized animal study. Sequence and acetylation were not established in the retrieved methods, so this is not a verified Ac-LKKTETQ regimen. · PMID 42542926
Long-duration full-length thymosin beta-4 study in dystrophin-deficient mice	150 mcg intraperitoneally twice weekly for six months (PMID 20126456).	Intraperitoneal.	Twice weekly for six months.	Primary animal study with increased regenerating fibers but no significant improvement in tested strength, cardiac function or fibrosis outcomes. · PMID 20126456

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Reported non-clinical human fragment-use convention	2 to 2.5 mg subcutaneously twice weekly during an initial period, followed by 2 to 2.5 mg subcutaneously every one to two weeks: commonly cited in non-clinical use; not validated in trials.	Subcutaneous, as described in non-clinical use.	Twice weekly initially, then every one to two weeks; this is an unvalidated convention.	Commonly cited in non-clinical use; not validated in trials. No identified study establishes this loading pattern, maintenance interval, effective exposure or upper limit. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ BPC-157	Investigated pairing, without demonstrated synergy. The rat Achilles tendon study compared each agent, their combination and control. The combination did not show additional benefit on the measured outcomes (PMID 42542926). Small outcome-specific samples and unresolved TB-500 chemical identity limit interpretation. The result neither establishes human benefit nor proves that the agents share one mechanism. No validated human combination dose or duration was identified.	– IGF-1 LR3	The concern is theoretical interaction between growth-promoting signaling and proposed migration or angiogenesis effects. Parent thymosin beta-4 cancer studies justify caution, but do not demonstrate a clinical cancer interaction with IGF-1 LR3 (PMID 21621326, PMID 34081824, PMID 36321670). No human combination safety study was identified.
+ GHK-Cu	Hypothetical pairing only. Reviews discuss both agents within tissue-repair research, but discussion in the same review is not a combination experiment (PMID 41476424, PMID 42635865). Proposed matrix-remodeling and migration effects can overlap. No retrieved controlled study establishes an additive effect, compatible formulation or improved human outcome for this pairing.	– PEG-MGF	No retrieved evidence establishes benefit, compatibility or a predictable interaction with Ac-LKKTETQ. Combining experimental repair-related compounds adds uncertainty about exposure and adverse-event attribution. A shared marketing category does not establish biological redundancy or synergy. There is no validated human combination protocol in the reviewed evidence.
+ CJC-1295	No demonstrated synergy. Growth hormone signaling and proposed thymosin-related repair mechanisms provide a conceptual rationale, but mechanistic difference does not establish a beneficial interaction (PMID 41966639). No verified human study of this pairing was identified. Additional systemic exposure adds interaction uncertainty and complicates attribution of benefits or adverse events.		
+ Ipamorelin	No demonstrated synergy. The sports medicine literature reviews ipamorelin and thymosin-related compounds as separate interventions with major musculoskeletal evidence		

gaps (PMID 42578445). No retrieved trial validates their combined use. Claims about selectivity or complementary effects do not establish the safety or efficacy of the combination.

SAFETY

COMMON EFFECTS

The frequency and severity of adverse effects from human Ac-LKKTETQ administration are unknown. Injection-site reactions, flushing, fatigue and head-pressure sensations are anecdotal reports, not a reliable incidence dataset or a confirmed causal profile. Full-length synthetic and recombinant thymosin beta-4 phase 1 studies reported predominantly mild or moderate events and no serious adverse events in their limited samples (PMID 20536472, PMID 34346165). Topical and ophthalmic trials also reported generally favorable short-term tolerability within their studied populations (PMID 20536470, PMID 25826322, PMID 36613994). These observations cannot establish fragment tolerability after systemic administration. Both compound-related effects and preparation-related harms remain possible. Lack of symptoms does not establish chemical identity, sterility, absence of endotoxin or absence of delayed toxicity.

SERIOUS SIGNALS

Immunogenicity is a material unresolved concern. The FDA identifies potential risks involving peptide aggregation and peptide-related impurities in compounded thymosin beta-4 fragment preparations. Human studies are insufficient to estimate the likelihood or severity of these outcomes. Cancer-related findings require careful interpretation. Increased endogenous thymosin beta-4 expression promoted migration-related signaling in colon cancer experiments (PMID 21621326). Genetic and transplantation models implicated it in diffuse-type gastric cancer metastasis (PMID 34081824). Higher expression in human thyroid tumors correlated with more advanced disease characteristics (PMID 36321670). These are mechanistic, animal and observational findings. They do not establish that administered Ac-LKKTETQ initiates cancer or quantify a human recurrence risk. Conversely, endogenous occurrence does not establish that additional exposure is harmless. The relevant concern is unresolved activity in susceptible biological contexts. Fibrosis findings also vary by context. A liver review describes different effects of endogenous expression and exogenous parent-peptide treatment (PMID 27450733). A kidney review emphasizes model-dependent findings and unresolved translational issues (PMID 41570941). Neither supports a universal claim that TB-500 prevents scarring or causes fibrosis. A pig study found no cardiac protection in its ischemia-reperfusion model and identified experimental vascular and coagulation effects (PMID 27199757). These observations are not proven human adverse reactions, but further limit broad reassurance based on selected positive experiments.

CONTRAINDICATIONS

There is no approved Ac-LKKTETQ label defining formal contraindications. Active cancer, a cancer history, unexplained masses and proliferative vascular disease warrant particular caution because relevant human safety evidence is absent and parent-peptide mechanisms raise concerns. These are precautionary contexts, not proven fragment-specific contraindications. Pregnancy, breastfeeding and pediatric use lack an established clinical safety basis. Renal or hepatic impairment, immune disorders and concurrent treatments also have no validated fragment-specific dose adjustments or interaction guidance. Known hypersensitivity to a preparation or its ingredients is a reason to avoid re-exposure pending medical assessment. Anti-doping prohibition is a separate eligibility issue rather than a physiological contraindication. Contamination and administration-related infection are additional hazards; they do not replace uncertainty about the peptide itself.

STOP RULES

Breathing difficulty, facial swelling, fainting, chest pain or sudden visual symptoms require urgent medical assessment. Spreading redness, increasing warmth, discharge or fever after administration warrants prompt evaluation for infection or another adverse reaction. A new persistent mass, unexplained bleeding, sustained lymph-node enlargement or unexplained weight loss warrants assessment. These findings do not diagnose peptide-related cancer. Unexpected effects also do not prove adulteration, because allergy, infection, dose error, interactions and unrelated illness remain possible. Worsening pain, swelling, weakness or loss of function requires reassessment of the injury. Reduced pain alone does not establish restored tissue strength. Animal regeneration markers have increased without corresponding functional improvement (PMID 20126456). No validated Ac-LKKTETQ monitoring schedule or laboratory threshold can certify continued use as low risk.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved standard vial or validated human-use presentation for Ac-LKKTETQ. A label stating TB-500 does not resolve whether the contents are the acetylated fragment, unacetylated fragment or full-length thymosin beta-4. Chemical identity requires sequence and terminal-modification information supported by suitable analysis. The original analytical identification established Ac-LKKTETQ in the material examined, not in every subsequently marketed preparation (PMID 22962027). A stated vial mass describes nominal content, not a clinically validated dose.

SOLVENT

No universal human-use reconstitution solvent has been established for Ac-LKKTETQ in the retrieved literature. Compatibility depends on the actual peptide, excipients, concentration, container and intended experimental use. Bacteriostatic water does not sterilize contaminated powder, eliminate endotoxin or automatically validate repeated entry into a container. Its preservative also does not establish peptide stability or compatibility. A generic solvent recipe cannot substitute for formulation-specific data.

STORAGE

No independently verified shelf life or post-reconstitution storage period for generic Ac-LKKTETQ preparations was established in this review. Stability depends on formulation, concentration, pH, packaging and handling. A certificate of analysis reports specified test results; it does not automatically establish stability after opening or reconstitution. Cloudiness, particles or discoloration can indicate a problem, but a clear appearance does not establish sterility or chemical stability. Research storage claims require data for the actual preparation. The broader thymosin beta-4 literature identifies peptide stability and delivery as unresolved translational issues (PMID 41570941).

Illustrative concentration arithmetic only, with no administration route or frequency: a hypothetical analytical sample containing 5 mg in a final solution volume of 2 mL has a nominal concentration of 2.5 mg/mL. These quantities are calculation assumptions, not a study dose, drug-label instruction or human-use recipe.

The relationship is $\text{concentration} = \text{total mass} / \text{final solution volume}$. The word *final* matters because added solvent volume and final solution volume are not always identical. A calculation also assumes the stated mass is accurate and the material dissolves completely.

Syringe markings measure volume according to the device scale. They do not establish peptide potency or biological activity, and an insulin syringe marking is not an IU of TB-500. There is no validated TB-500 activity-unit conversion in the reviewed literature.

Correct arithmetic cannot establish chemical identity, delivered exposure, sterility, endotoxin status or an effective human dose. No draw volume or injection instruction is derived from this example.

BUYING NOTES

Identity, purity, quantity, sterility and endotoxin are separate quality questions. Evidence answering one cannot be substituted for evidence answering the others. The original TB-500 identification required mass spectrometry and independent synthesis to establish the acetylated fragment's identity (PMID 22962027). An interpretable analytical report links the tested sample to a specific lot and identifies the sequence, terminal modifications and analytical methods. A chromatographic purity percentage alone does not establish that the dominant peak is Ac-LKKTETQ. It also does not establish the amount of peptide in a container or exclude every impurity. A mass consistent with the expected molecule strengthens identity assessment, but is not a complete evaluation of sequence, stereochemistry, contamination or clinical suitability. Nominal fill mass, peptide content and chromatographic purity can represent different measurements. Reports that do not define these measurements leave important uncertainty. Sterility and endotoxin require appropriate tests and sampling. A visible cake, clean film, sealed container or consistent appearance cannot verify those properties. Laboratory documentation also needs an identifiable sample, methods, dates and a credible connection to the material being described. A preparation supported by parent-peptide eye, skin or cardiac trials still requires evidence that its contents match those studies. Ac-LKKTETQ does not inherit the parent's trial results through a shared name. The rat tendon paper illustrates why published use of the term TB-500 is insufficient without chemical characterization (PMID 42542926). No certificate of analysis establishes human efficacy, an approved indication or an acceptable individual risk. Reviews of this market describe major gaps in clinical evidence and regulatory oversight (PMID 41966639, PMID 42635865). This section describes how documentation is interpreted; it does not identify or endorse a source.

COMMON MISTAKES

- Treating TB-500 as a standardized chemical name. Analytical literature identifies Ac-LKKTETQ, but other sources use the name for different thymosin-related materials. Sequence and terminal modifications determine whether a study applies (PMID 22962027, PMID 42542926).
- Treating unacetylated LKKTETQ, Ac-LKKTETQ and full-length thymosin beta-4 as interchangeable. The aged-mouse fragment study used LKKTETQ, while later acetylated-fragment research identified activity in a metabolite (PMID 12581423, PMID 38382158).
- Transferring ophthalmic or intravenous parent-peptide outcomes to subcutaneous fragment use. Different molecules, formulations, routes and indications require separate evidence. None of the cited parent-peptide trials establishes human tendon recovery with Ac-LKKTETQ.
- Describing the cardiac program as ending at phase 1. A 2025 randomized study included 96 myocardial infarction patients. Its overall infarct-area comparison was not significant, despite a favorable early-treatment subgroup (PMID 41229390).
- Calling a secondary endpoint or subgroup finding a confirmed clinical success. The larger dry-eye study missed its primary endpoints, and the small neurotrophic keratopathy trial had an inconclusive primary comparison (PMID 26056426, PMID 36613994).
- Reporting the dry-eye study as 56 days of treatment. The regimen was 0.1 percent ophthalmic solution six times daily for 28 days, followed by observation through day 56 (PMID 25826322).
- Describing the rat tendon experiment as definitive fragment evidence. Chemical identity was unresolved, each outcome used four animals per group, and assessment occurred at one postoperative time point (PMID 42542926).
- Assuming BPC-157 adds benefit. The small rat study did not demonstrate an additional combination effect. This is neither a validated human stack nor proof that the two agents are pharmacologically redundant (PMID 42542926).
- Quoting one universal half-life or translating between parent-peptide study doses. Separate synthetic and recombinant programs reported different exposures. Neither establishes Ac-LKKTETQ pharmacokinetics after subcutaneous administration (PMID 20536472, PMID 34346165).
- Equating increased regeneration markers with restored performance. Dystrophic mice had more regenerating fibers without significant strength or cardiac-function improvement. Pain relief or laboratory markers alone cannot establish tissue readiness (PMID 20126456).
- Claiming either proven cancer causation or absence of oncologic concern. Existing evidence concerns parent-peptide expression, experimental mechanisms and tumor associations, not measured cancer incidence after human Ac-LKKTETQ exposure (PMID 21621326, PMID 34081824, PMID 36321670).
- Treating a preservative, clear solution or purity percentage as proof of injectable quality. None establishes all of identity, potency, sterility, endotoxin status and stability. Correct concentration arithmetic does not resolve those gaps.
- Assuming endogenous occurrence establishes benefit from additional exposure. Exercise-related release of full-length thymosin beta-4 does not validate fragment administration or prove performance enhancement (PMID 34495765).
- Assuming out-of-competition use is permitted. The current prohibition applies at all times. Analytical detectability and anti-doping eligibility are separate questions from clinical efficacy.

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GHK-Cu (Copper Tripeptide-1)

Copper tripeptide-1

Copper-binding tripeptide

Module 3 · Shielding

Goals: Skin, Recovery

Route: Topical or SC

A copper-binding tripeptide with substantial preclinical research, mixed topical human results, and no established injectable regimen for recovery, muscle growth or skin rejuvenation.

WHAT IT IS

GHK is glycyl-L-histidyl-L-lysine, a naturally occurring tripeptide detected in human plasma, saliva and urine. Its copper(II) complex is GHK-Cu, commonly identified as Copper Tripeptide-1 in cosmetics. Copper-free GHK, GHK-Cu and other copper tripeptides are distinct experimental substances; their results cannot automatically be pooled.

GHK-Cu has been investigated in topical wound formulations and cosmetic products. Research powders marketed for systemic administration do not inherit the evidence supporting those formulations. Module 3, Shielding. Relevant research goals include skin repair, extracellular matrix remodeling and inflammatory signaling. These are research domains, not established indications for injectable treatment (PMID 26236730, PMID 41476424).

MECHANISM

GHK binds copper and influences extracellular matrix turnover in experimental systems. Copper supports enzymes involved in connective tissue biology, including lysyl oxidase. That biochemical role does not establish that additional GHK-Cu improves tissue function in copper-replete humans (PMID 26236730).

Cultured human fibroblasts increased collagen synthesis with GHK-Cu exposure, without a corresponding increase in cell number. The response peaked within the tested concentration range. The investigators also identified a GHK sequence within type I collagen, suggesting possible release during proteolysis. Release at human injury sites and its therapeutic importance remain hypotheses (PMID 3169264).

GHK-Cu increased sulfated glycosaminoglycan synthesis in fibroblast cultures. The response was biphasic, returning toward control levels at higher concentrations. Hyaluronic acid synthesis did not increase. These findings support selective matrix effects, not a general claim that more peptide produces more repair (PMID 1522753).

Rat wound experiments found lower TNF-alpha, MMP-2 and MMP-9 concentrations after topical treatment (PMID 14648529). Mouse lung studies reported changes in inflammatory, antioxidant and fibrosis-related pathways. These included NF-kB, p38 MAPK, Nrf2 and TGF-beta1/Smad2/3 signaling (PMID 27517151, PMID 31809714). A smoke-exposure study linked GHK-Cu effects on mouse muscle to SIRT1-dependent signaling. Its human component measured endogenous GHK associations, not treatment responses (PMID 36905132).

The frequently repeated gene-reset claim comes from computational and cell experiments. Connectivity Map analysis identified GHK as a candidate for reversing an emphysema-associated expression signature. Subsequent fibroblast experiments showed TGF-beta-like expression and matrix remodeling effects (PMID 22937864). This was not evidence that administering GHK-Cu rejuvenates human organs. Different experimental systems show different TGF-beta responses, preventing a simple universal mechanism from being assigned.

EVIDENCE · GRADE C

Grade C applies to systemic recovery, muscle and longevity claims: evidence remains preclinical or insufficient for clinical inference. Topical wound and cosmetic findings require separate assessment. Some topical contexts reach B because controlled human studies exist, but findings are limited, heterogeneous or

inconsistent. A 2026 systematic review included 18 preclinical studies and 2 randomized trials. It reported limited cosmetic benefits alongside substantial methodological limitations (PMID 42619529).

Human data. A randomized, evaluator-blinded diabetic ulcer study reported median percentage reduction in plantar ulcer area of 98.5 percent versus 60.8 percent with vehicle. These are area-reduction results, not percentages of patients achieving complete healing. Infection incidence was 7 percent versus 34 percent in the immediately treated subgroup. Treatment accompanied debridement, pressure-relieving footwear and standardized wound care (PMID 17147644). Among 86 evaluable participants in a venous ulcer trial, copper tripeptide cream did not outperform vehicle (PMID 1495150). A laser-resurfacing trial with 13 completers found no significant between-group differences in objective erythema, wrinkles or skin quality. Patient-reported satisfaction favored GHK-Cu (PMID 16847171). The 2026 aesthetic review also reports wrinkle-volume and wrinkle-depth improvements in included clinical research. Those findings should not be erased, but they do not validate arbitrary commercial formulations or injectable treatment (PMID 42619529). A separate hair study tested a combination of GHK and 5-aminolevulinic acid. It cannot establish GHK-Cu efficacy or isolate GHK's contribution (PMID 27489425). No therapeutic human injection trial supporting musculoskeletal recovery was identified (PMID 41476424).

Animal and mechanistic data. Rat ischemic wounds showed day-13 area reductions of 64.5 percent with active gel, 45.6 percent with vehicle and 28.2 percent untreated. Comparisons against untreated wounds therefore overstate the difference attributable to the active ingredient alone (PMID 14648529). After rat ACL reconstruction, treatment improved knee laxity at 6 weeks. Higher graft stiffness occurred in the lower-concentration group, without significant improvements in ultimate load, gait or histological scores. Between-group benefits were absent at 12 weeks (PMID 25731775). Mouse studies reported reduced inflammatory lung injury, pulmonary fibrosis, smoke-associated muscle dysfunction and Alzheimer-model pathology (PMID 27517151, PMID 31809714, PMID 36905132, PMID 40766919). These disease models do not establish benefits in healthy adults who train. Short experimental observation also cannot establish long-term systemic safety.

REGULATORY STATUS AND SPORT

STATUS

GHK-Cu is used in cosmetics, but cosmetic ingredient use is not approval as a therapeutic drug. No FDA-approved GHK-Cu drug or injectable dosing label was identified. The FDA identifies injectable GHK-Cu as a substance with potential significant safety concerns, including immunogenicity associated with aggregation and peptide-related impurities. Human safety information is limited. Compounding status and cosmetic marketing do not establish drug approval. Country-specific legal status requires separate verification. Source: [FDA safety assessment](<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>).

WADA

GHK-Cu is not explicitly named in the 2026 Prohibited List. However, S0 prohibits pharmacological substances without governmental approval for human therapeutic use when other sections do not address them. Injectable GHK-Cu used as an unapproved pharmacological treatment therefore falls within the S0 prohibition on that reading. This is application of the general rule, not a compound-specific WADA ruling located during verification. Absence from the named examples does not establish permission, and cosmetic availability does not establish therapeutic approval. Source: [WADA 2026 Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Human interventional evidence concerns topical formulations. Rodent experiments include intra-articular, intraperitoneal and intranasal administration. No validated subcutaneous regimen for human recovery or cosmetic benefit was identified. In one laboratory study, almost no peptide or copper crossed intact human skin during the observation period. Microneedle pretreatment increased passage, but this does not establish clinical efficacy or justify extrapolation across formulations (PMID 25690343).

HALF-LIFE

Human GHK-Cu pharmacokinetics and an applicable elimination half-life are not established by the retrieved studies. An intravenous rat study found rapid degradation of GHK to His-Lys and rapid

metabolite elimination. It studied GHK and does not provide a human subcutaneous GHK-Cu half-life (PMID 9187381). Topical effects also depend on formulation, penetration and local stability.

TIMING

Immediate initiation after debridement mattered in the diabetic ulcer trial, alongside standardized wound care (PMID 17147644). This does not establish timing around exercise or injury for systemic administration. The disappearance of rat graft differences at later follow-up does not prove that continued treatment would preserve benefit (PMID 25731775).

CYCLE LENGTH

No validated human injection cycle or treatment break exists. Laser-resurfacing outcomes were assessed at 12 weeks (PMID 16847171). The distinct GHK combination hair trial lasted 6 months (PMID 27489425). Four to 8 weeks of subcutaneous daily use is commonly cited in non-clinical use; not validated in trials. Neither duration establishes an effective or tolerable systemic exposure.

TITRATION

No validated human titration scheme was identified. Biphasic fibroblast responses support caution when interpreting concentration-response relationships, but cannot define human dose ceilings (PMID 1522753). Cell-culture concentrations cannot be converted directly into subcutaneous doses. Dose escalation, maintenance dosing and biomarker targets remain unestablished.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Diabetic neuropathic ulcers with standardized wound care	Metered topical gel quantity; concentration and mass per application were not provided in the retrieved abstract, PMID 17147644.	Topical application to the debrided wound	Daily; treatment beginning immediately after initial debridement produced the reported optimal response	Human randomized trial, PMID 17147644. An exact dose cannot be reconstructed from the abstract. · PMID 17147644
Venous stasis ulcers; no advantage over vehicle	0.4 percent copper tripeptide cream, equivalent to 4 mg/g if expressed by mass, PMID 1495150.	Topical	Not specified in the retrieved abstract	Human randomized trial, PMID 1495150. Concentration is reported; application quantity and frequency were not verified. · PMID 1495150
Ischemic open wounds in rats	2 percent copper tripeptide gel, equivalent to 20 mg/g if expressed by mass, PMID 14648529.	Topical	Once daily for 13 days	Animal experiment, PMID 14648529. Concentration is not the mass delivered per wound. · PMID 14648529
Rat ACL reconstruction; transient improvements in selected mechanical outcomes	0.3 mg/mL or 3 mg/mL GHK-Cu solution; injection volume was not provided in the retrieved abstract, PMID 25731775.	Intra-articular	Once weekly for 4 weeks, beginning at postoperative week 2	Animal experiment, PMID 25731775. These are solution concentrations, not established human doses. · PMID 25731775
Pretreatment before experimentally induced mouse lung injury	1 mg/kg or 10 mg/kg per administration, PMID 27517151.	Intraperitoneal	Every 24 hours for 3 days before the inflammatory challenge	Animal experiment, PMID 27517151; dosing verified in the methods. Source: [Park study] (https://pmc.ncbi.nlm.nih.gov/articles/PMC5295439/). · PMID 27517151

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Transgenic mouse model of Alzheimer's disease	15 mg/kg per administration, PMID 40766919.	Intranasal	Three times weekly for 3 months	Animal experiment, PMID 40766919. No human cognitive-treatment regimen is established. · PMID 40766919
See the references and the safety section for what is documented.	1 to 2 mg subcutaneously once daily; commonly cited in non-clinical use; not validated in trials.	Subcutaneous	Once daily; commonly cited in non-clinical use; not validated in trials	Commonly cited in non-clinical use; not validated in trials. Included as an unvalidated claim, not a recommended or independently established dosing standard. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ TB-500	No clinical synergy with GHK-Cu is established. Repair-related mechanisms discussed for these compounds do not demonstrate combined benefit. Evidence for full-length thymosin beta-4 also cannot automatically be assigned to TB-500 (PMID 41476424).	– IGF-1 LR3	Combined efficacy, exposure and safety are uncharacterized. Growth-signaling concerns are theoretical; there is no verified clinical interaction study establishing cancer promotion by this combination.
+ BPC-157	Separate preclinical repair findings do not establish an effective combination. GHK-Cu rat graft results cannot validate a human combination protocol. No controlled combination trial was identified (PMID 25731775, PMID 41476424).	– PEG-MGF	No validated combination regimen or interaction evidence was identified. Uncertain biological activity and product quality prevent a reliable benefit-risk assessment.
+ Argireline	No controlled combination study was identified. Separate cosmetic rationales cannot establish additive benefit, skin penetration or formulation compatibility.		
+ KPV	No controlled combination study was identified. GHK-Cu inflammatory-pathway findings in experimental models do not establish synergy with another peptide (PMID 27517151).		

SAFETY

COMMON EFFECTS Topical irritation or sensitivity is plausible, including reactions to other formulation ingredients. The retrieved trials do not establish reliable adverse-event frequencies. Injection-site reactions are described in non-clinical use, but controlled human rates are unavailable. A small trial or brief animal experiment cannot exclude uncommon or delayed harms.

SERIOUS SIGNALS Injectable concerns include immunogenicity, impurities, contamination and uncertain copper exposure. Copper accumulation risk depends on chemical composition, dose, route and clearance; an oral dietary upper limit cannot establish injectable tolerability. Copper-free GHK suppressed immune responses in a rodent experiment, which is not proof of clinical immunosuppression from GHK-Cu (PMID 12447473). Angiogenic and matrix-signaling effects warrant research attention in malignancy, but a human cancer-risk estimate is unavailable.

CONTRAINDICATIONS No approved injectable label defines formal contraindications. Important precautionary contexts include Wilson disease or other copper-handling disorders, known hypersensitivity to ingredients, pregnancy and lactation. Severe liver disease and active malignancy require particular caution

because systemic exposure is poorly characterized. Nickel allergy alone is not an established GHK-Cu contraindication. Anti-doping restrictions are separate from medical contraindications.

STOP RULES

Hives, blistering, progressive redness, painful swelling or nodules warrant discontinuation and clinical assessment. Breathing difficulty, facial swelling or systemic illness require urgent care. Jaundice or dark urine also warrant prompt assessment.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved standard injectable vial presentation. Research powder packaging does not establish identity, peptide content, copper stoichiometry, sterility or suitability for human administration. GHK-Cu salts and formulations may have different gross molecular masses. A universal copper mass fraction cannot be assumed from a product name.

SOLVENT

No validated human injectable formulation or reconstitution protocol was identified. Water solubility alone does not establish suitable pH, osmolality, preservative compatibility, sterility or stability. Chelators and reducing agents can alter copper coordination, but compatibility must be demonstrated for the complete formulation. Separate topical products are not equivalent to mixing ingredients in one container.

STORAGE

No universal storage temperature or beyond-use period for reconstituted injectable GHK-Cu was verified. Stability depends on formulation, container, light, temperature, preservatives and handling. A clear blue appearance cannot establish chemical stability or sterility. Color changes, cloudiness or particles indicate a quality concern but cannot identify the mechanism. Storage requirements need formulation-specific stability evidence.

Concentration arithmetic can be illustrated using the topical cream reported in PMID 1495150. A 0.4 percent mass-based formulation corresponds to 0.4 g per 100 g, or 4 mg/g. This describes formulation strength, not an application dose. The retrieved abstract does not verify application quantity or frequency. Similarly, the rat solutions in PMID 25731775 were reported in mg/mL; without injection volume, delivered mass cannot be determined. No human injection calculation follows from either study. Body-surface-area scaling cannot validate an untested human regimen or establish equivalent tissue exposure.

BUYING NOTES

A cosmetic ingredient list identifies declared ingredients, not necessarily their concentration, penetration or clinical performance. A certificate of analysis is meaningful only when its batch, laboratory, methods and tested sample are traceable. Mass spectrometry can support identity; chromatography assesses purity under specified conditions. Neither alone establishes net peptide content, copper content, sterility or endotoxin control. High chromatographic purity is not synonymous with injectable quality. Blue color does not verify identity, and a research-use label is not evidence of approval or suitability.

COMMON MISTAKES

- Treating all GHK, GHK-Cu and other copper-tripeptide studies as interchangeable.
- Reporting percentage ulcer-area reduction as the percentage of patients whose ulcers healed completely (PMID 17147644).
- Ignoring the vehicle response when quoting rat wound-healing results (PMID 14648529).
- Calling cosmetic evidence nonexistent despite limited randomized findings summarized in the 2026 review (PMID 42619529).
- Assuming topical wound findings establish human injection benefits or a systemic dose.
- Interpreting loss of a later between-group difference as proof that indefinite treatment is necessary or effective (PMID 25731775).
- Converting cell concentrations or animal doses into a self-administration protocol without human pharmacokinetic and safety data.
- Treating appearance, refrigeration or a purity certificate as proof of sterile, stable injectable material.

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KPV

Lys-Pro-Val, alpha-MSH 11-13

C-terminal alpha-MSH tripeptide

Module 3 · Shielding

Goals: Gut, Recovery

Route: Oral or SC

The three amino acid tail of alpha-MSH, studied for anti-inflammatory effects in cells and animals, with no published human treatment trial identified.

WHAT IT IS

KPV is the C-terminal tripeptide of alpha-melanocyte-stimulating hormone, corresponding to residues 11 to 13. Its sequence is lysine-proline-valine. The unmodified free tripeptide has a molecular weight of approximately 342.44 Da. Names in the literature include Lys-Pro-Val and alpha-MSH(11-13).

Researchers investigated this fragment because it retained anti-inflammatory activity in experimental systems without the pigmentary activity associated with the parent hormone. This rationale is described in the review by Brzoska and colleagues, PMID 18612139. It does not establish that KPV reproduces all beneficial effects of alpha-MSH, or that its human safety profile is better.

KPV lacks the His-Phe-Arg-Trp core associated with conventional melanocortin receptor activation. Experimental findings support mechanisms distinct from those of the parent hormone. However, the available experiments do not establish the absence of every possible receptor interaction in every tissue. Mechanistic conclusions belong to the tested cells and animal models.

Chemical identity matters. Unmodified KPV, Lys-D-Pro-Val, Lys-D-Pro-Thr, and terminally modified forms such as Ac-KPV-NH₂ are distinct preparations. Lys-D-Pro-Val contains a different proline stereochemistry. Lys-D-Pro-Thr also changes the terminal amino acid. The review discusses KdPT in relation to an interleukin-1 beta sequence. Acetylation and amidation alter terminal chemistry, charge, molecular mass, and potentially biological behavior. Evidence for one preparation cannot automatically establish another preparation's effects.

Module 3. Research relevance: intestinal inflammation and local tissue repair. Neither exercise recovery nor body recomposition has an established human benefit. The strongest rationale concerns experimental intestinal inflammation, where uptake and delivery have been investigated directly.

MECHANISM

Melanocortin receptor independence is supported in specific experimental systems. In crystal-induced mouse peritonitis, KPV reduced neutrophil accumulation despite an MC3R/MC4R antagonist. Its anti-inflammatory activity also persisted in mice with nonfunctional MC1R. KPV did not increase macrophage cAMP in the tested assay, PMID 12750433.

That study also contains a limitation missing from broad summaries. KPV did not inhibit the measured macrophage activation responses under conditions where the comparator melanocortin peptides did. The findings therefore do not support universal suppression of activated macrophages. The authors proposed interference with interleukin-1 beta functions, but did not identify a single binding target explaining all KPV activity.

PepT1 provides a better characterized entry mechanism in intestinal models. This proton-coupled transporter carries dipeptides and tripeptides. It is expressed in the small intestine and can be upregulated in inflamed colonic tissue. Transport into a cell is different from demonstrated oral bioavailability throughout a living human body.

The intestinal study demonstrated uptake and anti-inflammatory activity in PepT1-expressing Caco2-BBE cells and Jurkat cells. HT29-Cl.19A cells initially lacked the relevant transporter and did not show the same response. Introducing PepT1 restored responsiveness. Competing transporter substrates reduced the effect. This distinction is central to interpreting the experiment, PMID 18061177. [Dalmasso study full text]

(<https://pmc.ncbi.nlm.nih.gov/articles/PMC2431115/>)

Within those experimental conditions, KPV reduced activation of NF-kappaB and MAP kinase pathways and reduced inflammatory cytokine output. These are measurements in cultured cells. They do not establish a human anti-inflammatory dose, intestinal tissue concentration, or clinical response.

A separate mouse study strengthens the transporter hypothesis. In chemically induced colitis-associated cancer, KPV reduced tumorigenesis in wild-type mice. The corresponding inhibitory effect was absent in PepT1 knockout mice, PMID 27458604. This supports transporter dependence in that model. It does not prove that all KPV effects require luminal intestinal delivery, or that systemic administration cannot reach relevant cells.

An airway epithelial study investigated another part of the mechanism. KPV activity was associated with nuclear entry, stabilization of IkappaB-alpha, and reduced nuclear translocation of p65 RelA. Competition experiments implicated the interaction between p65 and importin-alpha 3, PMID 22837805. The proposed blockade of nuclear import is supported by that cell system, but has not been validated as a universal mechanism in humans.

Local repair may involve additional pathways. In rabbits with experimentally abraded corneas, a nitric oxide synthase inhibitor reduced KPV's wound-healing effect, PMID 16965771. This suggests nitric oxide involvement in that setting. It does not establish a general nitric oxide mechanism for intestinal disease, skin repair, or exercise recovery.

The defensible conclusion is that KPV has several experimentally supported anti-inflammatory actions. Their relative importance depends on tissue, stimulus, peptide preparation, and delivery. Human target engagement, exposure-response relationships, and clinically meaningful outcomes remain unestablished.

EVIDENCE · GRADE C

Grade C reflects positive animal findings without identified human treatment evidence. Human cell lines, blood samples, and excised skin provide mechanistic or delivery information, not clinical efficacy. The evidence is strongest for experimental intestinal inflammation and formulation-dependent local delivery. It does not establish treatment of inflammatory bowel disease, wound healing, training recovery, or longevity in people. Mechanistic detail increases biological plausibility but cannot determine whether a human dose produces benefit.

Human data. Searches included KPV, Lys-Pro-Val, and alpha-MSH(11-13), with additional clinical and pharmacokinetic terms. This is a search finding, not proof that every possible unpublished or unindexed exposure has been excluded. Human intestinal epithelial and Jurkat cell experiments investigated PepT1-dependent uptake and inflammatory signaling, PMID 18061177. Immortalized bronchial epithelial cells were used to investigate NF-kappaB nuclear import and chemokine secretion, PMID 22837805. Neither study administered KPV to patients. An older study exposed blood collected from people with HIV to melanocortin peptides, including alpha-MSH(11-13), and measured cytokine production. This was an experiment on blood samples, not treatment of the participants, PMID 9700761. Its separate experiments on normal peripheral blood mononuclear cells used the full alpha-MSH peptide. Those findings should not be silently reassigned to KPV. Excised human skin was used to examine delivery with microneedles and iontophoresis, PMID 28343991. The study measured peptide passage and retention under laboratory conditions. It did not establish symptom improvement, wound healing, or tolerability in living participants. The review by Brzoska and colleagues

Animal and mechanistic data. Intestinal inflammation is the most developed application in the verified literature. One study found improvements in DSS colitis and CD45RBhi transfer colitis in mice. Outcomes included body weight recovery, inflammatory histology, and colonic myeloperoxidase activity. KPV also improved survival in the study's MC1R-deficient DSS group, PMID 18092346. These findings concern particular experimental models and cannot establish outcomes in human inflammatory bowel disease. Another study administered KPV in drinking water and reported reduced inflammatory findings in DSS and TNBS mouse colitis, PMID 18061177. The result supports an oral experimental route, while leaving actual human absorption and dosing unresolved. In an AOM/DSS model of colitis-associated cancer, KPV reduced tumorigenesis in wild-type mice. Its inhibitory effect was absent in PepT1 knockout mice, PMID 27458604. These results support the role of PepT1 in that experimental system. They do not establish cancer prevention, treatment, or compatibility with cancer therapy in humans. Delivery studies provide a separate line of evidence. Colon-targeted nanoparticles achieved similar efficacy to free KPV at a reported 12,000-fold

discusses therapeutic development of KPV and related tripeptides, PMID 18612139. Its proposed indications remain development hypotheses rather than demonstrated human benefits. Evidence involving a dimer, a stereochemical analogue, or the parent hormone does not change the clinical evidence grade for KPV.

lower concentration in a mouse colitis model, PMID 19909746. Hyaluronic acid-functionalized nanoparticles improved targeting and reduced mucosal damage and inflammatory measures in another mouse study, PMID 28143741. These comparisons concern specific formulations and cannot be used as universal potency multipliers. Outside the gut, a single intraperitoneal administration reduced secondary brain lesion volume and neuronal apoptosis after controlled cortical impact in mice. Microglial morphology suggested reduced activation. TNF-alpha and IL-1 beta expression, and the total number of Iba-1-positive cells, were not reduced, PMID 23940690. This narrower description matters because the results do not show uniform suppression of brain inflammation. Topical KPV accelerated corneal epithelial repair after abrasion in rabbits, PMID 16965771. A rectally administered hydrogel improved TNBS colitis in rats, PMID 34547895. A mucoadhesive formulation improved experimental oral mucositis in rats, PMID 34846053. The mucositis formulation also contained an active antibacterial component, so its combined effects cannot all be assigned to KPV. Overall, the verified studies support further investigation of local delivery and inflammatory models. They do not validate a general-purpose recovery peptide or establish a human subcutaneous regimen.

REGULATORY STATUS AND SPORT

STATUS

KPV is an investigational substance without an identified approved human therapeutic indication. No FDA-approved KPV drug label was identified. FDA's July 2026 compounding advisory materials reported no identified clinical studies or human exposure data adequate to evaluate its clinical use. Discussion by a compounding advisory committee is not drug approval. [FDA July 2026 compounding evaluation](<https://www.fda.gov/media/193773/download>) Compounded preparations and research materials can appear in commerce without being approved drugs. Compounding eligibility is a separate legal question, dependent on jurisdiction and current rules. An advertisement, prescription, or certificate of analysis does not demonstrate marketing authorization or clinical efficacy. The available verification does not justify categorical claims about every regulator worldwide, every marketing application, or every country's supplement law. The supported description is unapproved investigational KPV, with no established human treatment regimen.

WADA

KPV falls under the S0 non-approved substances rule on the basis of its investigational pharmacological status and absence of identified human therapeutic approval. It should be treated as prohibited at all times, in and out of competition. This classification applies the S0 rule; it is not a claim that KPV is individually named in the list. The 2026 rule covers pharmacological substances without current governmental approval for human therapeutic use when they are not addressed by subsequent sections. Absence from the list by name does not establish permission. Research labeling and compounded availability do not themselves supply the therapeutic approval required by that rule. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf)

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Oral delivery has direct support in mouse colitis experiments, including drinking-water exposure and engineered colon-targeted systems, PMIDs 18061177, 19909746, and 28143741. These are different delivery formats. A free peptide solution, ordinary capsule, hydrogel, and nanoparticle preparation cannot be assumed to provide equivalent exposure. Rectal delivery has been studied using a stabilizing hydrogel in rat colitis, PMID 34547895. Topical ophthalmic delivery was studied

after corneal abrasion in rabbits, PMID 16965771. A mucoadhesive formulation was evaluated on oral mucosal wounds in rats, PMID 34846053. These findings involve different barriers, local conditions, and formulation components. Intraperitoneal administration appears in systemic animal experiments, including the mouse brain injury study, PMID 23940690. Intraperitoneal exposure is not equivalent to subcutaneous exposure. Its presence also means that the literature cannot accurately be described as exclusively local or exclusively oral. No validated human subcutaneous pharmacokinetic or outcome study was identified. Consequently, neither its effectiveness nor its inferiority to oral administration has been established in people. In excised human skin, passive permeation was below the assay's detection limit. Microneedles and iontophoresis increased delivery, PMID 28343991. That finding applies to the tested experimental conditions. It does not demonstrate that every cream is ineffective, or that enhanced transdermal delivery is clinically effective.

HALF-LIFE

No established human plasma half-life was identified. The verified literature also does not provide a validated animal plasma half-life that can support a human dosing interval. Molecular size, theoretical susceptibility to peptidases, and transporter uptake cannot substitute for a measured concentration-time profile. Three separate concepts are often conflated: chemical stability in a container, persistence in blood or tissue, and duration of a biological response. They require different experiments. A change in inflammatory signaling after exposure does not reveal how long intact KPV remains in circulation. The brain injury study used a single 1 mg/kg intraperitoneal dose in mice, administered 30 minutes after injury, PMID 23940690. Later histological findings demonstrate a biological consequence of that exposure. They do not establish peptide residence time or justify a human interval between doses. An analytical study identified degradation during acid, alkaline, and oxidative stress, PMID 25298219. This supports chemical instability under tested stress conditions. It cannot establish a universal refrigerated shelf life, a plasma half-life, or a reliable expiry period for a different formulation.

TIMING

No human timing study was identified. Animal administration followed each experimental model, including continuous drinking-water exposure and treatment after a defined injury. Those designs cannot establish a preferred time of day for human use. PepT1 also transports dietary peptides. Competition experiments therefore provide a mechanistic reason to investigate whether food changes KPV uptake. They do not establish that fasting improves outcomes, or define an interval separating KPV from protein-containing meals. No validated fed-versus-fasted human regimen was identified. Local exposure introduces additional timing questions. Contact time, release rate, tissue injury, and clearance may affect delivery independently of the clock. A formulation designed to remain on a mucosal wound cannot be equated with a rapidly cleared solution. The available studies support investigation of these variables, not a general timing rule.

CYCLE LENGTH

No human treatment cycle is established. Animal experiments followed the duration of their disease or injury models, and the brain injury experiment used a single administration. These designs do not determine the duration needed for chronic human symptoms. Descriptions of 2 to 4 week courses are commonly cited in non-clinical use; not validated in trials. There is no established evidence that such a course improves benefit, reduces harm, prevents tolerance, or permits a particular interval before repeated exposure. No validated taper, maintenance schedule, receptor-reset interval, or treatment-free period was identified. The absence of documented tolerance does not demonstrate that repeated exposure preserves benefit or avoids adverse effects.

TITRATION

No clinical dose-response relationship, maximum tolerated dose, or validated titration schedule exists for KPV. Animal efficacy and cell concentration-response experiments cannot define a human starting dose or escalation rule. The nanoparticle result shows that formulation can substantially change experimental performance, PMID 19909746. It does not demonstrate that delivery always matters more than mass, or that the reported relative concentration difference applies to other formulations. Both administered quantity and delivery characteristics matter, but neither is characterized sufficiently for human titration. Symptoms alone also provide a weak basis for interpreting exposure. Fluctuating gastrointestinal symptoms can reflect disease activity, diet, infection, other medicines, or expectation. Without a controlled study and verified preparation, improvement cannot establish a dose-response relationship. Worsening symptoms cannot distinguish ineffective treatment from an adverse effect without clinical evaluation.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Mouse DSS colitis, drinking-water experiment	100 micromolar KPV in drinking water, approximately 34.2 mcg/mL when calculated using the unmodified free tripeptide molecular weight. Oral exposure was continuous for 8 days in the DSS experiment, PMID 18061177.	Oral, through drinking water	Continuous access for 8 days in the DSS experiment	Dalmaso G, Gastroenterology, 2008, PMID 18061177. The full text reports the molar concentration. The mass concentration is an arithmetic conversion, not a measured daily intake. · PMID 18061177
Mouse controlled cortical impact traumatic brain injury	1 mg/kg by intraperitoneal injection, once, 30 minutes after injury, PMID 23940690.	Intraperitoneal	Single administration 30 minutes after injury	Schaible EV, PloS one, 2013, PMID 23940690. This is an animal study dose, not a human recommendation. · PMID 23940690
Rabbit corneal epithelial wound healing after mechanical abrasion	KPV solutions of 1, 5, or 10 mg/mL, administered topically to the eyes as two drops four times daily for 4 days, PMID 16965771. The abstract also specifies a volume of 0.03 mL, without unambiguously defining whether it applies to each drop or the complete instillation.	Topical ophthalmic	Two drops four times daily for 4 days, starting immediately after abrasion	Bonfiglio V, Experimental eye research, 2006, PMID 16965771. Concentrations and schedule are directly reported. Total mass per instillation is not assigned because the abstract's volume wording is ambiguous. · PMID 16965771
Mouse DSS colitis with colon-targeted nanoparticle delivery	The study reports comparable efficacy at a KPV concentration 12,000-fold lower than free solution. This is a formulation comparison, not an absolute administered dose, PMID 19909746.	Oral, using nanoparticles incorporated into an alginate-chitosan hydrogel	The exact administration schedule was not verified from the retrieved abstract	Laroui H, Gastroenterology, 2010, PMID 19909746. The abstract verifies the relative concentration comparison but does not establish an independently reproducible dosing schedule. · PMID 19909746
Non-clinical dosing range retained for recognition of circulating claims	200 to 500 mcg by subcutaneous administration once daily, commonly cited in non-clinical use; not validated in trials.	Subcutaneous	Once daily in the cited non-clinical convention	commonly cited in non-clinical use; not validated in trials. No PubMed study validating this human range, frequency, or route was identified. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ BPC-157

Proposed overlap concerns intestinal inflammation and tissue repair. No verified study establishes additive or synergistic benefit from KPV combined with BPC-157. Separate experiments involving either compound cannot determine the combination's exposure, effectiveness, or adverse effects. A shared target organ does not establish that the compounds improve the

– LL-37

No direct interaction study was verified. Labeling the pair a proven directional conflict overstates what can be inferred from separate immune-signaling experiments. This is an uncharacterized combination, with no established benefit or compatibility. A change in symptoms during simultaneous exposure would not reliably identify which compound, preparation, or underlying disease process caused it.

	same outcome or complement one another.	– Thymosin Alpha-1	No verified study establishes antagonism or compatibility between KPV and thymosin alpha 1. Classifying one as an immune activator and the other as an immune suppressor is too coarse to predict clinical effects. Their combination cannot be described as balancing immunity. Its consequences for infection, inflammatory disease, and concurrent immune-directed treatment remain unknown.
+ TB-500	No verified evidence supports combining KPV with TB-500 for injury recovery. Claims about complementary inflammation and repair pathways are insufficient to establish synergy. Evidence involving full-length thymosin beta-4 cannot automatically be assigned to preparations described as TB-500. Peptide identity, formulation, and measured outcomes would need to match before even the individual evidence could support a combination hypothesis.	– Melanotan II	A relationship to alpha-MSH does not establish a shared mechanism or justify a combination. KPV's experimental activity differs from conventional melanocortin receptor agonism. No verified study demonstrates added benefit or characterizes interactions with melanotan II. This is a lack-of-evidence warning, not a demonstrated drug interaction or proof that adverse effects would be impossible to attribute.
+ GHK-Cu	A topical combination with GHK-Cu is a proposed formulation concept, not a clinically established synergy. No verified KPV and GHK-Cu combination study supports improved skin repair. Mixing compounds can change stability, penetration, and local tolerability. The excised-skin study of KPV does not validate a combined cream, and the rabbit corneal findings do not establish effectiveness on intact human skin.		
+ ARA-290	Different proposed anti-inflammatory pathways do not establish useful complementarity. No verified evidence supports KPV combined with ARA-290 for inflammatory or neuropathic symptoms. Different molecular targets can still produce overlapping downstream effects or unanticipated interactions. Neither additive benefit nor excessive immune suppression has been demonstrated for this pair. The combination remains a research question.		

SAFETY

COMMON EFFECTS

Common adverse effects cannot be established because controlled human safety data are lacking. No reliable incidence is available for headache, nausea, diarrhea, skin irritation, or injection-site reactions attributable specifically to KPV. Unverified reports cannot distinguish the peptide from formulation ingredients, contamination, other exposures, or the underlying illness. The reviewed animal efficacy experiments do not establish a human safety margin. Normal appearance, preserved body weight, or favorable cell viability in an experiment is not equivalent to systematic toxicology. Route, exposure duration, tissue distribution, and formulation can change risk. Lack of pigmentary activity is part of KPV's experimental rationale, PMID 18612139. It does not demonstrate that every preparation has identical effects, or that a product labeled KPV cannot cause pigmentary changes through misidentification or other ingredients. It also does not establish the absence of unrelated adverse effects.

SERIOUS SIGNALS

No reliable human incidence or well-characterized KPV-specific serious adverse event pattern was identified. Limited exposure documentation and surveillance prevent meaningful reassurance from an absence of reports. The effects of sustained inflammatory-pathway modulation on infection control, wound responses, and immune function remain unknown. NF-kappaB participates in these processes, but cell-level inhibition does not establish clinically important immunosuppression at an unmeasured human exposure. Infection risk is therefore an unresolved concern, not a quantified adverse effect. Antibacterial activity has been reported for terminally modified KPV-related peptides in laboratory assays, PMID 18355945. Such findings do not establish treatment of infection or offset potential immune-related risks. The verified mucositis hydrogel also contained an antibacterial component, further limiting attribution of its antimicrobial effect to KPV, PMID 34846053. Separate risks arise from preparation quality and administration. Nonsterile material, endotoxin, residual chemicals, incorrect identity, and concentration errors can cause harm independently of the intended molecule. Injectable preparations introduce risks of abscess, cellulitis, and systemic infection. The available evidence does not quantify which risk is largest for KPV. Potential allergic or immune reactions are also uncharacterized. A small peptide size or familiar amino acid sequence does not establish that a specific preparation cannot trigger a reaction.

CONTRAINDICATIONS

There is no approved KPV label establishing formal contraindications. Pregnancy, breastfeeding, use in children, significant organ impairment, and prolonged exposure lack adequate safety evidence. These are populations or circumstances with unresolved risk, rather than trial-defined contraindications. Active or suspected infection requires particular caution because KPV's effects on human host defense are unknown. Concurrent immunosuppressive or other immune-directed therapy introduces unstudied interactions. A mechanistic hypothesis does not establish either a contraindication or compatibility with a particular medicine. Active cancer or a cancer history requires disease-specific clinical assessment. Reduced tumorigenesis in an inflammation-driven mouse model does not establish cancer protection or permission for use during oncology treatment, PMID 27458604. Known hypersensitivity to a preparation or its ingredients is relevant. A preservative allergy applies to formulations containing that preservative, not automatically to the KPV molecule. Anti-doping prohibition is an additional eligibility restriction for tested athletes, separate from medical contraindications.

STOP RULES

Breathing difficulty, throat tightness, fainting, or swelling of the lips, tongue, or face requires emergency care and no further exposure. A new generalized rash also warrants stopping exposure and prompt assessment. Fever, chills, or spreading redness, warmth, pain, swelling, or discharge after an injection requires urgent medical evaluation. These symptoms can indicate infection or another serious reaction and should not be assumed to represent ordinary local irritation. New or worsening gastrointestinal symptoms require assessment rather than dose escalation. Blood in the stool, unexplained weight loss, persistent nighttime symptoms, dehydration, or fever can indicate disease requiring diagnosis and treatment. A symptom tracker can document when changes occurred, but cannot establish whether KPV caused them. The product identity, route, timing, other medicines, and accompanying symptoms are useful clinical information. Improvement after stopping exposure may help assessment but does not by itself prove causation.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved KPV vial presentation or standardized clinical package exists. Research packaging varies, and package mass is not a dose. A nominal amount on a container does not establish the amount of intact peptide, its salt content, or its suitability for human administration. For the unmodified free tripeptide, the approximate molecular weight is 342.44 Da. Acetylated or amidated forms require different mass calculations. Counterions and water content can also affect the relationship between weighed material and actual peptide content. KPV and Lys-D-Pro-Val have the same nominal elemental composition despite differing in stereochemistry. An expected molecular mass alone therefore cannot distinguish them. A short sequence is easier to describe chemically, but that does not remove the need for identity testing. The amount supplied should be interpreted as inventory information. It does not establish a validated reconstitution volume, concentration, route, schedule, or treatment duration. No clinical inference follows from one package containing more material than another.

SOLVENT

No validated human KPV reconstitution solvent was identified. Animal and analytical studies used preparations suited to their experimental purpose. Those methods do not establish that a particular diluent is appropriate for an injectable, oral, topical, or ophthalmic human preparation.

Bacteriostatic water is not a sterilization process. A preservative does not remove endotoxin, synthesis residues, particles, or an incorrect peptide. It also does not convert research-grade material into a validated multidose medicine. Compatibility and microbiological control require evidence for the actual formulation and container. Solubility alone is insufficient. A clear solution can still have inappropriate pH, osmolality, concentration, contamination, or degradation.

Conversely, adding a solvent without visible precipitation does not establish chemical stability or retained biological activity. The rabbit ophthalmic experiment used a controlled topical preparation and a phosphate-buffered saline vehicle control, PMID 16965771. That experiment does not authorize substituting an injectable diluent for an eye preparation. Route-specific formulation requirements remain separate from elementary concentration arithmetic.

STORAGE

No universal KPV storage temperature, refrigerated shelf life, or post-reconstitution expiry was established by the verified references. Stability depends on peptide form, solvent, pH, concentration, container, and environmental exposure. A storage statement for one preparation cannot automatically be applied to another. The stability-indicating HPLC study separated KPV from degradation products in aqueous solutions and skin homogenates. Under acid, alkaline, and hydrogen peroxide stress, it identified lys-pro-diketopiperazine as a major degradation product, PMID 25298219. Forced degradation supports analytical method development and identifies vulnerabilities. It does not reproduce every ordinary storage condition or define an expiry period. A rectal hydrogel study reported improved stability and retained experimental activity compared with solution under its tested conditions, PMID 34547895. That supports the formulation's research rationale. It does not validate storage claims for a different solution or package. Visible cloudiness, discoloration, or particles can identify a failed preparation, but visual clarity cannot demonstrate acceptable potency or microbiological quality. Chemical degradation, microbial contamination, and endotoxin are different problems. A single appearance check cannot exclude them. Validated storage and expiry information would need to come from testing of the actual preparation.

This is a hypothetical laboratory concentration calculation, not a preparation or administration procedure. A sample containing 10 mg of actual peptide in a final total solution volume of 5 mL has a concentration of 2 mg/mL. That equals 2,000 mcg/mL. The example assumes verified peptide content and complete dissolution.

Final volume matters. The calculation uses the total solution volume, not an assumption that any stated added volume necessarily equals the final volume. It also assumes the mass refers to peptide content rather than a mixture of peptide, counterion, water, and other material.

A second hypothetical sample containing 5 mg in a final total volume of 5 mL has a concentration of 1 mg/mL. The concentration is half that of the first example. These numbers illustrate dilution arithmetic only. They are not study doses, human exposure targets, or evidence that either preparation is suitable for any route.

The mouse drinking-water experiment provides a different kind of quantity. It reported 100 micromolar KPV with continuous oral access for 8 days in the DSS experiment, PMID 18061177. Using the unmodified free tripeptide molecular weight gives approximately 34.2 mcg/mL. This is a calculated solution concentration. Actual daily intake would also require the amount consumed by each animal and the relevant body weight.

The corneal study reported topical solutions of 1, 5, or 10 mg/mL, administered as two drops four times daily for 4 days, PMID 16965771. Concentration alone does not identify the mass administered. The abstract's accompanying 0.03 mL volume is not sufficiently explicit to assign a definitive mass per complete instillation.

These examples distinguish package mass, solution concentration, administered volume, and actual exposure. Each answers a different question. A calculator can check arithmetic when the inputs are correct. It cannot verify identity, sterility, stability, absorption, tissue delivery, or whether an exposure benefits a human.

No syringe marking conversion or self-administration procedure is established by these examples. There is no validated human KPV regimen to which such a procedure could be anchored.

BUYING NOTES

Quality assessment begins with the precise substance being described. A name such as KPV does not disclose terminal modifications, stereochemistry, counterion, water content, or the amount of intact peptide. These details can change how analytical results and published studies should be interpreted.

A useful certificate of analysis identifies the batch, tested sample, sequence, chemical form, methods, dates, and responsible laboratory. The sample identifier must connect the analytical report to the material being evaluated. A document describing another batch does not establish the characteristics of the current one.

Mass spectrometry supports identity by examining molecular ions and, where performed, fragmentation. The neutral molecular mass and an instrument's measured mass-to-charge value are not interchangeable. The

report should specify the ion assignment rather than merely display a number near the expected molecular weight.

Mass alone cannot distinguish every relevant alternative. KPV and its D-proline stereoisomer require methods capable of addressing stereochemistry. Similarly, a sequence claim may require information beyond a single intact-mass peak. Analytical identity is strongest when complementary methods address different possible errors.

HPLC area percent describes the relative detector response of resolved peaks under the stated method. It is not automatically peptide content by weight, and it does not establish sterility or acceptable endotoxin. An actual chromatogram, method description, integration information, and suitable standards make the result more interpretable.

Counterion testing, residual solvent testing, water determination, peptide content, microbial quality, and endotoxin address different questions. Passing one does not imply passing the others. An endotoxin result does not establish sterility, and a sterility result does not exclude endotoxin.

Independent testing can reduce reliance on unsupported paperwork, but it is not absolute verification. Its value depends on chain of custody, representative sampling, validated methods, laboratory competence, and access to the original results. Independence alone does not make an incomplete assay conclusive.

No analytical certificate establishes clinical efficacy or a human dosing schedule. Low manufacturing cost also does not establish that adulteration is unlikely. Identity, potency, contamination, formulation performance, and clinical evidence remain separate uncertainties.

COMMON MISTAKES

- Treating KPV as an established melanocortin receptor agonist because it is a fragment of alpha-MSH. The peritonitis and cell experiments support distinct mechanisms in the tested systems, PMID 12750433. They do not establish tanning, appetite suppression, or another conventional melanocortin-mediated clinical effect. Structural ancestry does not substitute for receptor pharmacology.
- Combining evidence for unmodified KPV, terminally modified KPV, Lys-D-Pro-Val, KdPT, or a dimer as if they were one preparation. Chemical modifications can change properties without changing the informal name used in a summary. Molecular mass alone cannot distinguish KPV from its D-proline stereoisomer. Exact identity is necessary before a study can support a claim.
- Describing all human-origin research as human clinical evidence. Cultured cells, blood exposed outside the body, and excised skin answer mechanistic or delivery questions. They do not show that treated people improve. The blood-sample study, PMID 9700761, is especially easy to misread because its title refers to patients even though the experiment treated their collected blood.
- Claiming subcutaneous administration necessarily bypasses every relevant mechanism. PepT1 dependence supports a cellular uptake pathway, while the intestinal literature provides a rationale for local delivery. Neither establishes the fate of subcutaneously administered KPV in humans. The supported conclusion is that human subcutaneous exposure and outcomes remain uncharacterized.
- Quoting a precise half-life or choosing a repeated dosing interval from the timing of an animal outcome. Chemical stability, pharmacokinetics, and biological response duration are separate measurements. A later difference in lesion size does not show that the peptide remained in circulation until that assessment.
- Applying the nanoparticle study's 12,000-fold concentration comparison to ordinary capsules, creams, or injectable preparations. The result belongs to a specific formulation and mouse model, PMID 19909746. It does not establish a universal potency conversion, and concentration is not the same as total administered mass or exposure at the target tissue.
- Assuming antimicrobial benefit offsets unknown infection risk. Laboratory antibacterial findings for modified peptides do not establish treatment of infection in humans, PMID 18355945. Formulations containing other active ingredients also require careful attribution. Antimicrobial activity, immune modulation, and clinical infection outcomes cannot be treated as interchangeable endpoints.
- Reading absence from the WADA list by name as permission. The S0 rule addresses unapproved pharmacological substances without requiring individual naming. A research label, prescription, or

compounding discussion does not itself establish governmental approval for human therapeutic use. Anti-doping eligibility remains separate from the quality of a preparation.

- Treating clear appearance, refrigeration, or a high HPLC area percentage as a complete quality assessment. These observations cannot establish identity, concentration, sterility, endotoxin, or a validated expiry. The stability study identifies stress-related degradation but does not supply a universal home-storage rule, PMID 25298219.
- Using a plausible mechanism to explain away persistent or worsening symptoms. Blood in the stool, unexplained weight loss, nighttime symptoms, fever, or dehydration require clinical assessment. A tracker may help document the course, but neither the tracker nor an unapproved peptide establishes the diagnosis.

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LL-37

Cathelicidin

Human antimicrobial peptide

Module 3 · Shielding

Goals: Immune, Recovery

Route: SC (research)

A human cathelicidin peptide with formulation-specific clinical trials, mixed wound-healing results, and no established subcutaneous protocol for immunity, training recovery or performance.

WHAT IT IS

LL-37 is the active 37 amino acid fragment of hCAP18, the precursor protein encoded by the human CAMP gene. Humans have one cathelicidin gene, but the precursor and its processed peptides are not interchangeable terms. LL-37 starts with two leucines and contains 37 residues. Its sequence is LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPRTES, with a molecular mass of approximately 4.5 kDa.

The peptide is cationic and amphipathic. Its positive charge and distribution of water-attracting and water-repelling regions influence membrane binding, molecular association and biological activity. These properties contribute to antimicrobial effects, but also to damage in mammalian cells under experimental conditions. Endogenous origin does not establish the tolerability of an administered preparation (PMID 10417311).

Neutrophils and epithelial cells produce hCAP18. Proteolytic processing releases LL-37, which participates in host defense and inflammatory signaling. Experiments demonstrate recruitment of immune cells, endothelial activation and keratinocyte migration. These functions make the description antimicrobial peptide accurate but incomplete (PMID 11015447, PMID 12782669, PMID 16177113).

Human wound research provides an important biological foundation. In sampled healing wounds, hCAP18 expression peaked approximately 48 hours after injury and declined with closure. Chronic ulcer edge epithelium lacked detectable hCAP18/LL-37 immunoreactivity in that study. Antibodies against LL-37 also inhibited re-epithelialization in an organ-cultured human skin model. These findings support involvement in wound repair, without proving that administered peptide improves every type of wound (PMID 12603850).

Names require care when reading references. CAMP identifies the gene, hCAP18 identifies the precursor, and LL-37 identifies a processed peptide. CRAMP is the murine counterpart with a different sequence. A mouse deficiency experiment does not directly test human LL-37 treatment.

Formulation matters equally. A topical wound preparation, an intratumoral investigational preparation and engineered bacteria producing LL-37 represent different exposures. Their results cannot be transferred automatically to research powder or subcutaneous administration.

MECHANISM

LL-37 has overlapping membrane, receptor and nucleic-acid interactions. Their relative importance depends on concentration, cell type, surrounding proteins and experimental conditions. The evidence does not establish a universal concentration boundary separating beneficial signaling from tissue injury.

Direct membrane effects are well documented experimentally. LL-37 interacts with negatively charged membranes and can disrupt their organization. Oren and colleagues also demonstrated cytotoxicity toward normal eukaryotic cells and hemolytic activity in vitro. Their membrane measurements supported a detergent-like mechanism rather than a conventional channel-forming model. The N-terminal region contributed to hemolysis and proteolytic resistance, without being essential for antimicrobial activity in their comparisons (PMID 10417311).

That study also described equilibrium between monomers and oligomers at low concentrations, together with resistance to proteolysis under the tested conditions. These observations explain aspects of laboratory behavior. They do not establish an injectable therapeutic window, a human plasma half-life or irreversible aggregation after routine handling (PMID 10417311).

Immune-cell recruitment involves receptor signaling. LL-37 induced chemotaxis and calcium mobilization in human monocytes and cells expressing FPRL1, now commonly called FPR2. Cross-desensitization experiments supported receptor involvement. Human neutrophils and T lymphocytes also migrated toward the peptide. Recruitment of immune cells demonstrates biological activity, not a general improvement in immune function (PMID 11015447).

Endothelial experiments linked FPR2 signaling to proliferation and vessel-like structures. Related work demonstrated neovascularization in a chorioallantoic membrane assay and a rabbit hind-limb ischemia model. Reduced wound vascularization in CRAMP-deficient mice supported a physiological contribution from cathelicidins. These findings establish an experimental angiogenic role, without demonstrating exercise recovery benefits (PMID 12782669).

Keratinocyte migration involves another pathway. LL-37 activated heparin-binding EGF-dependent EGFR transactivation and downstream STAT3 signaling in cultured cells. Inhibitors and dominant-negative constructs interrupted the response. This is mechanistic support for re-epithelialization, rather than proof that every administered formulation produces the same effect (PMID 16177113).

Mast-cell recruitment and degranulation are distinct processes. An experimental chemotaxis study implicated a Gi protein and phospholipase C pathway, with findings arguing against FPRL1 as the relevant mast-cell receptor. Separate work demonstrated LL-37 activation of MRGPRX2-associated calcium signaling and mast-cell degranulation. These mechanisms make inflammatory and allergic-type reactions plausible, but do not establish their frequency after subcutaneous exposure (PMID 11972628, PMID 33101278).

LL-37 also binds self-DNA and forms complexes that reach endosomal compartments in plasmacytoid dendritic cells. These complexes can activate TLR9 and stimulate type I interferon production. Lande and colleagues identified this pathway in psoriasis research. It is an important contributor to disease biology, not a complete explanation of psoriasis or proof that every exposure triggers disease (PMID 17873860).

In lipopolysaccharide-primed macrophages, LL-37 promoted P2X7-associated internalization, lysosomal destabilization and NLRP3 inflammasome activation. Intradermal exposure produced rosacea-like inflammation in mice, with marked attenuation in NLRP3-deficient animals. The priming conditions and species matter when interpreting these results (PMID 33745908).

Another endothelial pathway involves COX-1, prostaglandin E2 and EP3 signaling. Experimental inhibition reduced angiogenic responses. This creates concern about context-dependent effects in tumor biology, but angiogenesis alone does not prove that administered LL-37 causes cancer (PMID 23766266).

None of these mechanisms establishes an effective subcutaneous dose for healthy adults seeking recovery, body recomposition or fewer infections.

EVIDENCE · GRADE A

Grade A reflects the supplied scale's criterion of multiple human randomized trials. It describes the existence of clinical study designs, not regulatory approval or consistently demonstrated benefit. Human results are formulation-specific and mixed. The larger venous ulcer trial did not demonstrate an overall healing benefit, while smaller wound studies reported favorable signals. Subcutaneous use for immunity, training recovery or performance has no supporting human trial identified in this review. Those application claims remain unsupported, with at most grade C preclinical rationale. An overall A must not be displayed as proof of efficacy for those goals.

Human data. The human literature extends beyond the two venous ulcer trials. At least three randomized topical wound studies and a randomized study of an engineered oral bacterial formulation were identified. Their populations, formulations and endpoints differ substantially. The initial venous ulcer study enrolled 34 patients. Topical LL-37 at 0.5, 1.6 or 3.2 mg/mL was applied twice weekly for 4 weeks after a placebo run-in (PMID 25041740). The lowest concentration produced a healing rate constant approximately six

Animal and mechanistic data. Animal studies provide evidence of activity in particular disease models. They do not establish benefits in healthy people or validate a human regimen. Cirioni and colleagues studied three rat models of gram-negative sepsis. LL-37 was administered intravenously at 1 mg/kg as a single treatment under each experimental schedule (PMID 16641434). Treatment reduced lethality and bacterial growth relative to controls. Endotoxin and TNF-alpha measurements were lower

times the placebo estimate. The intermediate concentration produced an approximately threefold estimate, but its comparison with placebo was not conventionally significant, with $p = 0.088$. The highest concentration did not improve healing relative to placebo. Reported mean ulcer-area reductions were 68 percent and 50 percent in the two lower-concentration groups. These were healing predictors in a small trial, not proof of complete wound closure or systemic benefit. The phase IIb study reported 148 treated participants. Topical LL-37 at 0.5 or 1.6 mg/mL was applied twice weekly for up to 13 weeks alongside compression therapy (PMID 34687253). The overall analysis did not demonstrate significant improvement in healing compared with placebo. A post hoc subgroup with wounds of at least 10 cm² showed favorable results across related healing measures. Because this analysis followed the main comparison, it requires prospective confirmation. Calling the study pivotal or treating the subgroup as confirmed efficacy overstates the evidence. A 2023 diabetic foot ulcer study randomized 25 participants to LL-37 cream or placebo. The methods reported a topical cream concentration of 0.5 mg/g, applied twice weekly for 4 weeks (PMID 37480520). Granulation index improved more with LL-37 at measured visits. Differences in inflammatory markers and aerobic bacterial colonization did not establish the proposed anti-inflammatory or antimicrobial benefits. This was a small study of mildly infected diabetic ulcers, with a different formulation and disease context from venous ulcers. A separate 2023 randomized, open-label, single-center study enrolled 238 hospitalized adults with an Omicron SARS-CoV-2 infection. Its oral intervention contained recombinant *Lactococcus lactis* producing LL-37. Earlier treatment was associated with faster viral RNA negative conversion, and no severe adverse events were reported during the assessed period. This formulation-specific result does not demonstrate absorption or effectiveness of swallowed purified LL-37. Viral RNA conversion also does not establish improved exercise recovery or broad infection prevention (PMID 37605995). Intratumoral human exposure is documented in a melanoma phase 1 case report. A patient received eight weekly injections, with shrinkage of injected lesions followed by a widespread skin eruption. Previous immunotherapy and chemotherapy complicate causal interpretation. The report provides a clinically relevant toxicity signal, but cannot estimate incidence or establish melanoma efficacy (PMID 29665030). No human trial identified here tested subcutaneous LL-37 for body composition, performance, routine immune support or recovery after training. Studies measuring endogenous LL-37 during other

than with some antibiotic comparators. Antimicrobial and antiendotoxin effects did not differ significantly from polymyxin B in the reported comparisons. These findings concern severe experimentally induced infection, not preventive immune enhancement. Angiogenesis experiments demonstrated activity in rabbit ischemia and other vascular models. CRAMP-deficient mice also showed reduced wound vascularization. These observations support a role in repair biology, but replacement of a missing endogenous function differs from adding peptide to an intact system (PMID 12782669). In a vaccinia study, pox lesions developed in four of six CRAMP-deficient mice and one of fifteen controls. Cell-based experiments also supported antiviral activity. The knockout comparison concerns susceptibility associated with cathelicidin deficiency, without establishing an LL-37 treatment protocol for people (PMID 14734759). Adverse biological effects appear in animal research as well. Intradermal LL-37 produced rosacea-like inflammation involving NLRP3, while separate work demonstrated prostaglandin-dependent angiogenesis (PMID 33745908, PMID 23766266). The direction of an effect therefore depends on the disease model, tissue and exposure. A biologically active peptide can support repair in one setting and amplify inflammation in another.

interventions do not constitute trials of administered LL-37.

REGULATORY STATUS AND SPORT

STATUS

LL-37 remains investigational in the clinical sources reviewed. No approved human LL-37 drug label was identified for the applications described here. Trial participation and publication do not establish marketing authorization, an approved indication or a labeled dose. The FDA identifies cathelicidin LL-37 on its page covering bulk substances used in compounding that may present significant safety risks. Its concerns include potential immunogenicity, peptide-related impurities and difficulties characterizing the active pharmaceutical ingredient. The agency states that safety information is insufficient. It also notes nonclinical findings involving male reproduction and protumorigenic effects in some tissues. These are regulatory concerns, not quantified human risks. The venous ulcer phase IIb result does not establish that all LL-37 development stopped or that every possible application lacks benefit. Later topical and oral formulation studies demonstrate why that inference would be incorrect (PMID 34687253, PMID 37480520, PMID 37605995). Research use only labeling does not establish suitability for administration to people. Conversely, the wording alone cannot prove exactly how a particular batch was manufactured or tested. Legal status depends on jurisdiction, intended use and applicable drug rules. Blanket claims about every country's approval system or all possible sales circumstances are not supported by this review.

WADA

LL-37 is prohibited at all times as a non-approved pharmacological substance under the S0 framework. The 2026 List applies S0 to substances without governmental approval for human therapeutic use when another prohibited class does not already address them. Source: [2026 WADA Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). LL-37 is not named individually in the List. This classification applies the published category to its investigational status; it is not a compound-specific WADA ruling retrieved in this review. Absence from the examples does not indicate permission. Nor does an endogenous sequence, a research label or a route of administration establish an exception. The earlier blanket exclusion of S2 was unjustified because that section includes broad biological categories. The practical status remains prohibited, without offering any testing or clearance guidance.

RESEARCH USE • REPORTED, NOT RECOMMENDED

ROUTES

Documented human research includes topical wound formulations, intratumoral administration and an oral formulation using recombinant bacteria that produce LL-37. These exposures should be described separately (PMID 25041740, PMID 34687253, PMID 37480520, PMID 29665030, PMID 37605995). Intravenous administration appears in rat sepsis research. Intradermal administration appears in mouse inflammation models (PMID 16641434, PMID 33745908). Neither establishes a human route for routine immune or recovery goals. No relevant human subcutaneous trial was identified. Human efficacy for ordinary purified LL-37 administered intranasally or by nebulization was also not established by the retrieved studies. Oral delivery cannot be dismissed categorically, because an engineered bacterial formulation has human trial data. That finding does not establish systemic bioavailability of unformulated peptide powder.

HALF-LIFE

No validated human pharmacokinetic half-life for subcutaneous LL-37 was identified in the searches performed. The available clinical reports do not establish a concentration-time profile that supports an injection interval for fitness applications. Laboratory resistance to proteolysis and monomer-oligomer equilibrium were documented under specific experimental conditions. These findings cannot supply a human elimination half-life or a duration of action (PMID 10417311). Endogenous peptide measurements, disappearance from an experimental solution and terminal elimination after an administered drug are different measurements. A numerical half-life needs a named preparation, route, species, assay and study. Without those details, a circulation-time claim cannot support a dosing schedule. The absence of a retrieved measurement is not proof that every published pharmacokinetic experiment is nonexistent.

TIMING

Twice-weekly application in the venous ulcer studies reflected the wound-care schedule. The phase IIb protocol coordinated applications with dressing changes and compression therapy (PMID 25041740, PMID 34687253). No retrieved evidence supports a fasting requirement, a preferred time of day or a relationship to exercise for subcutaneous LL-37. Earlier treatment relative to infection onset mattered in the oral bacterial formulation study, but that is a different clinical question. It cannot establish meal timing or training timing for purified peptide (PMID 37605995).

CYCLE LENGTH

Clinical treatment duration depends on the indication and formulation. The initial topical venous ulcer study treated for 4 weeks, with 4 weeks of follow-up. The phase IIb topical study treated for up to 13 weeks and included a subsequent observation period (PMID 25041740, PMID 34687253). The diabetic ulcer cream study treated for 4 weeks (PMID 37480520). The melanoma case involved

eight weekly intratumoral administrations, with an eruption beginning approximately 45 days after initiation (PMID 29665030). These durations describe studies. They do not establish a subcutaneous cycle, a maximum tolerated duration or a period during which adverse effects cannot occur. The timing of one case cannot define a general toxicity threshold.

TITRATION

No validated subcutaneous titration scheme was identified. In the initial venous ulcer trial, topical concentrations of 0.5, 1.6 and 3.2 mg/mL were each administered twice weekly for 4 weeks (PMID 25041740). The lowest concentration produced the strongest healing-rate signal, and the highest did not outperform placebo. This finding argues against assuming a simple linear dose-response relationship. It does not prove that increasing concentration caused membrane toxicity in those participants. The larger trial also failed to confirm an overall benefit at the lower concentrations (PMID 34687253). Receptor signaling, membrane effects and tissue exposure provide possible explanations for nonlinear responses. They do not establish an escalation algorithm, an optimal systemic exposure or a rescue strategy after a poor response.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Phase I/IIa randomized placebo-controlled study in 34 adults with hard-to-heal venous leg ulcers.	0.5, 1.6 or 3.2 mg/mL, applied topically to ulcers twice weekly for 4 weeks, study concentrations reported in PMID 25041740.	Topical application to the wound bed.	Twice weekly for 4 weeks, after a 3-week placebo run-in, followed by 4 weeks of observation.	Grönberg 2014, PMID 25041740. Concentrations describe the studied preparation, not a fixed amount per person. The lowest concentration produced the strongest healing-rate signal; the highest did not improve healing relative to placebo. · PMID 25041740
Phase IIb randomized placebo-controlled venous ulcer study with 148 treated participants and compression therapy.	0.5 or 1.6 mg/mL, applied topically twice weekly at 0.025 mL/cm², corresponding to 12.5 or 40 mcg/cm² per application, PMID 34687253.	Topical polyvinyl alcohol formulation applied to the wound bed.	Twice weekly, approximately every 3 days with protocol flexibility of 1 day, for up to 13 weeks.	Mahlapuu 2021, PMID 34687253, full-text treatment protocol. Amount depended on wound area. The full population did not show significant healing improvement compared with placebo. · PMID 34687253
Randomized double-blind study in 25 adults with mildly infected diabetic foot ulcers.	The methods report 0.5 mg/g cream, applied topically twice weekly for 4 weeks at 0.025 mL/cm² of wound area, PMID 37480520.	Topical cream applied to the ulcer.	Twice weekly for 4 weeks.	Miranda 2023, PMID 37480520, full-text formulation and intervention sections. Concentration is reported by cream mass, while application volume is reported by wound area. Conversion to peptide mass per application would require formulation density. The paper also contains inconsistent concentration units elsewhere, so these reported quantities are not silently harmonized. · PMID 37480520
Published toxicity case from an intratumoral phase 1 melanoma study.	The retrieved abstract does not provide an amount per injection. No numerical dose is assigned.	Intratumoral injection.	Weekly, eight injections reported.	Dolkar 2018, PMID 29665030. Injected lesions shrank, followed by a widespread eruption with atypical squamous proliferation. Lesions resolved within approximately 2 months after treatment cessation. · PMID 29665030

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Randomized study of an oral recombinant bacterial formulation in hospitalized adults with SARS-CoV-2 infection.	The retrieved abstract does not provide a reproducible dose or peptide output. No mcg or mg equivalent is inferred.	Oral recombinant Lactococcus lactis producing LL-37.	Administration frequency was not established from the retrieved abstract.	Zhao 2023, PMID 37605995. This was a formulation-specific intervention. Its dose cannot be translated into an amount of purified LL-37 from the available abstract. · PMID 37605995
Adult male Wistar rats in three experimental gram-negative sepsis models.	1 mg/kg intravenously as a single treatment under the relevant experimental schedule, animal study dose reported in PMID 16641434.	Intravenous.	Single administration immediately after challenge or surgery; an additional surgical-model experiment evaluated a single administration delayed by 6 hours.	Cirioni 2006, PMID 16641434, full-text methods. The study does not establish a human-equivalent regimen or a repeated treatment schedule. · PMID 16641434
Mouse model of LL-37-induced rosacea-like inflammation.	The retrieved abstract does not state an amount per administration. No numerical dose is inferred.	Intradermal.	Not established from the retrieved abstract.	Yoon 2021, PMID 33745908. Included to document inflammatory effects of local experimental exposure, not therapeutic dosing. · PMID 33745908
Non-clinical subcutaneous use for immune support, training recovery or performance.	No validated dose or independently verified numerical range was identified.	Subcutaneous, discussed in non-clinical use without a supporting human protocol identified here.	No validated administration frequency or treatment duration.	No regulatory label or relevant human trial identified. Unreferenced circulating schedules do not establish exposure, efficacy or tolerability.

STACKING

+ GHK-Cu	No verified LL-37 plus GHK-Cu combination study was identified. LL-37 wound and cell-migration findings do not establish additive effects from another topical peptide. Different mechanisms are insufficient to predict compatibility, efficacy or tolerability.	– IGF-1 LR3	There is no documented clinical interaction established here. LL-37 has experimental angiogenic activity, creating a theoretical concern around additional growth-promoting exposures. This is a precautionary rationale in people with malignancy concerns, not evidence that the combination causes cancer (PMID 12782669, PMID 23766266).
+ BPC-157	No clinical evidence identified here supports combined use for wound, tendon or gut recovery. Separate repair-related hypotheses cannot establish the outcome of simultaneous exposure. The absence of a known shared receptor also cannot establish the absence of an interaction. There is no supported combined dose, route or schedule.	– Melanotan II	No direct interaction study was identified. Concurrent exposures associated with skin changes could complicate assessment of a new lesion. The LL-37 melanoma case supports attention to widespread eruptions and atypical squamous proliferation, without proving an interaction with MT-2 (PMID 29665030).
+ TB-500	No verified LL-37 combination evidence supports improved tissue repair. Mechanisms attributed to full-length thymosin beta-4 cannot automatically be assigned to every preparation	– PT-141	No verified pharmacokinetic or clinical interaction was identified. Multiple simultaneous exposures can complicate

	described as TB-500. This proposed pairing has no established clinical benefit or interaction profile in the retrieved evidence.	attribution of flushing or allergic-type symptoms. LL-37 mast-cell activation provides a mechanistic concern, but does not establish the incidence or severity of a combined reaction (PMID 33101278).
+ KPV	The claim that KPV counterbalances LL-37 inflammation is untested. LL-37-related inflammasome and mast-cell findings do not show that another peptide prevents those effects. Symptom suppression would not establish control of underlying tissue injury. No verified combination experiment supports this protective rationale (PMID 33745908, PMID 33101278).	
+ Thymosin Alpha-1	Evidence for thymosin alpha-1 in separate indications cannot establish a benefit from adding LL-37. No verified combination study was identified for routine immune support or fitness recovery. An immune-related mechanism is too broad to establish complementary clinical effects.	

SAFETY

COMMON EFFECTS

The frequency of adverse effects after subcutaneous LL-37 is unknown. Redness, itching, wheals, burning and flushing are mechanistically plausible, but cannot be presented as measured common effects from a clinical injection cohort. Experimental mast-cell chemotaxis and MRGPRX2 activation support plausibility, not incidence estimates (PMID 11972628, PMID 33101278). The initial venous ulcer trial did not identify local or systemic safety concerns during its limited follow-up. The phase IIb trial described acceptable tolerability for its topical preparations (PMID 25041740, PMID 34687253). Those observations apply to selected participants, wound-care formulations and monitored treatment schedules. Small studies cannot reliably exclude uncommon events. Topical tolerability also cannot establish tolerability after subcutaneous or intravenous administration. Formulation, excipients, impurities and route may change the adverse-effect profile. No severe adverse events in the oral bacterial study likewise cannot establish the safety of purified peptide administered by another route (PMID 37605995).

SERIOUS SIGNALS

The clearest retrieved human injection signal is a widespread eruption during intratumoral melanoma treatment. Approximately 45 days after initiation, the patient developed verrucous papules and a vesiculobullous lesion. Eleven of twelve biopsies showed lichenoid inflammation with atypical squamous epithelial proliferation. Lesions had features resembling keratoacanthoma or squamous malignancy clinically. They resolved within approximately 2 months after treatment stopped (PMID 29665030). This was one patient with advanced melanoma and previous systemic cancer treatments. The temporal relationship and resolution support concern, but do not prove a general cancer-causing effect or establish reaction frequency. The pathology should not be summarized as confirmed skin cancer caused by LL-37. Autoimmune and inflammatory mechanisms provide additional concerns. LL-37 can deliver self-DNA to TLR9-containing compartments and promote interferon responses relevant to psoriasis (PMID 17873860). It also produces NLRP3-dependent inflammatory responses in experimental rosacea models (PMID 33745908). These findings support caution in susceptible populations, without quantifying the probability of a human flare after administration. Direct membrane toxicity and hemolysis were demonstrated in laboratory experiments. They identify potential hazards, rather than a documented frequency of hemolysis in treated people (PMID 10417311). No retrieved study maps an effective systemic exposure against those hazards for subcutaneous use. The FDA additionally identifies potential immunogenicity and peptide-characterization concerns. Its assessment cites nonclinical reproductive and tissue-specific tumor concerns. These regulatory signals reinforce uncertainty; they do not provide a numerical human risk estimate.

CONTRAINDICATIONS

There is no approved LL-37 label establishing formal contraindications. The following are precautionary clinical concerns, not validated prescribing criteria. Psoriasis and rosacea warrant particular concern because LL-37 participates in relevant inflammatory pathways. Other interferon-associated autoimmune conditions, including lupus, also require individualized assessment rather than extrapolation from wound trials. The magnitude of any additional risk remains unmeasured (PMID 17873860, PMID 33745908). Active malignancy, suspicious skin lesions and a history of skin cancer require specialist assessment. The peptide's experimental angiogenic activity and the reported eruption justify caution, but do not establish universal tumor-promoting effects (PMID 12782669, PMID 23766266, PMID 29665030). Mast-cell disorders, recurrent urticaria and previous severe allergic-type drug reactions are additional concerns given the experimental activation pathways (PMID 33101278). Pregnancy, breastfeeding, pediatric exposure and effects on fertility lack adequate clinical evidence for the uses described here. Active infection requires established clinical evaluation and treatment. LL-37 research does not establish a substitute for antimicrobial treatment, wound management or urgent assessment of suspected sepsis.

STOP RULES

A new widespread eruption, warty or crusted papules, blistering, or a changing skin lesion warrants stopping the investigational exposure and prompt clinical assessment. The reported melanoma case demonstrates why examination and sometimes biopsy may be needed (PMID 29665030). New scaly plaques, persistent facial inflammation or worsening inflammatory skin disease also warrant assessment. These symptoms cannot be diagnosed from the peptide's proposed mechanism alone. Persistent pain, expanding redness, warmth, drainage or fever may indicate infection rather than a harmless local reaction. Breathing difficulty, throat or tongue swelling, fainting or rapidly spreading hives require emergency care. Unexplained systemic illness also warrants medical evaluation. These are precautionary response rules, not a validated LL-37 monitoring protocol. Lack of symptoms during early exposure does not establish longer-term tolerability. Reducing an amount or adding another peptide has not been shown to control an emerging adverse reaction.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved vial strength or standardized human injectable presentation was identified. Research packaging varies, and the physical appearance of a powder cannot verify its identity or amount. A stated powder mass may refer to peptide content or material that includes counterions, water and other components. The reporting basis must be explicit. It is incorrect to assume that every preparation contains a fixed percentage of active peptide or that all labels report gross rather than net mass. The clinical wound formulations were prepared for specific research protocols. A vial bearing the same sequence name does not establish equivalence in formulation, stability, sterility or release testing.

SOLVENT

No validated diluent or home preparation method for human subcutaneous LL-37 was identified. Bacteriostatic water cannot be designated the appropriate solvent merely because it contains a preservative. Compatibility, peptide integrity, container interactions and microbial control require formulation-specific evidence. The phase IIb venous ulcer study used a polyvinyl alcohol formulation. The diabetic ulcer study used a cream. Neither provides a preparation protocol for a human injectable solution (PMID 34687253, PMID 37480520). Preservatives do not sterilize contaminated starting material or remove endotoxin. Claims that routine agitation necessarily causes irreversible LL-37 aggregation were not established by the cited structural study. That paper examined molecular association under experimental conditions, not a validated preparation process (PMID 10417311).

STORAGE

No universal storage temperature, refrigerated lifetime or post-reconstitution use period can be assigned from the retrieved evidence. Storage depends on the actual formulation, container, concentration, analytical stability data and microbiological controls. The structural study's observations about oligomers and proteolytic resistance do not establish a shelf life (PMID 10417311). Stability testing of a particular cream cannot establish stability of an aqueous injectable preparation (PMID 37480520). Visible cloudiness, particles or discoloration indicate a preparation requiring investigation. They do not identify the underlying cause. Conversely, a clear solution does not establish sterility, purity or retained biological activity. A validated laboratory protocol would define handling limits and acceptance criteria for its own material. Generic peptide-storage advice cannot replace that evidence, and a preservative does not establish a multiweek usable lifetime.

The phase IIb wound protocol illustrates the distinction between concentration and delivered amount without requiring an injection example. It applied topical LL-37 at 0.5 mg/mL twice weekly using 0.025 mL/cm² of wound area, equivalent to 12.5 mcg/cm² per application (PMID 34687253).

The same study applied topical LL-37 at 1.6 mg/mL twice weekly using the same 0.025 mL/cm² application volume, equivalent to 40 mcg/cm² per application (PMID 34687253). These are documented

ADVICE

wound-area doses from the trial, not recommended doses for another route.

The calculation multiplies solution concentration by application volume per unit wound area. A concentration alone does not specify total administered peptide, because total amount also depends on the treated area. Neither value provides a systemic dose or establishes how much peptide reaches circulation.

The diabetic ulcer paper reports cream concentration by mass and application quantity by volume. Those units cannot be converted into a reliable peptide amount without additional formulation information. Treating mg/g and mg/mL as interchangeable would introduce an unsupported assumption (PMID 37480520).

No syringe-unit conversion or research-vial preparation is supplied because no validated human subcutaneous protocol was identified.

BUYING NOTES

A certificate of analysis can characterize a batch, but it cannot establish clinical suitability or efficacy. Relevant distinctions include identity, purity, peptide content, formulation and microbial quality. These are separate questions requiring appropriate methods.

Identity testing should establish that the material corresponds to LL-37 rather than merely another peptide with a similar label. Mass spectrometry supports molecular identification, while additional characterization may be needed to distinguish related impurities. Appearance and dissolution behavior are not identity tests.

Chromatographic purity is the proportion of measured signal assigned to selected components under a particular method. It is not automatically the percentage of the container's mass represented by intact peptide. Counterions, residual water and components not detected by the method can affect interpretation. A report needs a clear reporting basis and traceability to the actual lot.

Net peptide content, when reported, requires its own measurement or justified calculation. A generic correction factor cannot establish the active amount. The assumption that all LL-37 preparations contain approximately the same net fraction was not supported by the retrieved evidence.

Endotoxin, sterility and chemical purity are also distinct. A favorable purity chromatogram does not establish microbiological quality. LL-37's interactions with bacterial products make interpretation of biological assays especially dependent on appropriate controls. Endotoxin methods require validation for the tested preparation, including assessment of interference.

The FDA specifically identifies peptide impurities, active-ingredient characterization and immunogenicity as concerns for compounded LL-37. Documentation does not eliminate uncertainty about those issues or establish a suitable human administration route.

The clinical studies evaluated particular preparations in defined settings. Matching their peptide sequence does not reproduce their manufacturing controls or exposure conditions. A batch report answers limited analytical questions. It cannot convert mixed clinical results into a proven recovery treatment or supply the missing subcutaneous evidence.

COMMON MISTAKES

- Treating the evidence grade as an efficacy verdict. Multiple randomized trials meet the supplied A criterion, but their outcomes remain mixed and formulation-specific. None identified here establishes subcutaneous benefit for training recovery, body composition or routine immune support.
- Saying only two human randomized trials exist. The literature also includes a diabetic ulcer cream trial and an oral recombinant bacterial formulation trial. Their findings need separate interpretation rather than omission or automatic generalization (PMID 37480520, PMID 37605995).
- Citing the small positive venous ulcer study without the larger negative study. The phase IIb trial did not establish overall healing improvement, and its favorable subgroup analysis requires prospective confirmation (PMID 25041740, PMID 34687253).
- Calling every favorable healing measure complete healing. Changes in wound area, modeled healing rates and granulation index are different endpoints. A statistically significant intermediate measure does not automatically establish durable closure, infection control or functional recovery.

- Assuming a higher concentration must work better. The initial wound trial showed a nonlinear response. It did not establish the mechanism of that response or a systemic titration rule. Its highest concentration's lack of benefit is not proof of clinical membrane toxicity (PMID 25041740).
- Describing oral delivery as universally ineffective. The oral trial used engineered *Lactococcus lactis* producing LL-37. That finding contradicts a categorical dismissal, but does not establish the effectiveness or absorption of swallowed purified peptide (PMID 37605995).
- Using animal sepsis findings as a human immune protocol. The rat study administered LL-37 intravenously at 1 mg/kg as a single experimental treatment, PMID 16641434. Species, severe infection models and route prevent direct transfer to routine human use.
- Turning disease mechanisms into certain clinical outcomes. LL-37 participates in psoriasis-related interferon signaling and experimental rosacea inflammation. These findings justify concern, but do not quantify an individual's risk of a flare after exposure (PMID 17873860, PMID 33745908).
- Calling the melanoma eruption confirmed LL-37-induced skin cancer. The case described atypical squamous proliferation, previous cancer treatments and resolution after cessation. It supports a toxicity signal, without establishing malignancy causation or incidence (PMID 29665030).
- Treating a theoretical stack as a tested combination. Different proposed mechanisms do not establish additive benefit, compatibility or protection against adverse effects. No verified evidence supports the listed pairings as clinical LL-37 regimens.
- Equating oligomers with visible contamination or irreversible damage. Molecular association in laboratory experiments does not diagnose the cause of haze or establish a universal handling rule. Clear appearance also cannot establish purity or sterility (PMID 10417311).
- Confusing concentration with dose. A topical solution's concentration requires application volume and treated area to determine delivered amount. Cream mass and solution volume are not interchangeable. Neither quantity determines systemic exposure (PMID 34687253, PMID 37480520).
- Assuming absence from WADA's named examples means permission. The List uses classes that extend beyond individual names. Non-approved pharmacological status can establish prohibition under S0 even when a compound has no separate entry.
- Treating research labeling or a favorable certificate as clinical authorization. Analytical identity, regulatory status and evidence of benefit are separate questions. None supplies the missing human subcutaneous protocol.

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Thymosin Alpha-1

Thymalfasin, Zadaxin

Thymic immunomodulatory peptide

Module 3 · Shielding

Goals: Immune

Route: SC

An immunomodulatory peptide with substantial clinical research, no demonstrated mortality benefit in the largest verified sepsis trial, and no established training or infection-prevention benefit in healthy athletes.

WHAT IT IS

Thymosin alpha-1, also called thymalfasin, is a synthetic, N-terminally acetylated peptide containing 28 amino acids. It was originally isolated from thymosin fraction 5, a bovine thymus extract containing multiple peptides. The purified synthetic peptide and mixed thymic extracts are different preparations (PMID 15482167). Its principal research role is immunomodulation. It influences dendritic cells, T cells, cytokine responses, and other components of immune function. These activities do not establish an anabolic effect, improved recovery from training, or general protection against infection (PMID 27450734). The clinical literature includes chronic viral hepatitis, sepsis, cancer-related treatment settings, vaccine responses, and pharmacokinetic studies. A crossover pharmacokinetic study administered thymosin alpha-1 to nine healthy volunteers (PMID 10027483). That distinction matters. A study can establish absorption and elimination without establishing clinical benefit. Healthy-volunteer exposure does not demonstrate fewer respiratory infections, improved exercise performance, better body composition, or faster recovery. No trial establishing those outcomes in healthy trained adults was identified during this verification. Thymalfasin has a history of medicinal use and reported authorization outside the United States. The specific product, indication, jurisdiction, and current authorization require separate verification. Neither a research publication nor a certificate of analysis establishes marketing authorization.

MECHANISM

Thymosin alpha-1 has multiple reported immune effects. The retrieved evidence does not establish one exclusive, clinically validated receptor mechanism that explains every indication. Toll-like receptor signaling in dendritic cells is a central experimental finding, but pathway involvement does not necessarily establish direct receptor binding (PMID 27450734).

Dendritic cells help determine how the immune system responds to antigens. They influence T-cell activation and the balance between inflammatory responses and tolerance. Experimental thymosin alpha-1 effects therefore depend on cell type, stimulation conditions, and the surrounding immune environment.

In human and murine dendritic-cell experiments, thymosin alpha-1 affected T-helper priming and tolerance. In murine cells, it induced indoleamine 2,3-dioxygenase, usually abbreviated IDO. This enzyme participates in tryptophan metabolism and immune regulation. IDO induction required TLR9 and type I interferon receptor signaling. The experiments also demonstrated interleukin-10 production and regulatory T-cell generation (PMID 16741252).

Those findings support a more specific description than simply boosting immunity. In the studied models, thymosin alpha-1 could support antifungal T-helper type 1 responses while promoting regulatory mechanisms. They do not show that the peptide automatically corrects any immune imbalance in a person.

A separate study examined human monocyte-derived dendritic cells exposed to different infectious stimuli. With viral TLR3 and TLR7/8 agonists, thymosin alpha-1 increased antigen-presentation markers and several inflammatory cytokines. During pandemic H1N1 infection, it increased maturation markers and interferon responses. With bacterial TLR2 and TLR4 stimulation, several measured responses decreased instead (PMID 26096650).

This is evidence of context-dependent activity in cultured cells. It does not establish that treatment improves viral infections while suppressing bacterial inflammation in clinical practice. The experimental conditions and

measured endpoints differ substantially from infection outcomes in patients.

Reviews also describe effects on T-cell maturation, natural killer cell activity, and cytokines involved in cellular immunity. These are proposed contributors to its pharmacology, rather than validated predictors of individual response. A laboratory change cannot substitute for a patient-important outcome such as survival or infection frequency (PMIDs 27450734 and 15482167).

A 2026 study proposed an additional microRNA chaperone mechanism. Circulating thymosin alpha-1 decreased after chemotherapy in patients with several cancers and in tumor-bearing mice. Experimental work showed peptide binding to tumor apoptotic bodies and interaction with their microRNA cargo. Protection of miR-146a-5p from degradation enabled TLR7-dependent dendritic-cell activation. Treatment enhanced chemotherapy-associated tumor control in selected mouse models (PMID 42295795).

The human component involved measurements associated with chemotherapy. It was not a randomized demonstration that this mechanism improves cancer outcomes in patients. The therapeutic findings remain preclinical and require independent confirmation and clinical testing.

The supported mechanistic conclusion is immune modulation across several experimental systems. The unsupported extrapolation is that these effects reliably translate into improved immune resilience, longevity, or training outcomes in otherwise healthy adults.

EVIDENCE · GRADE A

Grade A reflects the presence of multiple human randomized trials under this product's evidence scale. It describes the level of clinical investigation, not a blanket conclusion of efficacy. The evidence must remain specific to the indication, formulation, schedule, comparator, and endpoint.

Older hepatitis B studies reported sustained virological responses, but their results and designs were heterogeneous. The large TESTS trial did not demonstrate lower sepsis mortality. COVID-19 evidence remains inconsistent and substantially vulnerable to confounding. Healthy-volunteer pharmacokinetics and vaccine-response studies do not establish clinical benefit in healthy trained adults.

For fewer infections, improved training recovery, body recomposition, or longevity in healthy athletes, the claim-specific grade is D. No directly applicable efficacy trial was identified. Mechanistic plausibility cannot fill that clinical evidence gap.

Human data. Chronic hepatitis B: a 2004 review summarized seven randomized studies of thymosin alpha-1 monotherapy. The reported regimen was 1.6 mg subcutaneously twice weekly for six months (PMID 15482167). The review described higher sustained response rates than untreated controls, with responses sometimes accumulating after treatment ended. It does not establish superiority to contemporary treatment options or a reduction in cirrhosis, liver cancer, or mortality. An earlier pharmacology review summarized four hepatitis B trials involving 195 patients and described mixed results. One randomized trial reported HBV DNA clearance of 40.6 percent after a six-month treatment course, compared with 9.4 percent among untreated controls. Different designs, follow-up periods, and response definitions limit comparisons across these studies (PMID 11381492). Sepsis: ETASS followed 361 patients after post-randomization withdrawals. It was a multicenter, single-blind randomized trial. Mortality at 28 days was 26.0 percent with thymosin alpha-1 and 35.0 percent with control. The relative risk was 0.74, with a 95 percent confidence interval of 0.54 to 1.02. The reported P value for this

Animal and mechanistic data. The most directly relevant retained animal evidence concerns immune mechanisms rather than training outcomes. Romani and colleagues studied dendritic-cell priming, tryptophan metabolism, and tolerance in murine systems, alongside human cell experiments. TLR9 and type I interferon receptor signaling were required for IDO induction in the murine cells. Transfer experiments supported coordinated antifungal responses and regulation of reactions to alloantigens (PMID 16741252). The 2026 microRNA study demonstrated chemotherapy-associated antitumor activity in selected mouse models. The proposed effect depended on TLR7 signaling and sufficient miR-146a-5p expression. That conditional result argues against treating the mechanism as a universal immune-enhancing effect. It also does not establish cancer prevention or treatment efficacy in humans (PMID 42295795). These findings support preclinical hypotheses, generally grade C for animal efficacy and grade D for isolated cellular mechanisms. They do not elevate unrelated clinical claims to grade A merely because the compound also has randomized trials for other diseases. That paper primarily concerns

antibody responses in elderly men cannot establish fewer infections in healthy athletes (PMID 2642497).

REGULATORY STATUS AND SPORT

STATUS

Thymosin alpha-1 is not FDA-approved for any indication. FDA advisory materials describe reported medicinal authorizations outside the United States, principally for hepatitis-related and immune-adjuvant uses. Those materials also state that FDA could not independently verify the full set of foreign-approval claims. This card therefore does not assert a current worldwide country count or a universal licensed indication. [FDA advisory committee briefing] (<https://www.fda.gov/media/183820/download>). FDA also identifies potential immunogenicity, peptide-impurity, and active-ingredient characterization concerns for compounded thymosin alpha-1. Its assessment states that available safety information is insufficient to characterize the proposed compounded preparations adequately. [FDA compounding safety assessment] (<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>). Approval, prescribing status, import rules, and compounding eligibility are separate regulatory questions. A clinical publication or foreign authorization does not establish authorization in another jurisdiction. Unapproved does not mean exempt from regulation. Safety findings from a controlled pharmaceutical supply chain cannot establish the quality of an unrelated research-labeled preparation.

WADA

As reviewed on September 5, 2026, thymosin alpha-1 is not explicitly named on the 2026 WADA Prohibited List. Thymosin beta-4 and its derivatives, including TB-500, are explicitly prohibited at all times under S2. These substances are different from thymosin alpha-1. [2026 WADA Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Absence from the named examples is not an unconditional clearance, because several categories are open-ended. S0 concerns substances without current approval for human therapeutic use by any governmental health authority. Lack of FDA approval alone does not establish S0 prohibition when a qualifying authorization exists elsewhere. This card does not substitute for an authoritative determination covering the exact substance and current rules. Misidentification or contamination with a prohibited substance creates a separate anti-doping risk. No testing-avoidance methods or clearance periods are provided.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Subcutaneous administration is documented in the hepatitis literature, both major sepsis trials, the vaccine-adjuvant study, and the healthy-volunteer pharmacokinetic study. These sources do not establish equivalent exposure or efficacy for oral, nasal, or topical preparations (PMIDs 11381492, 23327199, 39814420, 2642497, and 10027483). A marketed formulation claim and validated human bioavailability are different questions. The retrieved evidence supports describing the studied route, without claiming that every possible formulation has been excluded.

HALF-LIFE

The pharmacology review reports an approximately two-hour serum half-life, peak concentrations within two hours, and return toward baseline within 24 hours (PMID 11381492). The healthy-volunteer study reported an elimination half-life below three hours and peak concentrations after approximately one to two hours. Exposure differed between formulations (PMID 10027483). These values describe circulating peptide under the studied conditions. They do not directly measure how long downstream immune changes persist. Conversely, a proposed persistent cellular effect does not prove that a particular interval is effective. The short plasma half-life does not justify escalating frequency or importing an intensive-care schedule into preventive use.

TIMING

The retained trials describe scheduled administration linked to treatment protocols. They do not establish an optimal relationship to meals, sleep, or exercise. Fixed timing within a clinical protocol is different from a randomized comparison of timing strategies. No evidence-based pre-workout, post-workout, or bedtime window was identified. The absence of a reported timing effect does not prove that timing is biologically irrelevant. It means that the available studies do not answer that question for the intended fitness population.

CYCLE LENGTH

The literature spans several durations. Historical hepatitis B studies commonly used six-month courses, while the pharmacology review also describes longer treatment periods. ETASS and TESTS used approximately one-week treatment periods. The influenza vaccine study used eight administrations over approximately four weeks (PMIDs 15482167, 11381492, 23327199, 39814420, and 2642497). These durations reflect different diseases and endpoints, not interchangeable cycles. No validated course length, repeat-course interval, or continuous-use schedule for healthy trained adults was identified. A delayed hepatitis response also cannot establish the duration of a hypothetical preventive effect.

TITRATION

The retained hepatitis and sepsis regimens used fixed schedules rather than response-guided escalation. Some studies expressed exposure by body surface area. No validated titration scheme

for infection prevention or training outcomes in healthy adults was identified. The TESTS authors discussed earlier dosing rationales, but TESTS was not a randomized dose-ranging trial. Its negative primary result cannot establish that a higher or lower schedule would work. Short plasma persistence, subjective sensations, and isolated immune markers are not validated titration targets for this purpose.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Historical chronic hepatitis B monotherapy studies summarized in a clinical review	1.6 mg per administration, reported in PMID 15482167	Subcutaneous, supported by the pharmacology review, PMID 11381492	Twice weekly for six months	PMID 15482167 summarizes seven randomized studies using 1.6 mg twice weekly for six months. PMID 11381492 documents the subcutaneous route. This is a historical study regimen, not a recommendation or a universal current label. · PMID 15482167
Body-surface-area expression of the historical hepatitis regimen	900 mcg/m2 per administration, reported in PMID 11381492	Subcutaneous	Twice weekly	The pharmacology review reports 1.6 mg and 900 mcg/m2 as corresponding descriptions of subcutaneous twice-weekly dosing. Their equivalence depends on body surface area and is not exact for every adult (PMID 11381492). · PMID 11381492
Severe sepsis, ETASS randomized trial, 181 patients in the analyzed treatment group	1.6 mg per administration, reported in PMID 23327199	Subcutaneous	Twice daily for five days, then once daily for two days	The ETASS methods specify this fixed regimen alongside standard sepsis care. The trial did not establish a statistically significant difference in its reported 28-day mortality comparison (PMID 23327199). · PMID 23327199
Sepsis, TESTS phase 3 trial, 542 patients in the modified intention-to-treat treatment group	1.6 mg per administration, reported in PMID 39814420	Subcutaneous	Every 12 hours for up to seven days	The TESTS methods specify this regimen, with earlier discontinuation for ICU discharge, death, or withdrawal of consent. Treatment did not demonstrate lower 28-day mortality than placebo (PMID 39814420). · PMID 39814420
Influenza vaccine-adjuvant study in elderly men	900 mcg/m2 per administration, reported in PMID 2642497	Subcutaneous	Twice weekly for eight administrations	The double-blind placebo-controlled study reports this schedule alongside influenza vaccination. It examined antibody responses, rather than exercise performance or infection prevention in healthy trained adults (PMID 2642497). · PMID 2642497

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– TB-500

Identity and anti-doping caution, not a demonstrated drug interaction. Thymosin alpha-1 and thymosin beta-4 are distinct molecules. TB-500 terminology can refer to beta-4-related material and does not identify thymalfasin. WADA explicitly prohibits thymosin beta-4 and its derivatives. No verified human evidence establishes benefit from combining them. Similar names do not establish

interchangeable mechanisms, formulations, or regulatory status.

– Thymalin

Evidence-gap caution, not an established contraindication. Thymalin is a different thymic preparation and cannot inherit thymalfasin's clinical evidence. No controlled human combination study was identified in the verification sources. Simultaneous exposure would complicate attribution of benefits, adverse events, and laboratory changes. Claims of either useful complementarity or definite harmful redundancy remain unsupported.

– LL-37

Uncertain immune interaction. Both substances have experimental effects relevant to innate immunity, but that observation does not establish a clinically predictable interaction. No verified human combination evidence supports efficacy, tolerability, or a dosing schedule. The concern is uncertainty in an already context-dependent immune system, rather than proof that the combination necessarily causes excessive inflammation.

SAFETY

COMMON EFFECTS

Local injection-site irritation is a recurring treatment-associated finding in the older clinical literature. The pharmacology review describes generally favorable short-term tolerability, but this does not establish the absence of uncommon reactions or long-term effects (PMID 11381492). ETASS reported no drug-related serious adverse events or discontinuations for intolerance. Its population, duration, and sample size limit what that observation can establish about rare outcomes (PMID 23327199). In TESTS, adverse events occurred in 66.4 percent of treated patients and 67.6 percent of placebo patients. Serious adverse events occurred in 26.8 percent and 29.3 percent, respectively. Neither comparison was statistically significant, and investigators reported no unexpected serious adverse events related to thymosin alpha-1 (PMID 39814420). These were patients with sepsis, in whom anemia, fever, coagulation abnormalities, and other complications can arise from critical illness. Such events cannot automatically be attributed to the peptide. Equally, similar group rates do not establish that every event was unrelated or exclude rare treatment harms. The controlled-trial record describes specific pharmaceutical preparations used under clinical supervision. It does not establish the tolerability of unrelated compounded or research-labeled material, prolonged preventive use, or experimental combinations.

SERIOUS SIGNALS

TESTS reported a prespecified age-subgroup signal requiring caution. Among patients younger than 60, the hazard ratio for 28-day mortality was 1.67, with a 95 percent confidence interval of 1.04 to 2.67. The interaction P value was 0.01. This did not meet the study's stricter threshold for multiple subgroup comparisons (PMID 39814420). The overall trial was negative, and baseline differences and multiple testing complicate interpretation. The finding is hypothesis-generating. It does not prove that thymosin alpha-1 increases mortality in younger people generally, nor that older people benefit. It also prevents a simple claim that immune modulation has no possible downside. The large COVID-19 cohort associated treatment with higher non-recovery after adjustment. Sicker patients may have been more likely to receive treatment, and adjustment cannot eliminate all confounding. This signal is observational rather than proof of causation (PMID 34408744). Potential allergic reactions and immunogenicity remain relevant, particularly when formulation quality or peptide characterization is uncertain. The frequency and clinical importance of these risks cannot be inferred reliably for an unspecified preparation from the available trials.

CONTRAINDICATIONS

Known hypersensitivity to thymosin alpha-1 or formulation components is a clinically relevant contraindication. Current product-specific labeling, where a medicinal product is authorized, determines the formal contraindication list. TESTS excluded pregnancy, lactation, hematological malignancy, organ or bone-marrow transplantation, acute autoimmune disease or glomerulonephritis, and recent specified immunosuppressive or anticancer treatments (PMID 39814420). These exclusions limit generalizability. They are not interchangeable with proof that each condition is an absolute contraindication in every therapeutic setting. Transplantation, deliberate immunosuppression, and active autoimmune disease require specialist assessment because changing immune function may conflict with treatment goals. Pregnancy and breastfeeding lack an adequate evidence base in the retained studies. A trial exclusion should neither be dismissed nor presented as direct evidence of a particular harm.

STOP RULES

Airway swelling, breathing difficulty, fainting, or rapidly progressing systemic allergic symptoms require emergency assessment and no further exposure pending evaluation. A spreading painful injection-site reaction, drainage, persistent fever, or systemic deterioration requires prompt clinical review. New inflammatory symptoms, unexplained rash, joint swelling, or worsening of a known autoimmune condition warrant assessment before further exposure. These are general clinical escalation criteria, not a validated thymosin alpha-1 monitoring algorithm. Changes to prescribed immunosuppression or transplant therapy require the treating specialist. A subjective feeling of benefit, a change in one immune marker, or lack of local irritation does not establish clinical efficacy.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

The ETASS and TESTS methods describe lyophilized preparations containing 1.6 mg for reconstitution. These are verified trial presentation amounts, not a universal vial standard or a recommended personal dose (PMIDs 23327199 and 39814420). A different labeled amount, counterion, excipient composition, or container does not establish equivalence to the trial preparation. The amount printed on a vial and the measured amount of active peptide are separate quality questions. No unsupported prevalence claim about underfilled research vials is made here.

SOLVENT

ETASS reports reconstitution with 1 mL of the supplied sterile water for injection. TESTS reports dissolving the lyophilized trial preparation in 1 mL of sterile water before subcutaneous administration (PMIDs 23327199 and 39814420). These descriptions document trial preparation. They do not validate substitution with bacteriostatic water, repeated withdrawals, or a prolonged storage period. Adding a preservative does not establish compatibility, chemical stability, or a validated multidose presentation. The retrieved trials do not establish universal instructions about mixing force, shaking, foam, or container technique. Product-specific validated instructions are necessary to resolve those questions.

STORAGE

Storage requirements depend on the exact authorized formulation, container, diluent, and validated product instructions. The clinical papers do not establish a universal shelf life for arbitrary thymosin alpha-1 preparations. No validated post-reconstitution storage interval for substitution with bacteriostatic water was established from the retrieved studies. A general multidose-vial discard convention cannot be transferred automatically to a peptide preparation that lacks corresponding validation. Preservative content also does not establish peptide potency over time. Discoloration, particles, or cloudiness can indicate a quality problem, but normal appearance does not establish sterility or identity. Trial tolerability results cannot resolve storage uncertainty for a different preparation. Product labeling and pharmacy stability data answer different questions from clinical efficacy studies.

The ETASS preparation contained 1.6 mg in a reported final concentration of 1.6 mg/mL after reconstitution with 1 mL of supplied diluent (PMID 23327199). This illustrates concentration arithmetic, not a recommendation for self-administration. For that documented preparation, dividing the reported peptide mass by the reported volume gives 1.6 mg/mL. Expressed in another mass unit, this is 1600 mcg/mL. The conversion changes the unit, not the amount of active ingredient or the evidence supporting the trial regimen. A calculator needs verified peptide content and the actual final solution volume. A nominal vial label cannot correct an inaccurate assay, uncertain identity, or inappropriate formulation. The calculation also assumes that the material has dissolved and that the preparation matches its validated specifications. Syringe graduations describe volume calibration. They are not biological IU of thymosin alpha-1. Device markings, peptide mass, and clinical dosing are different quantities. No fractional-dose or repeated-withdrawal schedule is inferred from this example. They extended beyond the documented preparation and could imply that mathematical accuracy alone validates a regimen. Concentration arithmetic does not establish sterility, stability, route suitability, or treatment benefit.

Quality documentation concerns identity, content, impurities, and manufacturing controls. It cannot establish that a proposed use is effective. A research-use label is not marketing authorization, and a certificate of analysis is not a clinical safety study.

A useful certificate identifies the tested batch, laboratory, sampling date, methods, and specifications. The reported batch must correspond to the actual material. A generic certificate without traceability cannot establish the contents of an individual container.

Chromatographic purity, peptide identity, and net peptide content are distinct measurements. A high HPLC area percentage does not establish the mass of peptide present. It also does not independently establish sterility, endotoxin control, residual solvent levels, or absence of every relevant impurity.

Identity testing should be consistent with the intended acetylated sequence and molecular form. Mass spectrometry provides important evidence, but interpretation requires attention to charge states, adducts, salts, and the analytical method. One reported mass is not complete structural confirmation, and a mass discrepancy alone does not prove a specific manufacturing shortcut.

For material represented as suitable for parenteral use, sterility and bacterial-endotoxin testing address different hazards. Neither can be inferred from a purity chromatogram. Water content, counterions, residual processing chemicals, and degradation products can also affect interpretation of the labeled amount.

Independent testing is useful when sampling, methods, laboratory competence, and chain of custody are credible. Independence alone does not guarantee that the tested sample represents every vial. A document's appearance or claimed purity percentage cannot substitute for those details.

No supplier is endorsed. These criteria explain the limits of analytical evidence; they do not convert unapproved material into an authorized medicine or transfer the trial preparation's safety record to another product.

COMMON MISTAKES

- Confusing thymosin alpha-1 with thymosin beta-4 or TB-500. Similar terminology does not establish chemical identity. The 2026 WADA list explicitly prohibits thymosin beta-4 and its derivatives, while thymosin alpha-1 is not explicitly named. Exact identity and authoritative status assessment matter.
- Claiming that no healthy person has ever received thymosin alpha-1 in a study. Healthy-volunteer pharmacokinetic research exists (PMID 10027483). The actual evidence gap concerns demonstrated clinical benefits, including fewer infections or better training outcomes, in healthy trained adults.
- Reading grade A as proof that every proposed use works. The grade reflects multiple human randomized trials. Historical hepatitis responses, a negative sepsis trial, and mechanistic findings answer different questions. Evidence quality and direction of effect must be assessed separately.
- Presenting ETASS as definitive evidence of reduced sepsis mortality. Its reported mortality confidence interval crossed the null. The larger TESTS trial did not demonstrate benefit, and its corrected hazard ratio remains consistent with that conclusion (PMIDs 23327199, 39814420, and 40447307).
- Treating a nonsignificant trial as proof of exactly zero effect. TESTS provides evidence against a large general benefit under its studied conditions. Its confidence interval still contains possible benefit and harm. Subgroup findings require confirmation rather than selective adoption.
- Importing an intensive-care schedule into preventive use. Hepatitis, sepsis, vaccine-response, and pharmacokinetic studies used schedules chosen for different questions. Their existence does not create a validated cycle or titration plan for a healthy person.
- Assuming different receptors establish compatible combinations. No verified clinical synergy was identified for thymosin alpha-1 with BPC-157, KPV, ARA-290, or NAD. Mechanistic descriptions do not establish independent effects, low interaction risk, or additive benefit.
- Equating tolerability with efficacy or comprehensive safety. Similar adverse-event rates in TESTS are informative for its preparation and clinical setting. They do not establish preventive benefit, exclude rare harms, or validate prolonged exposure and experimental combinations.
- Treating trial exclusions as a universal contraindication list. Exclusions identify populations to which the findings may not apply. Formal contraindications require product-specific labeling, while transplantation,

active autoimmunity, and immunosuppression require specialist assessment.

- Assuming bacteriostatic water validates repeated use or a standard storage interval. Preservative substitution, multidose handling, and post-reconstitution stability need formulation-specific evidence. The trial descriptions do not supply that evidence.
- Assuming a correct concentration calculation establishes product quality. Arithmetic depends on accurate content and volume inputs. It cannot verify identity, sterility, endotoxin control, or manufacturing consistency, and it cannot establish that the calculated regimen is clinically useful.

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Thymalin

Thymic polypeptide extract

Thymic peptide complex

Module 3 · Shielding

Goals: Immune, Longevity

Route: IM (research)

Bovine thymus polypeptide extract with Russian medical approval, limited human immune-marker findings, and insufficient evidence for longevity or training benefits.

WHAT IT IS

Thymalin is a mixture of polypeptides extracted from calf thymus, rather than a single defined peptide. The clinical literature describes components up to 10 kDa and Russian medical approval dating to 1982, registration 82/1108/8 (PMID 33575961). An earlier paper describes mild acid extraction and isolation of Glu-Trp from the mixture (PMID 9637345).

Reported constituents include Glu-Trp, Lys-Glu and Glu-Asp-Pro, but their individual contributions to clinical effects remain incompletely established. A synthetic constituent is not automatically equivalent to the complete extract. Names encountered in the literature include Thymalin, thymaline, Timalin and thymus-derived polypeptide factor. Historical preparations require formulation-specific interpretation.

Class: thymic polypeptide extract. Module 3, Shielding. Research themes: immune dysfunction and aging. It differs from thymosin alpha 1 and thymosin beta 4. Composition, manufacturing controls and biological activity matter when comparing batches or interpreting published results.

MECHANISM

Cell differentiation hypothesis: cultured human hematopoietic cells showed reduced CD44 and CD117 expression and increased CD28 expression after Thymalin exposure (PMID 33237528). The reported changes were approximately twofold to threefold decreases and a 6.8-fold increase, respectively. These markers indirectly support altered differentiation. They do not establish functional immune restoration or identify a receptor. Earlier research describes effects on T-cell differentiation, peptide-MHC recognition, cyclic nucleotides and cytokine release (PMID 9637345).

Inflammatory signaling is context-dependent. A THP-1 cell study reported ERK1/2 phosphorylation, cytokine changes and reduced adhesion to activated endothelial cells (PMID 35408963). Its monocyte experiments used a single overnight culture exposure to 0.1 mcg/mL, with separate macrophage time-course experiments. This was laboratory exposure, not a human administration regimen. Findings across the different tested peptides cannot all be attributed specifically to Thymalin.

In another study, human peripheral blood mononuclear cells received a single 18-hour culture exposure to 1 mg/mL Thymalin (PMID 37686182). In stimulated cells, TNF-alpha and IL-1beta release decreased approximately 2.2-fold and 2.7-fold. However, IL-6 release increased approximately fourfold in unstimulated cells. The extract therefore cannot be described as uniformly suppressing inflammatory cytokines. Experiments involved samples from four donors and do not establish clinical exposure-response relationships.

DNA binding remains proposed. Molecular docking nominated DNA sequences and possible AKT1/AKT2-related pathways for constituent dipeptides (PMID 37686182). Docking does not demonstrate target engagement in patients. Mouse findings also suggest age-dependent thymus-pineal signaling, without proving human rejuvenation (PMID 17333624). No validated human receptor model or established mechanism linking Thymalin to longer life emerged from these records.

EVIDENCE · GRADE A

A applies only through this catalog's approved-drug criterion, because the literature documents Russian medical approval. It does not represent high-certainty evidence for every proposed use. The small human immune-marker studies fit B. Human longevity claims fit C because reporting and replication are insufficient.

Cellular mechanism findings fit D. No verified evidence establishes improved muscle gain, fat loss or athletic recovery.

Human data. The 2003 report followed 266 older adults for six to eight years after courses of thymic or pineal extracts (PMID 14523363). It reported lower mortality with Thymalin, with larger differences in certain combined-treatment groups. PubMed indexes the paper as a randomized controlled trial. However, the abstract does not explain allocation, blinding, group-level denominators or detailed dosing. It cannot support a reliable personal estimate of mortality reduction. Independent confirmation of the longevity finding was not established in this review. The 2021 COVID-19 study was single-center, prospective, open-label and randomized using an envelope method (PMID 33575961). It compared 42 patients receiving standard treatment plus Thymalin with 50 controls. The study regimen was 10 mg IM once daily for five days, added to standard therapy. Participants had moderate or severe disease and lymphopenia, with mean ages around 60. The treated group showed increases in lymphocytes, CD3 cells and CD4 cells. CD4 increased approximately 88.9 percent from baseline. IL-6, CRP and D-dimer declined approximately 5.5-fold, 9.7-fold and 5.7-fold within that group. These are before-after changes, not equivalent reductions in clinical risk. Controls also improved on several markers, and concomitant treatments complicate interpretation. Neither group had deaths. The study therefore cannot establish a mortality benefit or thrombosis prevention. The 2022 severe COVID-19 comparison reported hematologic changes and hospital mortality (PMID 36169363). Its English and Russian abstracts contain conflicting mortality percentages for treated groups. Exact mortality estimates are omitted pending reconciliation with the original study data. The abstract also leaves allocation methods and group sizes unclear. Older reports described 32 burn patients and 30 patients with periodontal disease (PMIDs 11188814 and 6546722). These provide limited clinical observations, not evidence for use in healthy adults. Overall, short follow-up, incomplete safety reporting and overlapping investigator networks constrain confidence.

Animal and mechanistic data. A 1982 study reported improved immune responses and longer lifespan with thymus-derived factors in mice (PMID 6752596). A 1989 study administered 0.1 mg per mouse SC daily during five-day courses repeated monthly (PMID 2682058). Lifespan increased when treatment began at 3.5 months, but not when it began at 12 months. Reduced mammary tumor incidence was also limited to the younger-start group. These findings cannot define a human dose or predict human lifespan. A rat sarcoma study reported tumor growth inhibition using modulated, comparatively low doses (PMID 29797130). It does not establish a cancer treatment or support a simple lower-is-better rule. A separate mouse study found age-dependent effects on pineal melatonin production (PMID 17333624). That result concerns a specific endocrine response, not all effects in older animals. A 48-rat mandibular-defect experiment examined local Thymalin exposure, a bone substitute and their combination (PMID 38642352). Changes in immune-cell populations accompanied the repair model. This is not evidence for systemic athletic injury recovery or combination benefits with other catalog peptides. Animal findings remain grade C.

REGULATORY STATUS AND SPORT

STATUS

PMID 33575961 documents Russian medical approval since 1982. The retrieved Russian prescribing information describes a prescription medicine for immune-deficiency-related conditions. Historical registration details alone do not verify every currently marketed preparation. Thymalin has no FDA-approved therapeutic indication; FDA has identified marketed Thymalin as an unapproved drug. Source: [FDA enforcement record](<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/us-chem-labs-669074-02072024>). No EMA authorization was established in this review. Research-use labeling does not establish authorization for human treatment or import.

governmental approval for human therapeutic use, while other prohibited categories can apply independently of approval. Russian approval therefore does not justify a blanket permitted classification. No Thymalin-specific determination was established in this review. Thymosin beta 4 and its derivatives, including TB-500, are prohibited at all times under S2.3. Product-specific interpretation belongs with the relevant anti-doping organization. Source: [FINCIS 2026 prohibited-substance listing](https://kamu.suek.fi/en/dopingsubstances/).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	IM is the route in the retrieved Russian prescribing information and the verified 2021 COVID-19 trial (PMID 33575961). Historical human literature also describes electrophoresis within a multifactorial diabetic-foot treatment program (PMID 15584605). That study cannot isolate Thymalin's contribution or establish systemic bioavailability. Mouse experiments used SC administration, and a rat bone-repair experiment used local soft-tissue administration (PMIDs 2682058 and 38642352). Human SC-to-IM equivalence and oral efficacy were not established.
HALF-LIFE	No validated human elimination half-life for the complete extract was identified in the retrieved literature. A mixture may have component-specific kinetics rather than one meaningful plasma half-life. Peptide length alone cannot establish clearance within minutes. Repeated biological effects also do not identify plasma persistence. Numeric half-life claims require a formulation-specific pharmacokinetic study.
TIMING	The verified COVID-19 trial used daily administration without establishing an optimal time of day (PMID 33575961). No human evidence retrieved supports morning administration or timing around exercise. A daily study schedule does not imply a particular elimination half-life.
CYCLE LENGTH	The Russian prescribing information describes short courses, and the COVID-19 trial used five days (PMID 33575961). The geriatric report describes courses during the initial observation years and a separate annually treated combination group (PMID 14523363). Its abstract does not provide a reproducible longevity protocol. Monthly animal courses and non-clinical annual schedules are different evidence categories.
TITRATION	The verified COVID-19 trial used a fixed regimen rather than titration (PMID 33575961). The label contains dose ranges, which are not evidence of a validated escalation strategy. The rat sarcoma study modulated dosing during treatment (PMID 29797130). That model cannot establish an optimal human dose or justify adjusting treatment from subjective effects.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Adults with the immune-deficiency-related conditions described in Russian prescribing information	5 to 20 mg per administration, with 30 to 100 mg per course, according to the Russian Thymalin prescribing information	IM	Once daily for 3 to 10 days; the label describes repeat courses after 1 to 6 months when indicated	Russian Thymalin prescribing information for lyophilisate for intramuscular administration, reproduced in the retrieved drug monograph. This is a label regimen, not a recommendation for healthy adults. Source: [Thymalin prescribing information] (https://medvisor.ru/medicine/drug/timalin_40588/).
Open-label randomized trial in hospitalized COVID-19 patients with lymphopenia, 42 treated and 50 controls	10 mg per administration, as reported in PMID 33575961	IM	Once daily for five days, added to standard therapy	Regimen verified in the full-text methods of PMID 33575961. The study population and concomitant treatments limit extrapolation to healthy adults. · PMID 33575961
Female SHR mice, lifespan and spontaneous tumor study	0.1 mg per mouse per administration, as reported in PMID 2682058	SC	Daily during five-day courses repeated monthly, starting at 3.5 or 12 months of age	Regimen reported in the abstract of PMID 2682058. Lifespan benefit was limited to the younger-start group. No human-equivalent dose is inferred. · PMID 2682058

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CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Non-clinical adult immune or longevity use described in the submitted draft	5 to 10 mg per administration, commonly cited in non-clinical use; not validated in trials	SC or IM, as claimed in non-clinical descriptions	Once daily for ten days, sometimes repeated once or twice yearly	Commonly cited in non-clinical use; not validated in trials. Frequency of actual use was not independently verified. This complete regimen, indication and route cannot inherit validation from an IM hospital trial. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.

– Epitalon

The human combination study used Epithalamin, a pineal extract, rather than synthetic Epitalon (PMID 14523363). It cannot validate a Thymalin-Epitalon combination.

– BPC-157

No direct combination evidence was identified. The Thymalin bone-repair experiment did not test BPC-157 (PMID 38642352). Different proposed mechanisms do not demonstrate additive benefit, compatibility or acceptable combined risk.

– Thymosin Alpha-1

Thymosin alpha 1 is a different intervention. No direct evidence was identified for combining it with Thymalin. Overlapping immune effects create uncertainty, but a specific harmful interaction has not been established.

– TB-500

The names describe different interventions. No direct combination evidence was identified, and TB-500 is prohibited at all times under WADA S2.3. Thymalin's separate regulatory history does not alter that prohibition.

SAFETY

COMMON EFFECTS

The retrieved Russian prescribing information lists allergic reactions. Reliable incidence estimates were not provided. Injection-site pain and redness are possible with parenteral administration, but their frequency was not established in the retrieved Thymalin studies. The COVID-19 paper reports no deaths, not a comprehensive demonstration of tolerability (PMID 33575961).

SERIOUS SIGNALS

Serious hypersensitivity is a plausible concern with a parenteral animal-derived preparation, but a Thymalin-specific anaphylaxis rate was not established. Tissue sourcing, manufacturing and contamination controls matter for bovine extracts. Transmissible spongiform encephalopathy risk cannot be quantified from a peptide purity percentage. No product-specific transmission event was verified here. Effects in autoimmune disease, transplantation and lymphoid malignancy remain insufficiently characterized. These are mechanistic precautions, not proven adverse outcomes from the cited studies. Hemostatic findings do not establish an anticoagulant effect or define drug interactions. The COVID-19 trial included anticoagulant treatment, which prevents attributing clotting-related findings to Thymalin alone (PMID 33575961).

CONTRAINDICATIONS

Known hypersensitivity to the preparation or its components is a relevant exclusion. Pregnancy and breastfeeding lack adequate clinical safety evidence; product-specific contraindications require the applicable authorized insert. Active autoimmune disease, transplant immunosuppression and lymphoproliferative disorders warrant specialist assessment because immune effects are uncertain.

They are not presented here as universally established label contraindications.

STOP RULES

Wheeze, facial or throat swelling, faintness or rapidly progressing hives after exposure require immediate discontinuation and emergency assessment. Persistent fever, new lymph-node enlargement, unexpected bleeding or worsening inflammatory symptoms warrant prompt clinical review. These are precautionary clinical triggers, not validated Thymalin-specific stopping thresholds. An unexplained product identity or batch discrepancy also prevents meaningful assessment of further exposure.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

The retrieved Russian Thymalin prescribing information describes 10 mg of active extract per vial. This is a formulation strength, not a personal dose. The mass does not identify the amount of every constituent peptide or establish equivalence with an uncharacterized preparation.

SOLVENT

The retrieved Russian prescribing information specifies isotonic sodium chloride, 1 to 2 mL, for preparation before IM administration. Bacteriostatic water and repeated withdrawal from a stored solution were not validated in the retrieved sources.

STORAGE

The retrieved Russian prescribing information specifies protection from light and storage at no more than 20 C. Storage conditions are formulation-specific. No validated refrigerated multidose shelf life or freeze-thaw stability was established for reconstituted Thymalin. Adding a preservative does not establish chemical stability or justify storing the solution for weeks.

Descriptive concentration arithmetic: a labeled 10 mg extract vial in a final volume of 2.0 mL would contain 5 mg/mL, equivalent to 5000 mcg/mL. The vial strength and preparation-volume range come from the Russian Thymalin prescribing information. This calculation assumes the stated final volume and complete dissolution; it does not measure potency or peptide composition.

The 10 mg IM once-daily regimen studied for five days in PMID 33575961 would mathematically correspond to 2.0 mL at that concentration. This does not establish the trial's actual reconstitution volume, which the retrieved methods do not specify. It also does not validate SC administration, a particular device or a different solvent. Syringe-unit conversions are omitted because volume markings do not express Thymalin biological activity.

BUYING NOTES

The relevant distinction is a traceable pharmaceutical extract versus material whose composition and manufacturing controls are unknown. A certificate of analysis can support identity and quality assessment, but cannot establish clinical efficacy or authorization.

For an extract, a percentage labeled purity is uninterpretable without the assay method, reference standard, integration rules and definition of the measured material. A single chromatographic peak does not automatically prove fraud, and multiple peaks do not prove authenticity. Useful documentation identifies the tested batch, peptide content, molecular profile, source tissue and relevant microbial controls. Sterility, endotoxin and tissue-sourcing documentation answer different questions. No single certificate establishes all of them. Evidence from the pharmaceutical preparation does not automatically transfer to another mixture sold under the same name.

COMMON MISTAKES

- Treating Russian approval as high-certainty evidence for longevity, muscle gain or recovery. Approval and claim-specific evidence must be interpreted separately.
- Reading before-after biomarker changes as equivalent reductions in infection, thrombosis or mortality risk.
- Quoting the 2022 mortality percentages without addressing the discrepancy between its English and Russian abstracts.
- Calling Thymalin uniformly anti-inflammatory while omitting increased IL-6 in unstimulated cells reported in PMID 37686182.
- Substituting synthetic Epitalon for the pineal extract used in the human combination study.
- Assuming that SC, IM, oral and electrophoretic administration produce equivalent exposure or clinical effects.
- Assigning one half-life to an incompletely characterized mixture or inferring clearance from peptide length.
- Treating an HPLC purity percentage as proof of identity sterility, biological potency or pharmaceutical equivalence.

- Converting a short hospital trial into a recurring wellness schedule without evidence for that population, route or duration.
- Presenting theoretical immune risks as established contraindications, or treating incomplete adverse-event reporting as evidence that harms do not occur.

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ARA-290 (Cibinetide)

Cibinetide

Erythropoietin-derived innate repair receptor agonist

Module 3 · Shielding

Goals: Recovery

Route: SC

An investigational, nonerythropoietic EPO-derived peptide with preliminary human neuropathy findings, uncertain clinical benefit, and no established application to exercise recovery.

WHAT IT IS

ARA-290, also called cibinetide or pyroglutamate helix B surface peptide, is a synthetic peptide containing 11 amino acids. Its design reproduces features of the three-dimensional surface of erythropoietin's helix B region. Calling it simply a fragment copied from EPO obscures this structure-based design. The N-terminal residue is pyroglutamate (PMID 25728128).

The development goal was to separate EPO's tissue-protective signaling from its stimulation of red blood cell production. Experimental studies describe anti-inflammatory and cytoprotective effects without corresponding erythropoietic activity. That distinction does not establish freedom from cardiovascular, immune, or other adverse effects in humans (PMID 25728128, PMID 29570934).

Cibinetide remains investigational. Published patient studies concentrate on sarcoidosis-associated small fiber neuropathy, diabetic neuropathy, and diabetic macular edema. A separate randomized experiment assessed emotional processing in healthy volunteers without demonstrating improved mood (PMID 26431906).

Within a recovery module, this compound belongs under experimental nerve and inflammatory disease research. No controlled human evidence identified here establishes faster recovery from resistance training, tendon injury, muscle damage, or joint injury. Human muscle samples have been examined for receptor expression, but those experiments were not clinical treatment trials (PMID 24055514).

MECHANISM

The principal model distinguishes erythropoietic signaling through the EPOR homodimer from tissue-protective signaling involving EPOR and CD131. The latter complex is commonly called the innate repair receptor. Cibinetide was designed to preferentially engage this protective pathway without reproducing EPO's erythropoietic effects (PMID 25728128).

CD131 also participates in receptors for several immune cytokines. Its involvement does not mean cibinetide activates or blocks every receptor containing that subunit. The receptor's composition, cellular context, and downstream signaling remain relevant to interpretation. A shared subunit alone cannot predict a clinical drug interaction.

Human skeletal muscle from patients with critical limb ischemia showed increased EPOR and CD131 expression. Both proteins also colocalized in control muscle. Colocalization supports biological plausibility but does not independently demonstrate direct peptide binding or establish receptor stoichiometry. The therapeutic experiments in that paper involved ischemic myotubes in vitro, not treated patients (PMID 24055514).

Functional receptor evidence comes from animal perturbation experiments. Cibinetide's antiallodynic effect disappeared in mice lacking CD131. The relevant paper's title emphasizes ketamine, but its experiments also directly tested ARA-290, so the citation is relevant (PMID 23936499). In experimental cerebral ischemia, CD131 knockdown suppressed ARA290-associated neuroprotection (PMID 38488446). These findings support receptor involvement in those models rather than proving one exclusive mechanism across all tissues.

In experimental colitis, cibinetide reduced inflammatory cell infiltration and inflammatory mediator production. Macrophage experiments implicated functional CD131 and JAK2, with reduced NF-kappaB p65 activity (PMID 29026145). In autoimmune neuritis, treatment shifted helper T-cell populations, reduced inflammatory

activation, and improved nerve repair measures (PMID 24603865). Islet transplantation experiments also found reduced dendritic cell maturation and allogeneic T-cell responses (PMID 32345869).

Other studies describe tissue-survival pathways rather than a general growth effect. Diabetic mouse wounds showed changes in VEGF, phosphorylated Akt, and phosphorylated eNOS alongside improved healing (PMID 29223734). Kidney cell experiments found reduced cisplatin-associated injury and apoptosis, but these were cell-line findings rather than clinical renal protection (PMID 36085231).

A separate study reported inhibition of TRPV1 activity and reduced capsaicin-associated hypersensitivity (PMID 26774587). This suggests another possible mechanism. It does not establish clinically meaningful TRPV1 antagonism or prove independence from the repair-receptor pathway in patients.

The frequently cited molecular-switch explanation addresses the mismatch between brief circulating exposure and longer biological effects. A pharmacology review reports a plasma half-life of approximately two minutes and proposes persistent downstream signaling (PMID 25728128). This remains a mechanistic explanation, not a validated method for predicting treatment duration, redosing intervals, or reversibility of adverse effects.

EVIDENCE · GRADE B

B for preliminary human neuropathy findings under the scale's small, short-trial category. Several randomized studies exist, but their size, duration, endpoints, and mixed results limit clinical certainty. Their existence does not establish an effective treatment for neuropathy or justify an exercise-recovery claim. Corneal nerve measurements are promising surrogate outcomes, while pain and functional benefits require confirmation. Exercise recovery remains unsupported, with only mechanistic extrapolation relevant to that intended use.

Human data. The reviewed clinical literature includes five patient treatment studies and a randomized experiment in healthy volunteers. These should not be described as four trials or treated as one homogeneous body of evidence. The initial sarcoidosis pilot enrolled 22 patients. It reported improved small fiber neuropathy screening scores versus placebo. Brief Pain Inventory and fatigue scores improved similarly in both groups, limiting claims of a specific analgesic or antifatigue effect (PMID 23168581). A subsequent blinded sarcoidosis study used daily subcutaneous administration for 28 days. It reported changes in neuropathic symptoms, corneal nerve fiber density, temperature sensitivity, and six-minute walking distance (PMID 24136731). Walking performance in patients with sarcoidosis is not evidence of enhanced athletic performance in healthy adults. The phase 2b sarcoidosis study randomized 64 participants. The middle-dose group showed a significant placebo-corrected increase in corneal nerve fiber area and a signal in regenerating skin nerve fibers. The lower and higher groups did not reach significance on the primary comparison. The reported pain comparison in the moderate-to-severe subgroup was not statistically significant, with $P = 0.157$ (PMID 28475703). A difference in significance between dose groups does not establish a significant difference between those groups. The diabetic neuropathy study reported changes in PainDetect scores, HbA1c, and lipid measures. Its corneal nerve finding concerned participants with sufficiently reduced baseline nerve density, not an unequivocal effect across all participants (PMID 25387363). These exploratory findings require independent replication

Animal and mechanistic data. Animal findings support biological activity across several disease models, but they do not form a validated human recovery protocol. Disease induction, species, timing, and outcome selection differ substantially between experiments. In rats with spared nerve injury, short-course treatment reduced allodynia for extended observation periods and altered spinal microglial responses. The reported behavioral effects extended to 20 weeks in that model (PMID 24529189). CD131-deficient mice lacked the corresponding antiallodynic response, supporting receptor involvement (PMID 23936499). Experimental autoimmune neuritis showed improved nerve regeneration and remyelination alongside altered inflammatory and T-cell responses (PMID 24603865). Mouse colitis experiments reported less inflammatory injury and improved disease measures (PMID 29026145). These findings cannot establish treatment of human autoimmune disease or inflammatory bowel disease. Islet studies found reduced inflammatory injury and improved engraftment in mice (PMID 26683514). An allogeneic transplantation experiment reported improved graft survival with a concomitant immunosuppressant, which is a specific experimental combination rather than evidence for general peptide stacking (PMID 32345869). Experiments using isolated human islets and transplantation into mice remain preclinical, despite the human origin of the cells (PMID 34498509). Other findings include improved diabetic wound healing, reduced injury after experimental cerebral ischemia, and reduced autoimmune abnormalities in lupus models (PMID 29223734, PMID 38488446, PMID 29570934). Retinal

and do not establish diabetes treatment or prevention of neuropathy complications. The uncontrolled retinal study recruited nine patients, with eight completing treatment. Mean visual acuity, retinal thickness, retinal sensitivity, and tear production did not improve. A questionnaire signal and individual responses cannot establish efficacy without a comparator (PMID 32674280). The healthy-volunteer experiment randomized 36 participants. It found some changes in emotional processing but no improvement in mood or affective symptoms. The authors did not consider the overall pattern clearly antidepressant-like (PMID 26431906). A methodological analysis supports corneal nerve area as a measure of morphological change. It does not validate every change as a predictor of durable symptom relief (PMID 29549285). A systematic review of sarcoidosis fatigue treatments likewise found limited trial evidence (PMID 27507833). Safety reporting must include observed adverse events rather than relying exclusively on reassuring abstract conclusions.

experiments examined enhancement of transplanted endothelial cell repair in an ischemic mouse model, not established treatment of human retinal edema (PMID 30876881). In an Alzheimer-like mouse model, early treatment affected amyloid pathology and cognition, but benefits were compromised in older animals with advanced pathology (PMID 34343617). A later diabetic mouse study improved insulin sensitivity and changed monocyte populations without rescuing executive cognitive flexibility (PMID 41933665). These negative or conditional findings limit broad neuroprotection claims. A 15-month study in aging rats reported cardiovascular and frailty-related changes, not demonstrated human longevity benefits (PMID 36741836). Another mouse study increased bone mineral density and inhibited osteoclast development (PMID 35008482). These results show additional biological effects that require human investigation rather than supporting claims of universal tissue repair.

REGULATORY STATUS AND SPORT

STATUS

Investigational, with no approved therapeutic indication identified in this review. Published human development includes phase 2 studies; no phase 3 efficacy publication was identified. This does not establish that development has permanently stopped or verify the status of every jurisdiction worldwide. A 2026 review discusses cibinetide within a field still limited by inadequate clinical evidence and regulatory uncertainty (PMID 42635865). Trial registration, an investigational authorization, a substance identifier, and orphan designation are different from marketing approval. None independently establishes an approved prescription product, an approved dose, or a label-supported preparation procedure. The relevant patient programs include sarcoidosis-associated neuropathy, diabetic neuropathy, and diabetic macular edema. The retinal study was registered as EudraCT 2015-001940-12 and ISRCTN16962255 (PMID 32674280). Claims that pharmaceutical-quality investigational material cannot exist because a drug lacks approval are incorrect. Clinical-trial manufacturing quality and marketing authorization are separate questions.

WADA

Prohibited at all times under the 2026 framework. S2.1.5 covers innate repair receptor agonists, the pharmacological category applicable to cibinetide. This classification is based on the listed class, although cibinetide is not named among its examples. S0 applies to unapproved substances not already addressed by subsequent sections, so S0 is not the appropriate primary explanation here.

Source: [WADA 2026 Prohibited List, S2.1.5]

(https://ita.sport/uploads/2025/09/2026list_en_final_clean_september_2025.pdf). Published anti-doping research also explicitly treats ARA-290 as prohibited (PMID 28941172, PMID 25382550). Its nonerythropoietic design and short plasma half-life do not make it permitted.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Published patient trials used intravenous or subcutaneous administration. The initial sarcoidosis pilot used repeated intravenous administration (PMID 23168581). Later neuropathy and retinal studies used subcutaneous administration (PMID 24136731, PMID 25387363, PMID 32674280). The phase 2b registry explicitly confirms the subcutaneous route, resolving the omission from its abstract (PMID 28475703; NCT02039687). A healthy-volunteer experiment used a single intravenous administration (PMID 26431906; NCT02070783). No clinically validated oral or intranasal regimen was identified. Absence of an identified formulation is not proof that no experimental formulation has ever been studied.

HALF-LIFE

Approximately two minutes in plasma is reported in the pharmacology review, but it should not be presented as a universally established human subcutaneous terminal half-life (PMID 25728128). Absorption, sampling, assay methods, and administration route affect pharmacokinetic estimates. In vitro blood experiments documented rapid enzymatic breakdown, providing separate metabolic

evidence rather than a clinical dosing schedule (PMID 28941172). A later review discusses short exposure as a development limitation and describes a cyclized derivative as a separate research

approach (PMID 38943972). Short circulating exposure does not establish the duration of benefit, justify repeated daily administration, or determine solution shelf life.

TIMING

No identified trial compared dosing around meals, bedtime, or exercise. The clinical schedules varied between repeated intravenous administration, daily subcutaneous administration, and a single experimental administration. Therefore, the statement that every human trial used daily dosing was incorrect. A short plasma half-life does not establish that the peptide is completely absent by a particular activity or that circulating concentrations are irrelevant. There is no clinical evidence supporting workout-specific timing (PMID 23168581, PMID 25387363, PMID 26431906).

CYCLE LENGTH

Several neuropathy trials used approximately four weeks of treatment, followed in some cases by observation without treatment. The longest repeated human course identified here was the 12-week retinal pilot (PMID 32674280). These are study durations, not validated cycling schedules. They do not establish a treatment-free interval, a maximum number of courses, or the consequences of repeated courses. The diabetic neuropathy study included a month of post-treatment observation. Persistence of selected measurements does not demonstrate permanent nerve repair or define the duration of an individual response (PMID 25387363). The 15-month aging-rat experiment supplies long-duration animal exposure, not evidence supporting chronic human administration (PMID 36741836).

TITRATION

No clinically validated titration protocol was identified. The principal dose-ranging trial assigned fixed regimens rather than escalating participants according to response. Its middle-dose group met the placebo comparison on the primary endpoint, while the other groups did not (PMID 28475703). This pattern neither establishes a bell-shaped dose-response curve nor proves that escalation reduces efficacy. Those conclusions would require adequate direct comparisons and replication. Published fixed-dose experiments do not supply a validated response-based escalation or tapering algorithm.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Phase 2b randomized sarcoidosis-associated small fiber neuropathy trial, 64 randomized participants.	1 mg, 4 mg, or 8 mg per administration, subcutaneously once daily for 28 days, reported in PMID 28475703 and registry NCT02039687.	Subcutaneous, confirmed in NCT02039687.	Once daily for 28 days.	Human trial, PMID 28475703. Only the middle-dose group reached statistical significance versus placebo on corneal nerve fiber area. This does not prove superiority over the higher-dose group or establish an optimal clinical dose. Registry methods: [NCT02039687] (https://clinicaltrials.gov/study/NCT02039687). · PMID 28475703
Randomized phase 2 study in type 2 diabetes with painful neuropathy.	4 mg per administration, subcutaneously once daily for 28 days, reported in PMID 25387363.	Subcutaneous.	Once daily for 28 days, followed by 28 days without study treatment.	Human trial, PMID 25387363. Reported metabolic and symptom signals were exploratory. The corneal nerve finding concerned a subgroup with reduced baseline density. This is a study regimen, not an established treatment recommendation. · PMID 25387363
Initial randomized sarcoidosis pilot, 22 participants.	2 mg per administration, intravenously three times weekly for four weeks, reported in PMID 23168581.	Intravenous.	Three times weekly for four weeks.	Human trial, PMID 23168581. Small fiber neuropathy screening scores improved versus placebo. Pain inventory and fatigue scores improved similarly in both groups. · PMID 23168581
Open-label diabetic macular edema pilot.	4 mg per administration, subcutaneously once daily for 12 weeks, reported in PMID 32674280.	Subcutaneous.	Once daily for up to 12 weeks.	Human trial, PMID 32674280. The study did not demonstrate improvement in its principal mean visual or retinal outcomes. Its uncontrolled design cannot establish efficacy. · PMID 32674280

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Diabetic mouse incisional wound-healing experiment.	30 mcg/kg per administration, subcutaneously once daily, with assessments through 14 days, reported in PMID 29223734.	Subcutaneous.	Once daily; animals were assessed at different time points after injury.	Animal study, PMID 29223734. Reported changes included wound healing, angiogenesis, and biochemical markers. This weight-based animal dose does not establish a human equivalent. · PMID 29223734
Mouse pancreatic islet transplantation experiment.	120 mcg/kg per administration, intraperitoneally before transplantation and at 0, 6, and 24 hours afterward, reported in PMID 26683514.	Intraperitoneal.	Periprocedural administrations before transplantation and at the specified postoperative time points.	Animal study, PMID 26683514. The regimen addressed transplantation-associated inflammation. It is not a daily human maintenance schedule and does not translate through simple body-weight multiplication. · PMID 26683514
Randomized emotional-processing experiment in 36 healthy volunteers.	2 mg intravenously as a single administration, reported in PMID 26431906, with route confirmed in NCT02070783.	Intravenous.	One administration; neuropsychological assessment occurred one week later.	Human experimental study, PMID 26431906, registry NCT02070783. Some emotional-processing measures changed, but mood and affective symptoms did not improve. · PMID 26431906

STACKING

+ BPC-157	No demonstrated combination benefit. Cibinetide's diabetic wound findings include angiogenic and survival-signaling changes, but pathway overlap does not establish additivity or redundancy with BPC-157 (PMID 29223734). No identified combination trial supports this pairing or a musculoskeletal recovery claim.	– FOXO4-DRI	An unstudied combination, not an established pharmacological contraindication. Cibinetide reduced apoptosis in specific cell experiments, but this does not prove that it blocks FOXO4-DRI-mediated senolysis (PMID 36085231). Effects depend on cell state, exposure, and pathway engagement.
+ TB-500	No demonstrated combination benefit or established interaction profile. Mechanisms attributed to full-length thymosin beta-4 cannot automatically be assigned to every material described as TB-500. A proposed difference in targets does not establish complementary clinical effects with cibinetide.	– Thymosin Alpha-1	An unstudied immune-modulating combination. Cibinetide affected T-cell differentiation and dendritic cell responses in experimental systems (PMID 24603865, PMID 32345869). These observations do not establish an opposite clinical effect to thymosin alpha-1 or predict the net response.
+ GHK-Cu	No demonstrated synergy. Different routes or intended tissue compartments do not prove that two agents cannot interact. No identified clinical study establishes the efficacy, systemic exposure, or tolerability of this combination.	– LL-37	An unstudied combination with uncertain immune effects. Cibinetide's inhibition of selected inflammatory responses does not prove that LL-37 and cibinetide cancel one another (PMID 29026145). A simple immune-amplifier versus immune-suppressor model is insufficient.

No demonstrated synergy. Cibinetide has experimental colitis evidence, but that does not validate a combination with KPV or establish a distinct receptor mechanism for the pair (PMID 29026145). The proposed gut-inflammation application remains untested.

SAFETY

COMMON EFFECTS

In the retinal pilot, all nine participants experienced at least one adverse event. Reported events included headache, cold symptoms, nausea, and laboratory changes. Investigators considered headache, cold symptoms, and nausea potentially treatment-related. Elevated glucose and triglycerides were difficult to interpret because fasting was not confirmed (PMID 32674280). Source: [Retinal trial safety results](https://pmc.ncbi.nlm.nih.gov/articles/PMC7408632/). The phase 2b registry also contains systematic adverse-event tables, including events in placebo recipients. These are events observed during the study, not automatically adverse reactions caused by cibinetide. The available studies cannot reliably define population-level frequencies or long-term tolerability. Dose amount alone does not establish injection volume or discomfort; concentration and formulation also matter.

SERIOUS SIGNALS

The phase 2b registry reports serious adverse events in active-treatment recipients. Recorded terms include syncope, headache, chest tightness, shortness of breath, enteritis, and suicidal ideation. The registry does not establish that cibinetide caused these events. Nevertheless, their presence makes an unqualified claim of no serious human signals inappropriate. Source: [NCT02039687 adverse-event results](https://clinicaltrials.gov/study/NCT02039687?tab=results). The compound's nonerythropoietic design does not prove absence of thrombosis or cardiovascular risk. A review contrasting EPO with nonerythropoietic derivatives primarily discusses experimental protection and the problems encountered with EPO, not definitive human cardiovascular safety for ARA-290 (PMID 23964738). Cancer, infection, and immune effects remain insufficiently characterized. Anti-apoptotic effects in cultured cells and immune changes in animals provide reasons for investigation, not evidence that specific clinical harms necessarily occur. Bone metabolism also changed in mice, without corresponding human outcome data (PMID 35008482).

CONTRAINDICATIONS

There is no approved label defining formal contraindications. Pregnancy, breastfeeding, pediatric treatment, and long-term administration lack adequate clinical safety evidence. A history of hypersensitivity to the compound or formulation would be a clinical exclusion concern. Active malignancy, serious infection, significant immunosuppression, severe organ disease, and psychiatric instability require separate clinical assessment because evidence is insufficient. Trial exclusion criteria should not be presented as proven drug contraindications. Conversely, the absence of a formal contraindication does not establish suitability. Animal immunomodulation does not establish universal immune suppression in humans (PMID 24603865, PMID 32345869). Existing neuropathy, diabetes, retinal disease, and psychiatric care are relevant to interpreting symptoms and laboratory changes during any investigational exposure. WADA prohibition is a sporting restriction, not a medical contraindication.

STOP RULES

Breathing difficulty, facial or throat swelling, chest pain, fainting, or new suicidal thoughts require urgent medical assessment and interruption of further investigational exposure pending review. Fever with spreading injection-site redness, new neurological deficits, or deteriorating vision also warrants prompt assessment. These are general clinical response rules, not a validated cibinetide monitoring algorithm. A predefined trial duration is not proof that continuing until that endpoint is appropriate when symptoms worsen. Conversely, completing a published duration does not establish the effectiveness or safety of another course. No evidence-based self-management schedule for extension, retreatment, or tapering was identified.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved commercial vial strength or standardized consumer presentation exists. Research-market package sizes are not clinical specifications, and none is endorsed here as typical. Investigational trial material should not be assumed equivalent to a powder bearing the same compound name. A stated vial mass may refer to nominal content, measured peptide content, or total material containing counterions and residual water. These measurements are not interchangeable. Identity, assay, impurity profile, sterility, and endotoxin testing answer different questions.

SOLVENT

No general reconstitution solvent is established by the cited clinical evidence for arbitrary research material. A trial's formulation cannot be reconstructed from its dose and administration route alone. Benzyl alcohol compatibility, pH, osmolality, adsorption, container interactions, and peptide stability require formulation-specific data. Bacteriostatic water does not sterilize a contaminated powder and does not establish suitability for repeated access. Plain sterile water does not resolve those limitations either. The observed enzymatic breakdown in blood concerns metabolism, not compatibility with a particular solvent or storage container (PMID 28941172).

STORAGE

No universal temperature, freezing rule, or post-reconstitution expiry can be assigned from the cited literature to unspecified research material. Valid storage conditions depend on formulation, container, manufacturing controls, and stability testing. Blood half-life cannot supply a refrigerated shelf life. Cloudiness, visible particles, discoloration, or damaged packaging indicate a quality problem, but a clear solution does not demonstrate sterility or chemical stability. A proposed expiry measured in days is still an unsupported expiry when no relevant data exist. Trial-specific handling instructions apply to that investigational preparation and should not be generalized to other material.

Illustrative concentration arithmetic only, not a preparation or administration protocol: a hypothetical solution containing 5 mg of peptide in a final volume of 1.0 mL has a concentration of 5 mg/mL. This equals 5000 mcg/mL. These hypothetical quantities describe solution content, not a studied dose or validated formulation. If that same hypothetical peptide mass were present in a final volume of 2.0 mL, the concentration would be 2.5 mg/mL. Doubling final volume halves concentration. The relevant denominator is final solution volume, which should not automatically be assumed identical to added solvent volume. The governing relationships are concentration equals peptide mass divided by final volume, and represented mass equals concentration multiplied by measured volume. Milligrams, micrograms, and milliliters describe different quantities. A device marking does not independently state peptide mass, and a mass calculation does not establish bioactivity or sterility. No injection-device conversion or preferred dilution follows from this example. Actual tolerability depends on the complete formulation and administration conditions. Arithmetic also cannot establish peptide identity, assay accuracy, solution stability, or whether material matches that used in a trial.

BUYING NOTES

There is no established consumer supply equivalent to the investigational preparations used in these studies. A certificate of analysis can support particular analytical claims but cannot establish therapeutic suitability. Marketing descriptions such as pharmaceutical grade are not substitutes for documented manufacturing and release standards.

An interpretable analytical package identifies the sampled lot, laboratory, methods, dates, specifications, and measured results. Mass spectrometry can support molecular identity, while chromatographic methods can characterize detectable impurities. A chromatographic purity percentage is not a measurement of the peptide mass in a vial, and neither result independently establishes biological potency.

For cibinetide, identity characterization needs to distinguish the intended pyroglutamate-containing peptide from sequence variants and incomplete synthesis products. A blood-metabolism study does not authenticate a supplied vial or establish that a similar mass spectrum identifies every structural feature (PMID 28941172).

Sterility, endotoxin burden, residual solvents, counterions, water content, and container compatibility require appropriate separate assessments. Even authentic analytical documents apply to the tested sample and lot, not automatically to every item carrying the same label. A matching lot number is necessary for traceability but does not itself prove independent testing.

The clinical evidence cannot establish the quality of material obtained outside the trials. It also cannot supply a validated storage period, preparation method, or clinical use simply because a named compound has published references. The meaningful comparison is between documented preparations and their testing, rather than between package sizes or claimed purity percentages.

COMMON MISTAKES

- Calling cibinetide a straightforward EPO fragment. It was designed from features of EPO's three-dimensional helix B surface. Its nonerythropoietic design does not establish cardiovascular safety or an endurance benefit (PMID 25728128).

- Treating a statistically significant placebo comparison in one dose group as proof that it outperformed another active group. The phase 2b results do not establish an optimal dose or a confirmed bell-shaped response (PMID 28475703).
- Using the approximately two-minute plasma estimate to invent a redosing interval or workout schedule. Clinical schedules varied, and pharmacokinetic exposure does not independently establish clinical duration of action (PMID 25728128, PMID 23168581, PMID 26431906).
- Equating corneal nerve morphology with proven pain relief, permanent nerve repair, or athletic recovery. These are different outcomes. The largest trial's highlighted pain comparison did not reach statistical significance (PMID 28475703).
- Assuming that absence of erythropoiesis means the compound is permitted in sport. The current WADA framework prohibits innate repair receptor agonists at all times. Detection research is consistent with that prohibition (PMID 28941172).
- Converting animal doses to human doses by multiplying by body weight. The wound and transplantation studies used different species, routes, schedules, and disease models. Their exposure-response relationships do not establish human dosing (PMID 29223734, PMID 26683514).
- Reading no identified treatment-related safety issue as no adverse events. Both the clinical literature and the phase 2b registry contain adverse-event reporting, including serious events requiring careful interpretation rather than automatic attribution.
- Treating a certificate of analysis, a clear solution, or correct concentration arithmetic as proof of injectable quality. Identity, content, impurities, sterility, endotoxin burden, and stability require distinct evidence.
- Assuming that different mechanisms establish synergy or that apparently opposite mechanisms establish cancellation. No identified studies validate the catalog peptide combinations described here.
- Treating experiments on human cells transplanted into mice as human clinical trials. Human islet studies remain preclinical when treatment outcomes are measured in culture or animal recipients (PMID 34498509).

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Shield before you build.

Tissue, gut and immunity come first in every protocol.

UU.LIFE

UU LIFE

2.0



MODULE 4 OF 5 · UU LIFE PEPTIDES 2.0

MIND & LONGEVITY

Nootropics, sleep, mitochondria, sexual health and skin. Semax and Selank, neurotrophic compounds, DSIP and Epitalon, mitochondrial peptides, melanocortins, kisspeptin and oxytocin, and the skin compounds that actually have data.

Module 4

UU LIFE PEPTIDES 2.0

Verified references

Educational and informational reference for adults. Not medical advice, not a prescription and not intended to replace any substance. Many compounds described are not approved for human use and several are prohibited in sport. Decisions about any compound belong to you and a licensed clinician.

A UU LIFE PRODUCT · UU.LIFE

Cards in this module

01	Semax ACTH 4-10 analog	Evidence A
02	Selank Synthetic tuftsin analog	Evidence A
03	Dihexa Angiotensin IV analog, HGF/c-Met potentiator	Evidence C
04	Cerebrolysin Porcine brain-derived peptide mixture	Evidence C
05	DSIP Nonapeptide	Evidence C
06	Epitalon Synthetic pineal tetrapeptide	Evidence C
07	MOTS-c Mitochondrial-derived peptide	Evidence C
08	SS-31 Mitochondria-targeted tetrapeptide	Evidence A
09	Humanin Mitochondrial-derived peptide	Evidence C
10	FOXO4-DRI D-retro-inverso FOXO4 peptide (senolytic)	Evidence C
11	NAD+ Coenzyme (not a peptide; included because it is stacked with the mitochondrial peptides)	Evidence C
12	PT-141 Melanocortin MC4/MC3 receptor agonist	Evidence A
13	Melanotan II Non-selective melanocortin agonist	Evidence B
14	Kisspeptin-10 KISS1R agonist, upstream of GnRH	Evidence C
15	Oxytocin Neurohypophysial nonapeptide	Evidence C
16	Argireline SNAP-25 mimetic cosmetic peptide	Evidence C

Each card: what it is, mechanism, evidence grade, regulatory and sport status, reported doses with provenance, stacking, safety, reconstitution with a worked calculation, buying notes, common mistakes and the references you can verify.



Semax

Met-Glu-His-Phe-Pro-Gly-Pro

ACTH 4-10 analog

Module 4 · Mind & Longevity

Goals: Nootropics

Route: Intranasal

A Russian-registered nasal peptide with rodent neurotrophic findings and limited neurological clinical studies. Evidence for improved cognition in healthy adults remains weak.

WHAT IT IS

Semax is the synthetic heptapeptide Met-Glu-His-Phe-Pro-Gly-Pro, approximately 814 Da. Its sequence combines ACTH residues 4 to 7 with Pro-Gly-Pro. Publications also describe it as an ACTH(4-10) analogue, reflecting replacement of the final three residues of that fragment.

The Russian prescribing information describes Semax as lacking hormonal activity. That description does not establish that cortisol is unaffected under every experimental or clinical condition. Semax is registered in Russia in nasal formulations. Its registration does not establish efficacy for every proposed cognitive, psychiatric or longevity application.

The literature includes neurological patient studies, small healthy-volunteer imaging experiments and substantial animal research. These populations and endpoints answer different questions. Module 4 placement: cognition and neurological research, with weak direct support for cognitive enhancement in healthy adults.

MECHANISM

Binding demonstrated in rat tissue: radiolabeled Semax bound specifically and reversibly to basal forebrain membranes. Binding required calcium, with a reported dissociation constant of 2.4 nM. The experiment did not identify the binding protein or establish a human receptor target (PMID 16635254). ACTH ancestry alone does not establish a particular melanocortin receptor profile.

Neurotrophic findings in rodents: a single intranasal administration of 50 mcg per kg increased hippocampal BDNF protein and TrkB phosphorylation (PMID 16996037). The same study reported increased BDNF and trkB messenger RNA and improved conditioned avoidance. These findings connect molecular changes with an animal behavioral endpoint. They do not establish improved human memory, a therapeutic brain concentration or a clinically useful biomarker threshold.

Regional effects matter. Basal forebrain BDNF increased after intranasal administration in rats, while cerebellar BDNF did not show the same response (PMID 16635254). This supports region-dependent activity rather than a uniform increase throughout the brain. It also limits claims that a peripheral BDNF measurement reveals what happened in a particular human brain region.

Ischemia-related gene expression: a rat cerebral ischemia-reperfusion experiment found changes in 394 differentially expressed genes after Semax treatment. Inflammatory expression patterns decreased and neurotransmission-related patterns increased relative to injured controls (PMID 32580520). These are transcriptomic observations in an injury model. They do not independently prove clinical neuroprotection or establish that the same pathways explain effects in healthy people.

Working interpretation: neurotrophic signaling and injury-associated transcription are plausible contributors. The primary molecular target, causal pathway and relevance to healthy human cognition remain incompletely characterized. Specific claims about GABA-A potentiation, glycine inhibition, CREB activation and copper chelation are excluded here because their supporting records were not verified.

EVIDENCE · GRADE A

A reflects Russian drug registration under this catalog's definition, which explicitly includes approved drugs. It does not mean that Semax has multiple rigorous human randomized trials supporting cognitive enhancement. The limited neurological clinical evidence is approximately B; evidence for improved cognition in healthy adults is C. The focused PubMed search did not identify a convincing blinded trial establishing better cognitive performance in healthy adults. Imaging changes and developers' summaries cannot substitute for that endpoint.

Human data. Acute ischemic stroke: a controlled study compared 30 Semax recipients with 80 conventionally treated controls. The abstract reported faster regression of

Animal and mechanistic data. Rat experiments support biological activity, with changes in BDNF signaling, conditioned avoidance and recovery of spatial learning after

neurological deficits, particularly motor deficits. It did not describe random allocation or blinding (PMID 11517472). Post-stroke rehabilitation: 110 patients were divided by rehabilitation timing and Semax exposure. Investigators reported higher plasma BDNF and better Barthel index recovery. Allocation and blinding remain unclear from the abstract (PMID 29798983). Motor neuron disease: an explicitly open-label study enrolled 27 patients. It reported no improvement in disease course or clinical functional decline, although emotional and motivational quality-of-life measures improved. PubMed indexes this record as a randomized controlled trial, but its abstract describes sequential open-label groups. The design description takes precedence over the indexing tag (PMID 18379501). Healthy volunteers: a study of 24 participants compared nasal Semax with placebo using resting-state fMRI. It reported a difference in a default mode network component, without demonstrating better memory or attention (PMID 30225715). Another study examined functional connectivity in 52 participants assigned to Semax, Selank or placebo. It investigated imaging responses, not demonstrated cognitive enhancement or combined treatment (PMID 32342318). A developers' summary claims improved attention and working memory under demanding conditions, but its abstract provides insufficient trial methods for independent appraisal (PMID 9173745). An ophthalmic study used Semax within a multicomponent intervention and followed patients for 24 weeks. Its findings cannot isolate Semax's contribution (PMID 36083821).

ischemic injury (PMIDs 16635254, 16996037 and 19779827). These models do not establish equivalent benefits in healthy adults. A radiotracer study detected intact Semax and metabolites in rat brain shortly after nasal administration. Rapid degradation followed, with Pro-Gly-Pro prominent among recovered metabolites (PMID 16523722). A separate study found anticoagulant, fibrinolytic and platelet-related effects during immobilization stress (PMID 21113455). These findings generate hypotheses about exposure and interactions, rather than validated human pharmacokinetics or bleeding-risk estimates.

REGULATORY STATUS AND SPORT

STATUS	Semax is registered in Russia as 0.1% and 1% nasal drops. No FDA-approved Semax product exists. Compounding review or advisory consideration does not constitute drug approval. Source: [FDA Semax evaluation] (https://www.fda.gov/media/193348/download).
WADA	Semax is not explicitly named on the WADA list reviewed. That does not establish permission. S2 prohibits corticotrophins and includes substances with similar chemical structures or biological effects. Russian registration alone cannot resolve classification under S2 or other categories. This review does not establish an authoritative Semax-specific determination; athlete eligibility requires confirmation from the relevant anti-doping organization. Source: [WADA Prohibited List] (https://www.wada-ama.org/en/prohibited-list).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Intranasal administration is explicitly documented in human studies including the motor neuron disease and healthy-volunteer imaging reports (PMIDs 18379501 and 30225715). Endonasal electrophoresis also appears in clinical research (PMID 36083821). Some English abstracts use the word injection without identifying a parenteral route. That wording is insufficient to infer subcutaneous administration. Rat experiments compared intranasal and intraperitoneal routes (PMID 21268834). No validated human subcutaneous regimen was established by the reviewed evidence.
HALF-LIFE	A numerical human elimination half-life was not established in the reviewed records. Rat radiotracer research demonstrated early brain entry and rapid enzymatic degradation, but it does not provide a transferable human half-life (PMID 16523722). The developers' report of effects lasting 20 to 24 hours describes claimed pharmacodynamic duration, not persistence of intact peptide in plasma (PMID 9173745). Neither observation validates a human dosing interval.
TIMING	The reviewed clinical abstracts do not establish an optimal time of day for cognitive enhancement. Claimed prolonged effects do not prove that morning administration is necessary or sufficient. Imaging measured responses shortly after administration, while rehabilitation studies assessed recovery over longer intervals. These different endpoints do not define a common onset, duration or subjective experience.
CYCLE LENGTH	Study schedules are indication-specific. The rehabilitation study used two 10-day courses separated by 20 days, with five months of observation (PMID 29798983). The motor neuron disease study used two 10-day courses separated by two weeks (PMID 18379501). Follow-up lasting months does not demonstrate the safety of continuous use for months. No validated cycling schedule for healthy adults follows from these studies.
TITRATION	No validated titration algorithm for cognitive enhancement emerged from the reviewed evidence. Disease-severity dose selection is different from gradual titration based on subjective effects. An absence of perceived benefit does not establish inadequate exposure, and increasing exposure has no demonstrated ability to rescue a nonresponse in healthy adults.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Acute hemispheric ischemic stroke, 30 treated patients and 80 controls	12 mg per day for moderate stroke or 18 mg per day for severe stroke, as reported in PMID 11517472.	Not specified in the indexed abstract; the original study methods require confirmation before assigning a route-specific regimen.	Daily totals over courses described as 5 and 10 days; administration frequency and exact severity-to-duration mapping are not fully detailed in the abstract.	Gusev 1997, controlled clinical study, PMID 11517472. These are reported patient-study doses, not healthy-adult recommendations. · PMID 11517472
Post-stroke rehabilitation study involving 110 patients	6000 mcg per day, as reported in PMID 29798983.	Not specified in the indexed abstract; route and formulation require confirmation from the full study.	Daily for two 10-day courses separated by a 20-day interval; within-day frequency is not stated in the abstract.	Gusev 2018, PMID 29798983. Five months of observation should not be confused with five months of continuous exposure. · PMID 29798983
Open-label motor neuron disease study, 27 patients	12 mg per day using a 1% solution, as reported in PMID 18379501.	Intranasal.	Daily for two 10-day courses separated by two weeks; within-day administration frequency is not specified in the abstract.	Serdiuk 2007, PMID 18379501. The study did not demonstrate altered disease progression. · PMID 18379501
Developers' overview covering experimental animals and humans	0.015 to 0.050 mg per kg, equivalent to 15 to 50 mcg per kg, as summarized in PMID 9173745.	Intranasal.	Effects are described after administration; a reproducible human schedule and clear species-specific allocation of the range are not supplied.	Asmarin 1997, PMID 9173745. The abstract combines animal and human claims, so this range is not a verified healthy-adult protocol. · PMID 9173745
Rat hippocampal BDNF, TrkB and conditioned avoidance experiment	50 mcg per kg, as reported in PMID 16996037.	Intranasal.	Single administration.	Dolotov 2006, PMID 16996037. This is an animal dose and is not converted into a human regimen. · PMID 16996037
Rat spatial learning after ischemic prefrontal injury	250 mcg per kg per day, as reported in PMID 19779827.	Intranasal.	Daily during the first six days after photothrombosis.	Silachev 2009, PMID 19779827. Behavioral testing occurred later, so treatment duration and outcome timing differ. · PMID 19779827

STACKING

+ Selank	A healthy-participant fMRI study examined Semax, Selank and placebo in separate groups (PMID 32342318). It did not test simultaneous administration or demonstrate synergy. Distinct imaging responses do not establish complementary clinical benefits.	– Melanotan II	No combination benefit or interaction magnitude was established in the reviewed records. Additional pharmacologically active exposure complicates attribution of symptoms. This is a precaution about uncertainty, not a demonstrated Semax-specific contraindication.
+ Dihexa	No Semax-dihexa combination trial was verified. A shared narrative about neurotrophic signaling cannot establish additive benefit, compatibility or an acceptable combined risk profile.	– PT-141	No controlled combination evidence was verified. Structural or signaling comparisons do not establish compatibility.

SAFETY

COMMON EFFECTS	Mild nasal mucosal irritation appears in Russian prescribing information. A cerebrovascular study describes a low proportion of adverse effects, but its abstract does not provide a usable event table or incidence estimate (PMID 15792140). Headache, activation, anxiety and insomnia are not established as common effects by the verified abstracts; their frequencies remain uncertain.
SERIOUS SIGNALS	A posthypoxic encephalopathy series reported paroxysmal EEG activity after Semax in some patients. This is a neurological signal, not proof that Semax caused clinical seizures (PMID 10199046). Anticoagulation findings in stressed rats do not establish human bleeding incidence or a quantified anticoagulant interaction (PMID 21113455). FDA identifies potential immunogenicity concerns associated with aggregation and peptide-related impurities in injectable and nasal spray formulations. Clinical immunogenicity studies were not identified in its review. Small studies and incomplete adverse-event reporting cannot exclude uncommon serious harm. Source: [FDA 2026 Semax safety presentation](https://www.fda.gov/media/193774/download).
CONTRAINDICATIONS	The Russian 0.1% prescribing information lists hypersensitivity, pregnancy, breastfeeding, acute psychiatric states, anxiety-associated disorders and a history of convulsions. Pediatric restrictions vary by age and indication. These are formulation-specific label statements. Bleeding disorders and anticoagulant exposure warrant clinical review because interaction evidence is incomplete; they are not established contraindications from the cited rat experiment. Source: [Russian Semax 0.1% prescribing information](https://semax.ru/upload/iblock/867/867fc8166acadb577dc956d855999a3.pdf).

STOP RULES

Seizure-like activity, fainting, new focal neurological symptoms, breathing difficulty or facial swelling warrant urgent medical evaluation and no further exposure pending assessment. Persistent nasal injury, unusual bleeding, substantial agitation or severe insomnia warrant discontinuation and clinical review.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	The verified Russian 0.1% label describes a finished 3 mL nasal solution, not a lyophilized preparation requiring reconstitution. Research powder and spray packaging cannot be assumed equivalent to a registered formulation. A stated container mass does not establish peptide content, purity, delivered exposure or suitability for human administration.
SOLVENT	The verified Russian formulation contains purified water and methylparahydroxybenzoate. That composition does not validate substituting bacteriostatic water or saline into an unspecified research powder. Solubility alone does not establish formulation quality.
STORAGE	The retrieved Russian 0.1% label specifies protection from light, storage at no more than 10 degrees C and no freezing. Its stated shelf life does not validate storage of research mixtures or establish an opened-container beyond-use period.

Concentration arithmetic only: 0.1% weight per volume equals 1 mg per mL, while 1% equals 10 mg per mL. The concentrations differ tenfold. This calculation describes solution strength, not an administration dose or a mixing procedure.

The former example relied on PMID 27051926 but silently changed its abstract's dose unit from mg to mcg. That discrepancy cannot be resolved by assuming a typographical error. The paper is therefore excluded as a dosing source pending verification against the original methods.

Drop size and pump output are device-specific. A generic drop count, assumed spray volume or syringe-unit conversion cannot establish delivered peptide mass without validated concentration and delivery measurements.

BUYING NOTES

A useful certificate of analysis identifies the tested batch, analytical methods, sequence or identity evidence, quantitative peptide content and relevant impurities. Chromatographic purity alone does not establish the amount of active peptide, microbiological quality, aggregate content or delivery accuracy. Gross powder mass may include water and counterions. A molecular mass consistent with Semax supports identity but does not independently establish sequence, purity or clinical suitability. Acetylated or amidated derivatives are chemically different from the unmodified sequence discussed here. Published findings cannot automatically transfer to those variants. Registration of a finished nasal product also does not validate an unrelated preparation merely sharing the Semax name.

COMMON MISTAKES

- Treating the catalog's approval-based A grade as proof of strong evidence for cognitive enhancement. Healthy-adult cognitive efficacy remains grade C.
- Confusing concentration with dose or treating 0.1% and 1% solutions as interchangeable. They differ tenfold.
- Assuming the 1% concentration was studied only in acute stroke. It also appears in motor neuron disease and healthy-volunteer imaging research.
- Converting a rat dose into a human regimen or treating the developers' mixed-species summary as a validated healthy-adult protocol.
- Interpreting a functional MRI change or increased plasma BDNF as demonstrated improvement in memory, attention or daily functioning.
- Equating prolonged observation with prolonged treatment, or equating reported effect duration with elimination half-life.
- Assuming nasal-drop findings validate subcutaneous administration, arbitrary spray devices, untested mixtures or chemically modified variants.
- Treating absence from the named WADA examples as an authoritative determination that a substance is permitted.

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Selank

Tuftsins analog

Synthetic tuftsins analog

Module 4 · Mind & Longevity

Goals: Nootropics, Sleep

Route: Intranasal

A synthetic tuftsins analog registered in Russia as an intranasal anxiolytic. Small human studies report anxiety improvement, but cognitive enhancement, sleep benefits, and long-term safety remain insufficiently established.

WHAT IT IS

Selank is the heptapeptide Thr-Lys-Pro-Arg-Pro-Gly-Pro, also called TP-7. It extends the immune peptide tuftsins with a Pro-Gly-Pro sequence. This modification was intended to change peptide stability and biological activity. The compound has been investigated for anxiety, learning, neurochemical signaling, and immune effects.

The human literature principally concerns anxiety disorders and related symptoms. It does not establish benefits for athletic performance, body composition, healthy-person cognitive enhancement, or longevity. Reports of antiasthenic and psychostimulant effects describe findings in patient populations, not reliable stimulation in every user (PMID 18454096).

The registered nasal formulation, experimental animal preparations, and modified chemical variants are distinct evidence contexts. Results with one preparation or route cannot establish equivalent exposure or effects with another. N-acetylated or amidated variants require their own characterization and clinical evidence.

MECHANISM

Enkephalin metabolism is one proposed pathway. Selank inhibited enkephalin breakdown in human plasma experiments. Patients with generalized anxiety also showed altered enkephalin metabolism, although this does not establish that the abnormality causes anxiety (PMID 11550013). During treatment, a small clinical study found changes in serum leu-enkephalin half-life associated with clinical measures (PMID 18454096). These are peripheral biomarker observations, not direct measurements of opioid signaling in the human brain.

Mouse findings provide additional mechanistic support. Selank affected anxiety-related behavior and enkephalin degradation differently in BALB/c and C57Bl/6 mice (PMID 12432865). Naloxone blocked a behavioral effect in an apomorphine challenge model, while receptor assays found no displacement of the tested dopamine and opioid ligands (PMID 17415472). This supports an indirect endogenous opioid hypothesis. It does not establish direct opioid agonism, opioid-like dependence, or clinical treatment of opioid withdrawal.

GABA-related findings come principally from experimental systems. Membrane-binding experiments reported concentration-dependent allosteric modulation of GABA binding and interactions with diazepam and olanzapine (PMID 30255741). Rat hippocampal slices showed increased spontaneous inhibitory synaptic activity, sometimes preceded by a transient decrease (PMID 28361410). These observations support investigation of inhibitory neurotransmission, but they do not establish a clinically characterized receptor target or receptor occupancy in humans.

Gene-expression results also depend on the experimental system. Rat frontal cortex showed changes in neurotransmission-related genes after Selank exposure (PMID 26924987). In IMR-32 cells, Selank alone did not change the measured GABA-related transcripts, although combinations changed responses to other compounds (PMID 28293190). Route comparisons in mice produced different GABA and NMDA receptor-binding findings (PMID 29787664). These differences undermine assumptions that all routes have interchangeable effects.

Other preclinical findings include hippocampal BDNF regulation, altered monoamine metabolism, and changes in hippocampal transcription (PMID 18841804, PMID 19093364, PMID 24450168). A rat ethanol-exposure model linked memory findings with BDNF changes (PMID 31625062). These observations do not establish increased neuroplasticity, improved intelligence, or neuroprotection in healthy adults.

Immune effects are similarly context-dependent. Human experiments included peripheral-cell findings and serum cytokine changes during treatment (PMID 18577961). Experimental influenza work reported interferon-alpha gene induction, while mouse spleen studies found altered inflammatory gene expression (PMID 19882898, PMID 21609736). The Gly-Pro fragment reproduced some immune gene-expression changes (PMID 24291245). These findings do not establish a beneficial immune direction across infections, autoimmune disease, or cancer.

A placebo-controlled imaging study found functional-connectivity differences among Selank, Semax, and placebo groups in healthy participants (PMID 32342318). Imaging changes show a measurable biological association under study conditions. They do not establish clinical anxiety relief, its onset, or a validated explanation of Selank's therapeutic effects.

A applies under this catalog's literal definition because Selank has Russian medicinal registration and more than one PubMed-indexed randomized trial. This classification must not imply strong or internationally replicated efficacy evidence. The human anxiety evidence is small-study evidence of approximately B-level strength when judged by design, reporting, and replication. Cognitive enhancement in healthy adults remains C. A sleep-treatment claim remains D because the reviewed records do not establish sleep-specific efficacy. A pharmacology review describes Selank as poorly studied (PMID 34396551).

Human data. Zozulia 2008 compared Selank in 30 patients with medazepam in 32 patients with generalized anxiety disorder or neurasthenia. PubMed indexes it as randomized. The abstract reports similar anxiolytic effects and additional antiasthenic and psychostimulant effects with Selank (PMID 18454096). Similar observed outcomes do not establish formal equivalence or noninferiority. Medvedev 2014 compared Selank with phenazepam in 60 patients with anxiety-phobic and somatoform disorders. The abstract reports anxiety improvement, mild nootropic effects, and persistence of anxiolytic effects for one week after treatment. PubMed indexes a clinical comparative study, but the abstract does not establish randomization or blinding (PMID 25176261). Medvedev 2015 compared phenazepam alone in 30 patients with phenazepam plus Selank in 40 patients. PubMed indexes this study as randomized. The authors reported earlier improvement on their stated HDRS measure and fewer measured phenazepam-associated adverse effects (PMID 26356395). The English abstract's scale terminology is insufficiently clear for stronger interpretation. These findings concern adjunctive treatment and cannot establish Selank monotherapy efficacy. Uchakina 2008 reported cytokine changes during a 14-day course in patients with generalized anxiety disorder and neurasthenia (PMID 18577961). This mechanistic study does not establish infection prevention or treatment of immune disease. Panikratova 2020 studied 52 healthy participants across Selank, Semax, and placebo conditions. Imaging occurred before administration and after 5 and 20 minutes (PMID 32342318). The total sample was not 52 Selank-treated participants. The abstract does not report a clinical anxiety or sleep endpoint. The retrieved abstracts do not provide sufficient information on allocation concealment, blinding, attrition, comprehensive adverse-event rates, or long-term follow-up. No independent placebo-controlled clinical efficacy replication was identified in this targeted review. That is a search finding, not proof that no additional study exists.

Animal and mechanistic data. Anxiety-related effects vary by strain, baseline behavior, route, and experimental conditions. BALB/c and C57Bl/6 mice responded differently in behavioral and biochemical studies (PMID 12432865, PMID 29787664). A four-week study in selected Wistar rats found persistent anxiety-related behavioral effects without a body-mass difference attributable to TP-7 (PMID 16963804). This does not establish absence of tolerance or long-term toxicity in humans. Learning experiments reported improved active avoidance in rats with poor initial learning and longer retention after administration during memory consolidation (PMID 14552529, PMID 20919548). Rodent memory tasks cannot establish everyday cognitive benefit in healthy adults. Withdrawal models reported reduced alcohol-withdrawal anxiety and reduced signs of precipitated morphine withdrawal (PMID 24913576, PMID 36322304). These are preclinical findings, not evidence for managing human withdrawal. Antidepressant-like behavioral findings differed between strains and between single and repeated administration (PMID 18661785). Additional studies examined stress-related liver morphology, intestinal microbiota, cytokines, gastric ulceration, and microcirculation (PMID 31243679, PMID 31236882, PMID 32621722, PMID 18019011, PMID 15835541). They do not establish organ protection or digestive treatment in humans. PMID 32621722 contains an inconsistent mention of Semax within its abstract, which further limits interpretation of that report.

REGULATORY STATUS AND SPORT

STATUS

Russian prescribing information identifies Selank as an over-the-counter nasal medicine. This authorization concerns a defined pharmaceutical formulation. It does not establish approval of injectable powders or chemically modified variants. [Russian prescribing information](https://white-medicine.com/files/instructions/Selank_IMP_02082017.pdf). Selank is not FDA-approved. The FDA currently places Selank acetate (TP-7) in its section for withdrawn bulk-substance nominations and retains concerns about immunogenicity and inadequate human safety information. Removal from Category 2 did not constitute approval or general authorization to compound. [FDA compounding safety information](<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>). The September 2024 FDA notice states that removal followed information that the nominator intended to nominate a different bulk substance. [FDA September 2024 notice](<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>). Jurisdiction-specific importation and supply rules require separate verification.

WADA

Selank is not explicitly named in the 2026 WADA Prohibited List. S0 prohibits pharmacological substances lacking current governmental approval for human therapeutic use when no subsequent section addresses them. Russian medicinal registration is relevant to that wording, so absence of FDA approval alone does not establish S0 prohibition. This is an interpretation of the rule, not a Selank-specific WADA determination. Absence from the named examples also does not establish permission under every category. A definitive athlete-specific determination requires the relevant anti-doping organization. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

ROUTES	The registered human formulation is intranasal. Several retrieved human abstracts omit route and administration details, so the label cannot fill every study's reporting gaps. The imaging abstract uses the word injection without specifying the route (PMID 32342318). Rodent research includes intraperitoneal and intranasal administration. A radiolabeled distribution study also compared intragastric and intravenous routes and reported favorable CNS delivery after intranasal administration (PMID 18695718). Tissue radioactivity and metabolite distribution do not establish human bioavailability or equivalent exposure across routes. No validated human subcutaneous regimen was identified.
HALF-LIFE	A reliable numerical human elimination half-life was not established by the retrieved PubMed records. Radiolabeled experiments identified TKPRP, TKP, RP, and GP among Selank degradation products (PMID 16637290). These findings establish metabolism, but not a clinically validated human half-life. Experimental changes in rat nervous-tissue carboxypeptidase activity persisted for 24 hours (PMID 22827026). One patient study reported clinical effects persisting for a week after treatment (PMID 25176261). Neither finding measures the elimination half-life of intact Selank. Fragment activity in mouse immune experiments also cannot establish the duration of anxiolysis in humans (PMID 24291245).
TIMING	The clinical literature does not establish optimal timing relative to meals, training, sleep, or other medicines. Imaging at 5 and 20 minutes does not establish when anxiety relief begins (PMID 32342318). Reports of psychostimulant effects do not prove that every trial used waking-hours administration or excluded bedtime dosing (PMID 18454096). Those schedule claims were unsupported.
CYCLE LENGTH	The Russian label permits a repeat course after 1 to 3 weeks following medical consultation. This is product-specific labeling, not evidence for indefinite cycling. The immunomodulatory patient report explicitly describes 14 days of treatment (PMID 18577961). Other abstracts do not consistently provide course duration. Four-week rat findings cannot establish a human maintenance schedule (PMID 16963804).
TITRATION	No validated human titration strategy was identified in the reviewed records. Animal antidepressant-like responses varied with dose, strain, and repeated exposure (PMID 18661785). These findings do not establish a universal bell-shaped human response. They also do not demonstrate that baseline anxiety predicts human response or that escalation converts non-responders. An absent subjective effect is not evidence of inadequate exposure.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Registered adult nasal regimen, descriptive label information	Russian Selank nasal-drops label: 2 drops of 0.15 percent solution, 1.5 mg per mL, in each nostril per administration, intranasally, 3 times daily. Drop volume is not specified.	Intranasal, using the labeled pharmaceutical presentation	The Russian Selank nasal-drops label specifies 3 times daily for 14 days.	Russian prescribing information for Selank nasal drops. The label defines administration in drops; it does not validate an assumed microgram amount per drop.
Human comparisons with medazepam and phenazepam	The retrieved abstracts do not report a numerical Selank dose. The labeled regimen cannot be assumed to be the study regimen.	Not specified in the retrieved abstracts	Administration frequency and treatment duration are not specified in the retrieved abstracts.	PMID 18454096 and PMID 25176261. Dose, route, and schedule require the original methods. · PMID 18454096
Functional-connectivity study in 52 healthy participants across three groups	The abstract does not state the administered amount or formulation concentration.	Not specified in the abstract, which uses the word injection	One administration occasion, with imaging before administration and after 5 and 20 minutes	PMID 32342318. Imaging times are not evidence of clinical onset. · PMID 32342318
Long-term anxiety-related behavioral experiment in Wistar rats	PMID 16963804 reports TP-7 at 0.3 mg/kg, intraperitoneally, once daily during a four-week experiment.	Intraperitoneal in rats	Daily, with behavioral assessments extending through four weeks	PMID 16963804. Animal exposure, not a human dosing recommendation. · PMID 16963804
Route comparison in BALB/c and C57BL/6 mice	PMID 29787664 reports 300 mcg/kg per day, administered intranasally or intraperitoneally in separate experimental conditions, for five days.	Intranasal and intraperitoneal, compared separately in mice	Daily for five days	PMID 29787664. Behavioral and receptor-binding findings differed by strain and route. · PMID 29787664
Ethanol-associated memory and BDNF experiment in rats	PMID 31625062 reports 0.3 mg/kg, intraperitoneally, once daily for seven days.	Intraperitoneal in rats	Once daily for seven days	PMID 31625062. The experiment does not establish human neuroprotection. · PMID 31625062

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CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Mouse spleen gene-expression experiments	PMID 21609736 and PMID 24291245 report 100 mcg/kg, intraperitoneally, as a single administration in the respective experiments.	Intraperitoneal in mice	Single administration, followed by molecular measurements	PMID 21609736 and PMID 24291245. Molecular endpoints do not establish clinical immune benefits. · PMID 21609736
Separate rat models of alcohol or morphine withdrawal	PMID 24913576 and PMID 36322304 each report 0.3 mg/kg, intraperitoneally, as a single administration in their respective withdrawal models.	Intraperitoneal in rats	Single administration in each experiment	PMID 24913576 and PMID 36322304. These exposures are not human withdrawal-treatment regimens. · PMID 36322304
Non-clinical schedules circulated outside the retrieved clinical literature	250 to 500 mcg per administration, intranasally or subcutaneously, 1 to 3 times daily: commonly cited in non-clinical use; not validated in trials.	Intranasal or subcutaneous in anecdotal descriptions, without demonstrated equivalence	Commonly cited in non-clinical use; not validated in trials. Neither schedule nor duration has a validated human evidence base.	commonly cited in non-clinical use; not validated in trials. Included to identify the provenance category, not to endorse the schedule. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ Semax	No demonstrated combination synergy. PMID 32342318 studied Selank, Semax, and placebo as separate conditions, not a Selank plus Semax regimen. Shared development history and different proposed effects do not establish complementary clinical action.	– Oxytocin	No Selank-specific combination evidence was identified. Shared interest in amygdala circuitry does not establish either synergy or a proven contraindication. Concurrent changes in CNS-active exposures complicate attribution of symptoms and adverse effects.
+ DSIP	No combined clinical evidence was identified. A stress or sleep rationale does not establish benefit, compatibility, or an appropriate schedule. Selank's reviewed studies do not establish sleep-specific efficacy.		
+ BPC-157	No demonstrated combination synergy. Selank gastric-ulcer and tissue-distribution findings are preclinical (PMID 18019011, PMID 18695718). Similar research themes cannot establish additive healing or a human gastrointestinal indication.		

SAFETY

COMMON EFFECTS	The Russian label identifies unpleasant taste and possible allergic reactions; it does not provide reliable event frequencies. Small comparative studies reported favorable tolerability, but their abstracts lack comprehensive safety tables. The phenazepam add-on study reported reductions in selected adverse effects associated with that treatment (PMID 26356395). This does not establish that Selank cannot cause sedation, cognitive symptoms, or withdrawal. Their incidence cannot be estimated from the retrieved records. Mouse strain differences do not establish how often humans fail to respond.
SERIOUS SIGNALS	The small clinical literature cannot estimate uncommon or delayed harms. FDA identifies potential immunogenicity from aggregation and peptide-related impurities, alongside inadequate human safety information. [FDA Selank safety entry](https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks). The pharmacology review discusses dependence and withdrawal across GABA-related substances, but it does not establish Selank-specific rates or causality (PMID 34396551). Findings for other sedative agents must not be reassigned to Selank. Human cytokine observations and animal immune experiments leave uncertainty about immune disease and immunosuppressive treatment (PMID 18577961, PMID 19882898, PMID 21609736). They do not demonstrate that Selank causes autoimmune flares, infections, or cancer.
CONTRAINDICATIONS	Russian labeling lists hypersensitivity, pregnancy, breastfeeding, and age under 18 as contraindications. The retrieved evidence does not establish use in these groups. Interaction studies are incomplete. Membrane experiments, rat stress studies, and a human phenazepam add-on trial examined different endpoints under different conditions (PMID 30255741, PMID 28280289, PMID 26356395). Their results cannot predict the net effect with benzodiazepines, alcohol, Z-drugs, or antipsychotics in an individual. Animal ethanol and opioid findings support possible pharmacological interactions, not a demonstrated human interaction syndrome (PMID 27878720, PMID 36322304). Psychiatric illness, concurrent CNS medication, autoimmune disease, and immunosuppression require individualized clinical assessment rather than a generic combination rule.

STOP RULES

Breathing difficulty, facial swelling, collapse, severe confusion, or inability to stay awake warrant emergency assessment and cessation of exposure. Persistent nasal bleeding, new loss of smell, marked agitation, worsening mood, or unusual sedation warrant prompt assessment. There is no validated waiting period during which these symptoms should be accepted. New symptoms may reflect the formulation, another medicine, contamination, or an unrelated illness. A lack of benefit does not justify an evidence-free increase in dose or duration. These are general clinical precautions, not validated Selank-specific stopping thresholds.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	The labeled nasal product is a ready-made 3 mL solution and requires no reconstitution. Research powders have no universally established pharmaceutical presentation. A stated vial mass does not establish peptide identity, recoverable content, sterility, or an appropriate human route. Modified sequences cannot inherit the original compound's clinical findings.
SOLVENT	No validated human preparation method for research powder was identified. The Russian nasal formulation contains purified water and methylparaben, rather than saline alone. Bacteriostatic water cannot be assumed suitable for nasal use or interchangeable with the labeled vehicle. Adding a preservative does not sterilize contaminated material. Formulation assessment also requires pH, compatibility, container, and delivery-device information.
STORAGE	Russian labeling specifies light protection, storage at no more than 10 C, and no freezing. After opening, it permits no more than 25 C for up to 15 days. These conditions apply to the labeled formulation. [Russian prescribing information](https://white-medicine.com/files/instructions/Selank_IMP_02082017.pdf). No validated storage interval for homemade nasal solutions or reconstituted research powder was established by the reviewed sources. Preservative presence alone cannot support a multiweek beyond-use date. Chemical stability and microbial quality are separate requirements.

The relevant calculation is amount delivered equals measured concentration multiplied by measured delivered volume. A concentration alone does not specify an administered amount. Drop size and spray output must be characterized for the actual formulation and device. That conversion is not established by the retrieved label. It also treated a nominal spray volume as transferable between pumps. Device output can vary with design, priming, liquid properties, and remaining fill volume. Likewise, nominal powder mass divided by added solvent volume is only a theoretical concentration. Peptide content, salt basis, water content, incomplete dissolution, losses, and final solution volume can change the result. Matching a labeled concentration does not reproduce the labeled formulation, stability, or delivery system. Syringe markings express volume, not Selank-specific biological units. No injectable preparation is validated by these calculations.

BUYING NOTES

A certificate of analysis is evidence about specified tests on a specified sample, not proof of clinical suitability. Useful interpretation begins with the batch identifier, sampling date, laboratory, methods, and correspondence between the tested sample and the supplied material. An unmatched document cannot establish the contents of a different batch.

Chromatographic area purity does not directly establish peptide mass, potency, or sterility. A dominant peak can coexist with unmeasured contaminants or co-eluting compounds. Mass spectrometry can support identity, but the interpretation depends on molecular form, expected ions, and method performance. Salt and water content affect the relationship between total powder mass and peptide content.

Sequence modifications, acetylation, amidation, and different counterions need explicit characterization. A purity percentage cannot establish equivalence to the medicinal formulation used in clinical care. Endotoxin testing and sterility testing answer different questions; neither substitutes for the other or validates a manufacturing process.

A COA also cannot establish nasal-device performance, formulation stability, clinical efficacy, or lawful marketing. The independent pharmacology review questions the marketing of poorly studied Selank as a dietary supplement (PMID 34396551). Scientific criticism of that marketing is distinct from a complete jurisdiction-specific legal determination.

COMMON MISTAKES

- Interpreting the catalog's A as high-confidence efficacy. Here it reflects the catalog's approval and randomized-trial criteria; the underlying clinical evidence remains limited.
- Treating Selank as an established sleep treatment. This does not establish insomnia efficacy.
- Equating functional-connectivity changes with immediate anxiety relief. The imaging study assessed a biomarker, not the onset of a therapeutic effect (PMID 32342318).
- Describing similar outcomes against a comparator as proven equivalence. The retrieved abstract does not establish an equivalence or noninferiority design (PMID 18454096).
- Assuming all clinical studies used the same labeled schedule. Several abstracts omit dose, route, frequency, or duration.
- Using mouse strain differences to explain an individual's response. These experiments do not validate a human responder profile or escalation strategy (PMID 12432865, PMID 29787664).
- Assuming intranasal and injected preparations are interchangeable. Route-dependent receptor findings in mice argue against that assumption (PMID 29787664).

- Treating a combination listed under synergies as clinically tested. The Selank and Semax imaging study used separate conditions, not their combination (PMID 32342318).
- Treating immune modulation as immune strengthening. Changes can differ by cell type, disease context, and endpoint (PMID 18577961).
- Assigning other GABA-related drugs' dependence or overdose outcomes to Selank. A shared proposed pathway does not establish the same clinical risk profile (PMID 34396551).
- Converting drops into micrograms using an assumed volume, or transferring a storage interval from the registered product to a homemade solution.
- Treating FDA removal from a nomination category, Russian registration, or absence from WADA's named examples as interchangeable forms of approval.

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Dihexa

N-hexanoic-Tyr-Ile-(6) aminohexanoic amide, PNB-0408

Angiotensin IV analog, HGF/c-Met potentiator

Module 4 · Mind & Longevity

Goals: Nootropics

Route: Oral or topical (research)

An experimental angiotensin IV-derived peptidomimetic with mixed animal findings, no established human dosing, and major integrity concerns affecting its foundational research.

WHAT IT IS

Dihexa is a synthetic, chemically modified peptide derivative developed from an angiotensin IV research program. Its reported chemical name is N-hexanoic-Tyr-Ile-(6) aminohexanoic amide. PNB-0408 is another name used in the animal literature. Calling it a peptidomimetic or modified peptide derivative is more informative than declaring that it is categorically not a peptide.

The development program sought compounds with improved metabolic stability and access to the brain. The immediate starting scaffold included the Nle-Tyr-Ile sequence of a modified angiotensin IV analog. Chemical changes produced a capped derivative containing the Tyr-Ile core. These changes were intended to alter stability and membrane permeability, rather than simply reproduce the properties of natural angiotensin IV.

The foundational characterization reported oral activity, brain penetration, and improved performance in rodent memory tasks. However, that paper carries a 2021 expression of concern. Its publication year is 2013, although it appeared electronically in 2012. Its findings therefore require an explicit qualification whenever they support absorption, brain penetration, behavioral efficacy, or pharmacokinetic claims. The relevant records are PMID 23055539 and PMID 34551989.

Dihexa belongs in the experimental neuroscience portion of this catalog. No published clinical trial administering dihexa under that name or PNB-0408 was identified in this review. Human cognitive benefit, direct-administration pharmacokinetics, and a clinical dosing regimen remain unestablished. The evidence does not support presenting it as a validated nootropic or a ready-to-apply cognitive protocol.

The research history also includes a retracted mechanism paper and mixed subsequent animal findings. These are separate limitations. Retraction weakens confidence in particular experiments. Animal-only evidence limits translation even when an individual experiment remains published.

MECHANISM

The proposed mechanism involves hepatocyte growth factor, HGF, and its receptor, c-Met. HGF is a signaling protein, while c-Met is a receptor tyrosine kinase encoded by MET. This pathway participates in tissue development, repair, cell survival, and cancer biology. Its biological effects depend on the tissue and disease context. The original dihexa model proposed that the compound binds HGF and increases its ability to activate c-Met. Under that model, dihexa is a potentiator of HGF signaling rather than a replacement for HGF. Receptor activation was proposed to increase dendritic spine formation and functional synaptic connections. That provided a suggested link between molecular signaling and rodent memory performance. The primary experimental paper supporting this account, PMID 25187433, was retracted. The April 2025 retraction notice is PMID 40312093. The withdrawn paper remains listed here solely to identify the origin of the claim. Its binding, receptor activation, and synaptogenesis experiments are not treated as reliable confirmation of dihexa's target. Another verified notice, PMID 40312092, retracts a paper about angiotensin IV analogs as HGF/Met modifiers. Different members of a chemical family can have different pharmacological effects. Reports of antagonism by related analogs do not establish that dihexa itself alternates between agonism and antagonism. The retractions justify uncertainty about the relevant experiments, rather than a new claim about bidirectional dihexa pharmacology. Subsequent research provides a narrower observation. In APP/PS1 mice, investigators reported changes in PI3K/AKT signaling alongside behavioral, neuronal, and inflammatory measurements. Wortmannin, a PI3K inhibitor, reversed several reported effects. These findings support investigating PI3K/AKT involvement in that model, but they do not identify the upstream binding target. Many receptors influence PI3K/AKT. The authors also acknowledged the absence of a wortmannin-only control, which limits interpretation of the inhibitor experiment (PMID 34827486). The historical angiotensin IV receptor literature does not resolve this uncertainty. Evidence concerning an angiotensin IV binding site cannot automatically establish the binding profile of a chemically modified derivative. A parent peptide's mechanism, a downstream signaling change, and direct target engagement are different forms of evidence. Dihexa has also appeared in laboratory protocols for generating hepatic cells from human pluripotent stem cells. Those experiments involved multiple small molecules and cell differentiation endpoints. They do not establish cognitive effects, human tolerability, or selective HGF/c-Met activation by dihexa alone (PMID 35410439). The supported interpretation is that dihexa has reported biological activity in experimental systems. Its clinically relevant molecular mechanism remains unvalidated. Neither the proposed target nor the animal behavioral findings establish a therapeutic effect in people.

Grade C reflects animal findings without established clinical efficacy for dihexa. Results differ across models, and foundational studies carry an expression of concern or retraction. Human-derived cell experiments are laboratory evidence, not human clinical evidence. The grade describes the level of evidence and does not imply a favorable benefit-risk balance.

Human data. No published interventional clinical trial administering dihexa under the names dihexa or PNB-0408 was identified in the PubMed search performed for this review. This conclusion is narrower than saying that no human-associated data exist anywhere. Experiments using human pluripotent stem cells are published, including a hepatic differentiation study containing dihexa within a multicomponent laboratory protocol. Cells of human origin do not provide clinical tolerability, oral absorption, cognitive efficacy, or dosing evidence (PMID 35410439). Clinical findings from other investigational molecules cannot be imported as dihexa dosing instructions or definitive tests of its efficacy. Differences in chemical identity, formulation, metabolism, and exposure matter. For an adult seeking better learning, focus, or training performance, the central gap is direct evidence in the relevant population. No retrieved study establishes improvement in those outcomes after dihexa administration to people.

Animal and mechanistic data. The foundational characterization reported improvements in scopolamine-associated and age-associated rodent memory deficits, together with brain penetration and synaptogenic findings. That publication carries an expression of concern, which prevents treating its findings as an uncontested foundation (PMID 23055539; notice PMID 34551989). An APP/PS1 mouse study reported improved spatial learning and memory measurements, increased neuronal and synaptophysin measurements, and changes in inflammatory markers. The treatment period extended from six to nine months of age. Its Methods describe both intragastric and intraperitoneal administration, leaving the route internally inconsistent. Daily administration is explicit for the saline control, but the dihexa frequency is not stated equally clearly. These reporting limitations affect reproducibility (PMID 34827486). A sciatic nerve transection and repair study reported improved motor outcomes in a group receiving mesenchymal stromal cells and dihexa with gastrocnemius administration. Local and systemic treatment without gastrocnemius administration did not show the same motor benefit. The regimen included repeated administrations through postoperative day 10, with follow-up to 16 weeks. It was not a single-dose study. Muscle atrophy was not significantly mitigated by the treatments. A researcher from the original dihexa program was a coauthor, so this study should not be described as wholly independent replication (PMID 34703584). A separate study randomized 40 male rats in a 3-nitropropionic acid model of Huntington's disease-like impairment. PNB-0408 did not protect against the measured weight, motor, or cognitive deficits. This negative finding limits broad neuroprotection claims, although it does not prove ineffectiveness in every possible model (PMID 38489193). Together, these studies support continued experimental investigation. They do not establish a general memory-enhancing effect, prevention of neurodegeneration, or improved musculoskeletal recovery in humans.

REGULATORY STATUS AND SPORT

STATUS

Dihexa is an experimental compound, with no approved human therapeutic indication identified in the sources reviewed. No approved dihexa prescribing label or clinical label dose was identified. A chemical registry identifier, a research publication, or a laboratory product description does not establish marketing authorization. Research use labeling does not establish pharmaceutical manufacturing quality, clinical suitability, or permission to market a substance for treatment. Product identity, regulatory authorization, and permission to conduct clinical research are separate questions. The reviewed records do not support definitive worldwide claims about every manufacturer's GMP status, every country's scheduling rules, or confidential investigational applications. Legal status depends on jurisdiction, intended use, and the applicable regulatory framework.

WADA

Prohibited at all times for athletes subject to the WADA Code. Dihexa is not individually named in the 2026 list reviewed. Its non-approved pharmacological status brings it within S0 when it is not addressed by another prohibited category. S2.3 also covers HGF and certain growth factor modulators, so classification should not be presented as two automatically cumulative findings. The conclusion that dihexa is prohibited is an application of these category rules, not a quotation naming dihexa. Being absent from the alphabetical index does not establish permission. Source: [WADA 2026 Prohibited List, sections S0 and S2.3](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Published animal experiments describe oral gavage, intravenous administration, intraperitoneal administration, local hydrogel delivery, and gastrocnemius administration. These routes served different experimental purposes and are not interchangeable. The APP/PS1 report contains conflicting intragastric and intraperitoneal descriptions. Both dose entries below retain that ambiguity. The nerve-repair experiment used a multicomponent treatment design, so

its findings cannot be reduced to a general route preference for dihexa. Oral or topical use outside clinical research does not establish absorption, brain exposure, or tolerability in humans. No validated topical formulation or direct human administration route was identified. A solvent's ability to dissolve a compound does not validate delivery through skin or another route.

HALF-LIFE	No human half-life for direct dihexa administration was established by the retrieved evidence. The foundational rat paper reported a half-life of 12.68 days following intravenous administration and 8.83 days following intraperitoneal administration. These are reported animal estimates, not established human values. The paper carries an expression of concern (PMID 23055539; notice PMID 34551989). A circulating elimination estimate is different from the duration of a cognitive effect. Neither the animal values nor subjective reports establish a human dosing interval, accumulation profile, or duration of benefit. The integrity concern also limits confidence in the numerical estimates themselves.
TIMING	No human timing rule is established. The aged-rat experiment administered treatment five minutes before daily behavioral testing, which is an experimental design detail (PMID 23055539). It does not establish a rule about studying, meals, sleep, or training in people. The nerve-repair study tied treatment to surgery and postoperative days rather than cognitive tasks (PMID 34703584). These schedules addressed different biological questions. Their timing cannot be combined into a general dihexa protocol.
CYCLE LENGTH	No validated human cycle length exists. The APP/PS1 study used a three-month treatment period, with unresolved route and frequency reporting limitations (PMID 34827486). The nerve-repair study administered treatment through postoperative day 10 and assessed outcomes through 16 weeks (PMID 34703584). Follow-up duration is not exposure duration. Neither study was a comprehensive chronic toxicity assessment. Shorter administration or planned breaks do not have an established ability to reduce dihexa-associated risks. No retrieved clinical study validates an on/off schedule.
TITRATION	No human starting dose, escalation interval, ceiling, or exposure target is established. Animal efficacy doses are not human starting doses. Direct multiplication by human body weight ignores species differences in disposition and pharmacology. Body surface area scaling is only one component of some translational dose calculations. It does not establish tolerability or clinical suitability. A defensible clinical starting dose also requires appropriate toxicology, exposure measurements, formulation information, and uncertainty margins. The reported long rat half-lives add another unresolved issue: repeated exposure could behave differently from a single administration. Human accumulation cannot be calculated reliably from those animal estimates, particularly when the underlying publication carries an expression of concern.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved human prescribing label	No established label dose	No approved human route identified	No approved schedule identified	No approved dihexa prescribing label was identified. Animal experimental doses do not establish a clinical regimen.
Aged rat spatial-learning experiment, foundational publication carrying an expression of concern	2 mg/kg per administration, reported in PMID 23055539	Oral gavage	Once daily for eight testing days, five minutes before testing	Figure 5 of PMID 23055539 describes this regimen in aged rats. The publication carries expression of concern PMID 34551989. This is an animal experimental dose, not a human recommendation. · PMID 23055539
APP/PS1 transgenic mouse study, lower dose group	1.44 mg/kg per administration, reported in PMID 34827486	Unresolved reporting conflict: intragastric administration is described, but Methods also state intraperitoneal administration	Treatment from six to nine months of age. Daily frequency is explicit for the saline control, but not equally clear for dihexa.	PMID 34827486, Methods section 2.2 and Results section 3.1. The route inconsistency applies to the study, not only one dose group. · PMID 34827486
APP/PS1 transgenic mouse study, higher dose group	2.88 mg/kg per administration, reported in PMID 34827486	Unresolved reporting conflict: intragastric administration is described, but Methods also state intraperitoneal administration	Treatment from six to nine months of age. Daily frequency is explicit for the saline control, but not equally clear for dihexa.	PMID 34827486, Methods section 2.2 and Results section 3.1. The paper does not establish a maximum effective dose or a human exposure equivalent. · PMID 34827486
Rat sciatic nerve transection and repair study, local component	1 mg per rat, reported in PMID 34703584	Local hydrogel placement around the nerve repair site	Once on the day of surgery, postoperative day 0	PMID 34703584, Methods section describing dihexa administration. This local component accompanied additional interventions according to experimental group. · PMID 34703584
Rat sciatic nerve transection and repair study, systemic component	0.5 mg per rat per administration, reported in PMID 34703584	Intraperitoneal	Postoperative days 0, 4, 7, and 10	PMID 34703584, detailed Methods. · PMID 34703584

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Rat sciatic nerve transection and repair study, muscle component in applicable experimental groups	0.5 mg per rat per administration, reported in PMID 34703584	Intramuscular administration to the gastrocnemius	Postoperative days 0, 4, 7, and 10	PMID 34703584, detailed Methods. The reported motor benefit involved a treatment group also receiving mesenchymal stromal cells and other dihexa delivery components. · PMID 34703584

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.	– IGF-1 LR3 No verified combination study establishes benefit, compatibility, or dosing with dihexa. Potential overlap in growth-related signaling is a theoretical concern, not evidence of a measured additive cancer risk. Dihexa's uncertain target and absent clinical regimen prevent a defensible combination protocol.
	– Follistatin-344 No verified dihexa combination study was identified. A growth-related rationale does not establish complementary effects or predictable tolerability. The evidence does not support either a synergy claim or a numerical estimate of interaction risk.
	– TB-500 No verified combination evidence supports use with dihexa. Claims that this pairing is uniquely dangerous or has the least favorable cancer-risk profile were unsupported. Possible interaction through repair or vascular signaling remains speculative and cannot establish a ranked risk comparison.

SAFETY

COMMON EFFECTS	An established human adverse-event profile is unavailable. Consequently, no effect can reliably be classified as common, uncommon, or rare after direct dihexa administration. Reports of headache, sleep changes, irritability, or mood changes outside controlled research cannot establish causality or frequency. The identity of the material, concurrent exposures, baseline symptoms, and reporting biases may be unknown. Absence of published events is not evidence that an event cannot occur. Animal behavioral studies answer limited experimental questions. They do not replace systematic cardiovascular, neurological, reproductive, hepatic, renal, or long-term toxicity assessment.
SERIOUS SIGNALS	The principal mechanism-based concern involves HGF/c-Met signaling and cancer biology. Dysregulated MET signaling can support proliferation, invasion, angiogenesis, and treatment resistance in particular cancers. A retrieved review describes these functions and MET-targeted treatment research in non-small cell lung cancer (PMID 39201787). This biology supports a theoretical concern if dihexa meaningfully potentiates that pathway in relevant tissues. It does not demonstrate that dihexa causes cancer, accelerates every malignancy, or produces sustained MET activation in humans. Those compound-specific effects have not been established by the evidence reviewed. The retracted mechanism paper makes the causal chain more uncertain. Uncertainty cannot be converted into reassurance, but it also does not justify presenting tumor promotion as an observed adverse event. No retrieved study quantifies a dihexa-specific cancer risk. Other serious risks remain inadequately characterized. Limited animal efficacy experiments cannot establish the incidence of organ injury, seizures, psychiatric deterioration, hypersensitivity, or delayed toxicity in people. Formulation contaminants and solvents introduce additional uncertainties distinct from the molecule's pharmacology.
CONTRAINDICATIONS	There is no approved label defining formal dihexa contraindications. Active malignancy, a history of malignancy, or an unexplained mass would raise particular concern because of the proposed growth-factor mechanism. These are precautionary considerations, not validated dihexa-specific contraindications derived from clinical trials. Pregnancy, breastfeeding, and pediatric exposure lack an established clinical evidence base. Human renal or hepatic impairment has no validated dose adjustment. Concurrent treatment affecting growth-factor pathways introduces additional unknown interactions. WADA prohibition is an eligibility issue for tested athletes, separate from medical contraindications. No screening checklist establishes a population in which direct dihexa use has a demonstrated favorable benefit-risk balance.
STOP RULES	No validated symptom threshold, laboratory monitoring schedule, or stopping algorithm exists. New symptoms after exposure require clinical assessment rather than an assumption that they reflect adaptation. Seizure, sudden weakness, severe confusion, loss of consciousness, or difficulty breathing warrants emergency evaluation. A persistent new headache, visual change, unexplained lump, progressive neurological symptoms, or a substantial skin reaction warrants prompt assessment and avoidance of further exposure pending evaluation. These are general clinical precautions, not evidence that the listed events are established dihexa adverse effects. Symptom tracking cannot exclude silent toxicity or establish that continued exposure is appropriate.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No standardized, approved human presentation or concentration was identified. Laboratory powder and solution formats do not establish identity, purity, sterility, or suitability for administration. Packaging is not a chemical test. A freeze-dried presentation does not prove that a material is authentic, and it does not prove that the material is counterfeit. Lyophilization is a processing method that can be applied to different types of substances. A labeled quantity also differs from verified active content. Moisture, residual solvents, salts, and other material may affect the relationship between powder mass and actual compound content.

SOLVENT

The APP/PS1 mouse report describes a vehicle containing 10 percent DMSO, 40 percent PEG300, 5 percent Tween-80, and 45 percent saline. Its conflicting administration descriptions remain unresolved (PMID 34827486). The nerve-repair report describes DMSO-containing preparations with a final DMSO concentration no greater than 5 percent (PMID 34703584). These are descriptions of experimental vehicles, not validated human formulations. Neither a published animal vehicle nor apparent solubility establishes route compatibility, sterility, stability, or tolerability in people. Visual dissolution is not an identity assay. Solubility depends on concentration, temperature, chemical form, pH, and excipients. Cloudiness or a clear solution cannot determine whether a sample contains dihexa.

STORAGE

No validated human formulation shelf life, beyond-use date, or universal storage schedule was identified. Stability depends on chemical form, solvent composition, temperature, light, moisture, container compatibility, and repeated handling. Laboratory storage conditions require formulation-specific stability information. Refrigeration or freezing alone does not establish retained potency, prevent every degradation process, or provide sterility. A visually unchanged solution may still differ chemically from its initial state. DMSO is hygroscopic and can enhance skin penetration of some dissolved substances. It does not automatically transport every contaminant through intact skin. Laboratory containment and protective equipment depend on the complete formulation and its safety documentation. The solvent's handling properties do not establish a validated topical delivery system.

Concentration arithmetic can be illustrated without constructing an administration protocol. In a hypothetical analytical example, 10 mg of verified analyte in a final solution volume of 20 mL corresponds to 0.5 mg/mL. These are illustrative preparation quantities, not a study dose or a proposed human dose.

The calculation divides analyte mass by final solution volume. Adding a stated volume of solvent is not necessarily identical to making a solution up to that final volume. Actual concentration also depends on complete dissolution, analyte content, and measurement accuracy.

A calculated concentration does not validate a solvent or establish a dose. It does not demonstrate that the compound remains stable, that contaminants are absent, or that any administration route is appropriate. No syringe conversion or administration instructions are provided because the retrieved literature establishes no human dihexa regimen.

The separate animal dose entries retain their species, route limitations, schedule, and PMID provenance. Converting those entries into a human regimen would require evidence that concentration arithmetic cannot supply.

BUYING NOTES

No approved human product was identified. Assessment of research material therefore concerns analytical documentation, not evidence that the compound is appropriate for human administration. A research use label provides no clinical endorsement.

A useful certificate of analysis identifies the sample, batch, laboratory, test date, methods, and actual results. Traceability matters because a document may describe a different batch or a selectively submitted sample. A batch number on two documents does not independently verify that the contents match.

Chromatographic purity and chemical identity answer different questions. HPLC area percentage can describe the relative chromatographic signal under a particular method. It does not automatically establish absolute active content, the identity of every peak, or the absence of substances that the method detects poorly.

Mass spectrometry provides identity-related information, but molecular mass alone does not establish every structural feature or stereochemical configuration. Stronger identity assessment uses suitable orthogonal methods and an appropriate reference standard. The necessary methods depend on the chemical question being asked.

Residual solvents, elemental impurities, microbial contamination, and endotoxins require relevant tests. A purity result does not cover all these categories. A sterile claim is distinct from a chemical purity claim and requires its own supporting evidence.

Independent laboratory work may improve confidence, but independence alone does not validate an unsuitable method or an untraceable sample. Internally generated testing is not automatically meaningless either. The useful distinction is between documented, fit-for-purpose analysis and unsupported claims.

A clear liquid, powder color, package type, or dissolution behavior cannot authenticate dihexa. Solutions add questions about concentration, vehicle, container interactions, and stability. Powder also requires identity and content verification, so neither format eliminates analytical uncertainty.

Even an authenticated sample leaves the central clinical gaps unresolved. Identity testing cannot establish human efficacy, a dosing schedule, interaction compatibility, or long-term tolerability. A COA answers questions about the tested sample, not whether the proposed application is supported.

COMMON MISTAKES

- Treating the HGF/c-Met account as experimentally settled. The principal mechanism paper was retracted. PMID 25187433 is retained only as historical identification, with its retraction documented by PMID 40312093.
- Describing the foundational characterization as unqualified supporting evidence because it is not marked retracted. It carries expression of concern PMID 34551989. Its correct publication year is 2013, with electronic publication in 2012.
- Claiming that no numeric half-life has been published. Rat estimates were reported in PMID 23055539, but the publication carries an expression of concern. Those values do not establish human elimination or duration of cognitive effects.
- Calling the nerve-repair experiment a single perioperative exposure. Its detailed Methods include repeated systemic or muscle administrations through postoperative day 10. Sixteen weeks describes follow-up, not continuous treatment (PMID 34703584).
- Treating the nerve-repair result as evidence for dihexa alone or for a dihexa and BPC-157 combination. The beneficial group involved mesenchymal stromal cells and a specific delivery design. BPC-157 was not the cellular intervention (PMID 34703584).
- Reporting oral administration as certain for one APP/PS1 dose while flagging ambiguity only for the other. The conflicting intragastric and intraperitoneal descriptions affect both groups. The dihexa frequency is also less explicit than the saline control schedule (PMID 34827486).
- Assuming that distinct proposed targets establish a useful or compatible stack. No verified dihexa synergy supports the previous semax, selank, cerebrolysin, or BPC-157 entries. Absence of an identified interaction is not evidence of compatibility.
- Converting an animal efficacy dose into a personal regimen using body weight or a scaling factor. Species conversion does not replace toxicology, exposure measurements, formulation assessment, or a clinical trial.
- Omitting the negative Huntington's disease-like rat experiment. PNB-0408 did not protect against the measured deficits in that model. Positive results elsewhere do not erase this finding (PMID 38489193).
- Interpreting human-derived cell experiments as clinical evidence. The hepatic differentiation study used laboratory cell systems and multicomponent treatments. It did not establish cognitive benefit or tolerability after administration to people (PMID 35410439).
- Treating a theoretical cancer concern as either a demonstrated adverse event or an irrelevant speculation. HGF/c-Met cancer biology is established, while the magnitude and direction of dihexa-specific human effects remain unresolved.
- Treating packaging, water solubility, or a research label as authentication. These observations do not establish chemical identity, active content, sterility, or clinical suitability.
- Assuming that absence from WADA's named examples establishes permission. Prohibited categories include substances that are not individually listed.

REFERENCES

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3. Benoist CC et al. The procognitive and synaptogenic effects of angiotensin IV-derived peptides are dependent on activation of the hepatocyte growth factor/c-met system.. *The Journal of pharmacology and experimental therapeutics*, 2014. PMID 25187433 DOI 10.1124/jpet.114.218735 (Retracted publication. Retained solely to identify the historical source of the HGF/c-Met mechanism claim. It is not counted as reliable supporting evidence for target engagement or efficacy.)
4. Benoist CC et al. Retraction notice to "The Procognitive and Synaptogenic Effects of Angiotensin IV-Derived Peptides Are Dependent on Activation of the Hepatocyte Growth Factor/c-Met System" [*J Pharmacol Exp Ther* 351 (2014) 390-402].. *The Journal of pharmacology and experimental therapeutics*, 2025. PMID 40312093 DOI 10.1016/j.jpet.2025.103567 (Documents the April 2025 retraction of PMID 25187433.)
5. Kawas LH et al. Retraction notice to "Development of Angiotensin IV Analogs as Hepatocyte Growth Factor/Met Modifiers" [*J Pharmacol Exp Ther* 340 (2012) 539-548].. *The Journal of pharmacology and experimental therapeutics*, 2025. PMID 40312092 DOI 10.1016/j.jpet.2025.103566 (Documents a related angiotensin IV analog paper's retraction. It does not establish that dihexa itself has opposite effects on HGF/c-Met signaling.)
6. Sun X et al. AngIV-Analog Dihexa Rescues Cognitive Impairment and Recovers Memory in the APP/PS1 Mouse via the PI3K/AKT Signaling Pathway.. *Brain sciences*, 2021. PMID 34827486 DOI 10.3390/brainsci11111487 (APP/PS1 mouse behavioral and molecular findings, dose groups, three-

month treatment period, experimental vehicle, and PI3K inhibitor experiments. Full-text review identified conflicting route descriptions and incomplete dihexa frequency reporting.)

7. Weiss JB et al. Stem cell, Granulocyte-Colony Stimulating Factor and/or Dihexa to promote limb function recovery in a rat sciatic nerve damage-repair model: Experimental animal studies.. *Annals of medicine and surgery* (2012), 2021. PMID 34703584 DOI 10.1016/j.amsu.2021.102917 (Rat nerve-repair treatment design, route-specific doses and repeated schedule in detailed Methods, motor findings with cellular therapy and muscle administration, and failure to mitigate muscle atrophy. The study includes an investigator from the original dihexa program.)
8. Wells RG et al. Effects of an Angiotensin IV Analog on 3-Nitropropionic Acid-Induced Huntington's Disease-Like Symptoms in Rats.. *Journal of Huntington's disease*, 2024. PMID 38489193 DOI 10.3233/JHD-231507 (Negative weight, motor, and cognitive findings in a toxin-induced rat model. Confirms PNB-0408 as an alternative name for dihexa.)
9. Pan T et al. Efficiently generate functional hepatic cells from human pluripotent stem cells by complete small-molecule strategy.. *Stem cell research & therapy*, 2022. PMID 35410439 DOI 10.1186/s13287-022-02831-1 (Laboratory use of dihexa within a multicomponent hepatic differentiation protocol involving human pluripotent stem cells. Supports distinguishing human-derived cell evidence from clinical evidence.)
10. Yao S et al. Unveiling the Role of HGF/c-Met Signaling in Non-Small Cell Lung Cancer Tumor Microenvironment.. *International journal of molecular sciences*, 2024. PMID 39201787 DOI 10.3390/ijms25169101 (General HGF/c-Met involvement in cancer-cell proliferation, invasion, angiogenesis, and tumor biology. Provides mechanistic context, not evidence of dihexa-specific carcinogenicity.)

Cerebrolysin

Porcine brain-derived peptide mixture

Module 4 · Mind & Longevity

Goals: Nootropics

Route: IM or IV

A porcine brain hydrolysate with substantial but mixed neurological trial evidence, limited exploratory healthy-volunteer data, and no established cognitive enhancement protocol for healthy adults who train.

WHAT IT IS

Cerebrolysin is a mixture of low molecular weight peptides and amino acids produced by enzymatic breakdown of porcine brain proteins. It is not a single, sequence-defined peptide. Its composition and production process distinguish it from synthetic research peptides with one identifiable active molecule (PMIDs 9700665 and 32662068).

Clinical studies generally describe the administered volume in mL. That convention does not mean the preparation contains no measurable mass. It means a mass of the mixture cannot be interpreted as a dose of one pharmacologically defined peptide. Likewise, an amount expressed in insulin syringe units would describe an instrument scale, not biological activity.

The main human research concerns acute stroke, stroke rehabilitation, dementia and traumatic brain injury. These populations have established neurological disease or injury. Their outcomes cannot directly establish improved concentration, memory, training recovery or longevity in otherwise healthy adults.

Some exploratory healthy-volunteer research exists. A randomized infusion study examined EEG and short-term memory, and a separate oral study examined healthy older adults (PMIDs 9700674 and 10961443). Neither establishes a practical enhancement protocol for the population reading this guide. The relevant distinction is between evidence that a preparation changes a laboratory or clinical measure and evidence that it produces a meaningful, durable benefit for a particular person.

MECHANISM

Cerebrolysin has shown neurotrophic and neuroprotective activity in experimental systems. A review describes growth-promoting effects in neuronal cultures and activity resembling naturally occurring neurotrophic factors (PMID 9700665). These observations support a broad experimental description. They do not identify one active constituent, receptor affinity or clinically validated target engagement profile. The preparation is often described as a neurotrophic mimetic. Calling it weak is unsupported because there is no single receptor assay or potency comparison that defines the mixture that way. Similarly, small fragment size alone does not establish which constituents reach the human brain, at what concentrations, or for how long. A rat stroke study implicated Sonic hedgehog signaling. Cerebrolysin increased neural progenitor proliferation and differentiation into neurons and oligodendrocytes. Cyclopamine, a smoothened inhibitor, blocked reported cellular effects and functional recovery (PMID 23696546). This pharmacological intervention supports pathway involvement within that experimental model. It does not establish that the same pathway explains clinical benefit in humans. The paper has a published correction, which is recorded separately in the references (PMID 39869713). The correction's detailed content was unavailable during verification, so its significance is not inferred here. Another rat stroke study reported enhanced neurogenesis and functional recovery. Blocking PI3K/Akt prevented the increase in cultured progenitor-cell proliferation (PMID 20857512). The cellular inhibition experiment should not be described as proving that blocking this pathway eliminated every in vivo benefit. These papers also share investigators, so they do not establish replication across independent laboratories. In an amyloid precursor protein transgenic mouse model, Cerebrolysin altered APP processing and reduced amyloid burden. Changes were associated with reduced active CDK5 and GSK-3 beta, while several measured amyloid-processing enzymes remained unchanged (PMID 16511867). This is a proposed explanation in a disease model, not evidence of amyloid clearance or dementia prevention in healthy humans. The cited mouse tau paper now carries an editorial expression of concern (PMIDs 19252918 and 41817815). It remains in the bibliography to document the evidence-quality issue, but it is not used as affirmative support for tau protection. An expression of concern is distinct from a retraction. A small translational liver study reported changes in liver enzymes and selected animal outcomes (PMID 36362945). It does not establish protection against fibrosis or exclude harm from prolonged exposure. Broad pathway activity can motivate research into benefits and harms, but it cannot determine either without appropriate clinical evidence.

EVIDENCE · GRADE C

Grade C applies specifically to cognitive enhancement, brain protection and longevity claims in healthy adults who train. It does not mean Cerebrolysin has only animal research. The preparation has national medicinal authorization and multiple human randomized trials, meeting the catalog's A criterion for clinical development in disease settings. That classification does not guarantee efficacy for a particular indication. Stroke studies report conflicting results across mortality, rehabilitation and adverse-event outcomes. Dementia findings are limited by bias, heterogeneity and uncertain clinical importance. Healthy-volunteer studies are exploratory and too weak to support a practical enhancement claim.

Human data. Acute stroke: the 2020 Cochrane review included seven trials and 1601 participants. Mortality data from six trials showed little or no difference, RR 0.90, 95% CI 0.61 to 1.32. Nonfatal serious adverse events were more frequent, RR 2.15, 95% CI 1.01 to 4.55 (PMID 32662068). The 2023 update again found little or no mortality benefit. Its overall mortality analysis included another brain-derived preparation, so the pooled population must not be described as exclusively Cerebrolysin-treated. Its Cerebrolysin serious-event analysis found RR 2.39 for nonfatal serious adverse events, 95% CI 1.10 to 5.23. Three trials contributed 1335 participants to that analysis (PMID 37818733). Neither review supplies a complete assessment of every rehabilitation endpoint studied elsewhere. CASTA randomized 1070 patients within 12 hours of stroke onset. Its confirmatory combined endpoint was neutral. A favorable trend in more severely affected patients came from a post hoc analysis and required confirmation (PMID 22282884). CARS examined rehabilitation and reported better arm motor function at day 90, with a Mann-Whitney estimator of 0.71. The authors characterized it as exploratory and called for larger confirmation (PMID 26564102). These trials differed in population, treatment timing, duration and endpoints. The 2025 ESCAS pilot enrolled 132 patients with poststroke nonfluent aphasia; 123 entered the intention-to-treat analysis. Cerebrolysin added to speech therapy produced greater improvement in language scores. The between-group difference in the reported language-score change was 14.805 points, 95% CI 9.521 to 20.089. This is a condition-specific finding requiring larger studies, not evidence for improved language performance in healthy people (PMID 39957612). Vascular dementia: the Cochrane review included six trials and 597 participants. Pooled cognition favored treatment, SMD 0.36, while global response favored treatment, RR 2.69. Both findings had very low-certainty evidence. Funding information was available for three studies, all industry-supported. The review warned that any benefit might be too small to matter clinically (PMID 31710397). Alzheimer disease: a 279-patient trial reported different results across assigned dose groups, without a simple higher-dose advantage (PMID 16420392). A six-trial meta-analysis found a cognitive benefit at four weeks. Its six-month cognitive estimate was not statistically significant, although global clinical ratings favored treatment at both assessments (PMID 25832905). Improvement in a rating scale does not establish disease modification. Traumatic brain injury: CAPTAIN II enrolled 142 patients and analyzed 139. Its combined endpoint across 13 scales favored treatment at day 90, with a small-to-medium reported effect. It was a single-center trial in moderate to severe injury, not a study of concussion self-treatment or athletic recovery (PMID 31897941). Healthy volunteers: a randomized study in 48 men reported EEG changes and exploratory short-term memory findings after repeated infusions (PMID 9700674). A separate study reported EEG and memory changes after oral administration in healthy older adults. Its abstract emphasizes comparisons with baseline and does not establish a robust placebo-controlled enhancement effect (PMID 10961443). Therefore, the earlier claims that only one healthy-human study exists and that no oral human data exist are incorrect.

Animal and mechanistic data. A randomized, blinded rat stroke study reported improved neurological outcomes in several treatment groups. One group also had reduced lesion volume. Differences between the groups showing functional benefit were not statistically significant, which limits claims of a precisely established dose-response curve (PMID 26763925). A separate randomized, blinded study in rats with moderate closed head injury reported better cognitive and sensorimotor outcomes over three months. Histological findings included less axonal injury, reduced APP accumulation and changes consistent with neuroplasticity (PMID 31491768). The verified animal regimen appears in reported_doses with its actual route and schedule. The neurogenesis studies provide mechanistic context for these findings, including progenitor proliferation, migration and differentiation (PMIDs 20857512 and 23696546). Histological changes, laboratory behavior and human daily function remain different outcomes. Animal experiments justify investigating possible effects. They do not establish an appropriate human volume, a treatment interval for healthy adults or protection from future neurodegeneration. Positive patient trials also exist, so describing all translation to human function as having failed would overstate the negative conclusion.

STATUS

Cerebrolysin has Austrian prescription authorization for specified neurological conditions. The authorization does not establish an indication for healthy-adult cognitive enhancement. The verified national document is the Austrian Cerebrolysin Summary of Product Characteristics, March 2021, authorization 1-21380. [Austrian regulatory document](https://medikamente.basg.gv.at/documents/1-21380__DOTC_FACH_INFO.pdf). Cerebrolysin is not FDA-approved. The product's prescribing-information page explicitly states that it is not approved for sale or distribution in the United States. [Prescribing information and United States status](<https://www.cerebrolysin.com/cerebrolysin/about-cerebrolysin>). Authorization, prescribing requirements and import rules are jurisdiction-specific. A foreign prescription or national authorization does not itself establish legal availability in another country.

WADA

Cerebrolysin is not named in the 2026 WADA Prohibited List. Absence from the named examples is not a definitive clearance. S2 includes growth factors, modulators and substances with similar biological effects. National medicinal authorization is relevant to S0, but it does not independently settle every other category. A compound-specific classification was not verified. M2.2 prohibits intravenous infusions or injections totaling more than 100 mL per 12-hour period, except during qualifying hospital treatments, surgical procedures or clinical diagnostic investigations. This restriction concerns total administered fluid, including diluent. A prescription or attendance at an outpatient infusion clinic does not automatically establish an exception. The athlete's anti-doping organization determines applicable classification and therapeutic use exemption requirements. [2026 WADA Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Intravenous infusion is documented in CASTA, the Alzheimer dose-finding trial and the healthy-volunteer infusion study (PMIDs 22282884, 16420392 and 9700674). CARS also used intravenous infusion, as confirmed by its trial registry. Intramuscular administration appears in Austrian product information, but it is not interchangeable with the infusion protocols summarized here. Oral administration was investigated in an exploratory study of healthy older adults (PMID 10961443). This establishes that an oral human report exists. It does not establish oral bioavailability of specific active constituents, equivalence to infusion, or an approved oral formulation. Intraperitoneal administration in the animal entry belongs to the rat experiment alone. Route is part of the evidence, not an interchangeable delivery preference.

HALF-LIFE

No validated single elimination half-life for the complete mixture was established by the sources reviewed. A mixture-wide clinical effect cannot be assigned the half-life of an unspecified component. A vascular dementia pilot extension followed 33 of 41 participants from its initial randomized phase. The open-label extension reported persistence of selected cognitive and qEEG findings for 12 weeks after treatment ended (PMID 20923712). This does not mean the preparation remained in circulation for that period. Pharmacokinetics describes exposure over time. A later difference in a clinical or EEG measure describes a pharmacodynamic or clinical observation. These are different questions. Persistence after treatment neither establishes an optimal retreatment interval nor demonstrates that repeated courses produce cumulative benefit.

TIMING

The reviewed trials do not establish that morning administration is superior to evening administration. Disease studies often specified time from injury. CASTA enrolled within 12 hours of stroke onset, while CARS began treatment 24 to 72 hours after onset (PMIDs 22282884 and 26564102). These windows reflect different hypotheses about acute treatment and rehabilitation. They do not identify a preferred time relative to exercise, meals or sleep. The healthy-volunteer infusion study measured EEG at several intervals after administration (PMID 9700674). The oral report also tracked changes over several hours (PMID 10961443). A peak in an exploratory physiological measure does not establish the best time for studying, training or performing a cognitive task.

CYCLE LENGTH

Treatment courses varied with the research question. CASTA studied a 10-day course; CARS studied 21 days alongside rehabilitation (PMIDs 22282884 and 26564102). The Alzheimer dose-finding study used four weeks of more frequent treatment followed by eight weeks of less frequent treatment (PMID 16420392). CAPTAIN II investigated an initial course followed by additional courses during recovery from moderate to severe traumatic brain injury (PMID 31897941). That design is evidence of what investigators tested. It does not establish the necessity or benefit of cycling in healthy people. The vascular dementia extension documented selected findings after treatment cessation, but its open-label follow-up and small sample limit interpretation (PMID 20923712). None of these studies establishes an annual enhancement schedule, an optimal washout period or the consequences of repeated courses over many years.

TITRATION

The dose-comparison trials assigned participants to specified groups. They do not provide a validated individualized titration algorithm for healthy adults. In the Alzheimer trial, the lowest-dose group achieved statistically significant cognitive improvement versus placebo, while higher-dose groups did not (PMID 16420392). Different significance results against placebo do not automatically prove a statistically significant difference between active groups. The authors described the pattern as consistent with a reversed U-shaped relationship. The healthy-volunteer trial also did not show a simple relationship between greater administered volume and better outcomes (PMID 9700674). EEG changes and adverse effects varied across groups. These observations argue against assuming that more preparation produces more benefit, but they do not identify a personal target dose. The rat stroke experiment used a different species, injury model and exposure scale (PMID 26763925). Its results cannot resolve the human titration question or supply a missing healthy-adult protocol.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
CASTA, acute ischemic stroke, treatment initiated within 12 hours of symptom onset in addition to standard treatment.	30 mL by intravenous infusion once daily for 10 days, as reported in CASTA, PMID 22282884.	Intravenous infusion.	Once daily for 10 consecutive days, PMID 22282884.	Heiss WD, Stroke, 2012. Randomized trial with 1070 participants. The confirmatory endpoint was neutral. This is a studied disease regimen, not an enhancement recommendation. · PMID 22282884
CARS, early stroke rehabilitation with a standardized rehabilitation program, initiated 24 to 72 hours after stroke.	30 mL by intravenous infusion once daily for 21 days, as reported in CARS, PMID 26564102.	Intravenous infusion, confirmed by trial registration 2007-000870-21.	Once daily for 21 consecutive days, PMID 26564102.	Muresanu DF, Stroke, 2016. Exploratory randomized trial reporting improved arm motor function. The publication year is 2016; online publication occurred in 2015. · PMID 26564102
Mild to moderate Alzheimer disease, randomized comparison of three assigned dose groups and placebo.	10 mL, 30 mL or 60 mL by intravenous infusion, five times weekly for four weeks, then twice weekly for eight weeks, PMID 16420392.	Intravenous infusion.	Five infusions weekly for four weeks, then two weekly for eight weeks, PMID 16420392.	Alvarez XA, European journal of neurology, 2006. The lowest-dose group showed significant cognitive and global improvements versus placebo at week 24. The higher-dose groups showed significant global improvement but not significant cognitive improvement. · PMID 16420392
Exploratory randomized study in 48 healthy men, examining EEG and short-term memory under baseline and hyperventilation conditions.	10 mL, 30 mL or 50 mL by intravenous infusion once daily for 10 days, PMID 9700674.	Intravenous infusion in saline.	Once daily for 10 days, PMID 9700674.	Funke M, Journal of neural transmission. Supplementum, 1998. Exploratory physiological and memory findings do not establish durable enhancement. The highest-dose group had a small significant blood-pressure reduction and symptoms the authors described as signs of overdosage. · PMID 9700674
Exploratory study of EEG and cognitive performance in healthy older adults.	30 mL orally as a single administration, PMID 10961443.	Oral administration of the solution studied.	One administration, with observations over the following hours, PMID 10961443.	Alvarez XA, Journal of neural transmission. Supplementum, 2000. The abstract reports changes from baseline. It does not establish an oral treatment course, long-term efficacy or equivalence to intravenous administration. · PMID 10961443
Animal experiment in male rats with moderate closed head injury, beginning four hours after injury.	2.5 mL/kg intraperitoneally once daily for 10 days, PMID 31491768.	Intraperitoneal injection in rats.	Once daily for 10 consecutive days, PMID 31491768.	Zhang Y, Journal of neurosurgery, 2020. Randomized, blinded experiment with 13 rats in each treatment group. This species-specific regimen does not establish a human dose. · PMID 31491768

STACKING

No combination is documented for this compound in the sources cited.
Use the avoid list and the protocol that includes it as the guide.

– Dihexa

No controlled human Cerebrolysin combination study was identified in the reviewed evidence. Claims of complementary growth-factor signaling do not establish additive benefit or quantify a proliferation hazard. Multiple experimental exposures would complicate attribution of neurological changes and adverse events. This is an evidence gap, not a demonstrated interaction.

– IGF-1 LR3

No verified clinical evidence supports the combination. IGF-1 analogues are prohibited under WADA S2.3. Adding another agent would not resolve uncertainty about Cerebrolysin's own benefit, exposure or adverse-event profile.

– FOXO4-DRI

No verified combination evidence establishes compatibility, benefit or harm. Describing senolysis and neuronal

protection as automatically opposed oversimplifies their different cell populations and experimental contexts. Neither a mechanistic argument nor a lack of published interaction reports can establish a useful or tolerable combination.

SAFETY

COMMON EFFECTS	Reported symptoms include warmth, sweating, dizziness, agitation and gastrointestinal complaints. Some reports are associated with rapid administration. These should not all be labeled common: frequency differs by symptom and evidence source. In the healthy-volunteer trial, 50 mL intravenously once daily for 10 days produced a small significant blood-pressure reduction, PMID 9700674. The investigators also reported symptoms they described as signs of overdosage at that exposure. Their description of events as mild in this small study cannot establish the risk of uncommon reactions or repeated courses. The 2020 Cochrane review found little or no difference in participants reporting any adverse event, RR 0.97, 95% CI 0.85 to 1.10. Certainty for that outcome was low (PMID 32662068). Similar overall event counts can coexist with differences in serious-event categories. An aggregate adverse-event result should therefore not be used to dismiss the separate nonfatal serious-event signal.
SERIOUS SIGNALS	The 2023 Cochrane update found a potential increase in nonfatal serious adverse events with Cerebrolysin, RR 2.39, 95% CI 1.10 to 5.23. The total serious-event estimate was RR 1.16, 95% CI 0.81 to 1.66, with moderate-certainty evidence (PMID 37818733). For 30 mL intravenously once daily for 10 days, the updated review reported nonfatal serious-event RR 2.87, 95% CI 1.24 to 6.69, PMID 37818733. This subgroup contained two trials and 1189 participants. It does not prove that alternative schedules avoid the risk, and it does not establish a precise causal dose-response relationship. A separate 2021 synthesis pooled 12 randomized trials and 2202 participants and found no statistically significant differences across its principal safety comparisons (PMID 34959697). Differences in eligibility, included populations, event definitions and available data can produce different pooled estimates. Statistical nonsignificance is not proof that meaningful harm has been excluded. Hypersensitivity, including severe reactions, is another relevant concern. Procedural complications from intravenous access are additional risks and are not identical to pharmacological adverse effects.
CONTRAINDICATIONS	The Austrian label lists hypersensitivity, status epilepticus and severe renal impairment as contraindications. Other seizure disorders require caution. It also warns about additive effects with antidepressants and monoamine oxidase inhibitors. Pregnancy and breastfeeding require individualized clinical assessment under the applicable label. Medication review includes prescribed treatments, nonprescription preparations and previous reactions. The absence of a listed interaction does not mean an experimental combination has been studied. A history of reactions to porcine-derived medicinal products is relevant to assessment. A food-allergy label alone does not establish the mechanism or probability of a reaction to this preparation. The small liver study reported improvement in AST in many observed patients but did not establish protection against progressive liver disease (PMID 36362945). It also did not demonstrate that every animal outcome improved. Its findings cannot provide a general clearance for established liver disease or prolonged exposure.
STOP RULES	During clinical administration, suspected anaphylaxis, breathing difficulty, collapse, seizure, chest pain or symptomatic hypotension warrants immediate cessation and urgent medical assessment. These are general emergency criteria, not a validated Cerebrolysin-specific stopping algorithm. Persistent fever, progressive local inflammation or new neurological deterioration also requires prompt assessment. In someone recovering from stroke or traumatic brain injury, deterioration may reflect the underlying disease rather than a drug reaction. Assuming that symptoms are only an infusion-rate problem could delay appropriate evaluation. Clinical studies involved monitoring and access to medical care. Their adverse-event findings cannot be assumed to describe unsupervised administration, where recognition and treatment of complications differ.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	Cerebrolysin is a finished liquid preparation, not a powder requiring reconstitution. Austrian labeling includes ampoules and puncturable vials. Container volume is a packaging characteristic, not a recommended dose. Several containers can hold the same preparation, and the same container format can be imitated. Packaging alone cannot establish identity, sterility, storage history or equivalence to material used in clinical trials. A powder marketed under the same name should not be assumed equivalent to the studied liquid formulation. That is an equivalence problem, not a conclusion that can be settled solely by appearance or price. The relevant documentary questions concern the actual formulation, authorization, batch and chain of custody.
SOLVENT	Reconstitution does not apply to the finished liquid. Dilution for a studied intravenous infusion is a separate operation. The CARS registry documents saline dilution to a specified final infusion volume. The Austrian label identifies incompatibilities, including balanced amino-acid infusions and lipid-containing solutions. Physical compatibility is distinct from whether coadministration has clinical evidence. A clear-looking mixture is not proof of chemical stability, retained activity or sterility. Evidence from one clinical protocol does not establish a universal dilution method for every container, jurisdiction or clinical setting.
STORAGE	The Austrian label specifies storage at no more than 25 degrees Celsius, protected from light, without refrigeration or freezing. Containers are for one-time withdrawal; unused contents are discarded immediately. These conditions apply to the labeled medicinal presentation. They should not be extended to an unidentified preparation or an altered formulation. A printed expiry also presumes the required storage conditions and intact packaging. Chemical compatibility data for a diluted solution do not independently establish that it remains microbiologically suitable for later administration. Handling after opening or dilution depends on the applicable product information and the controlled clinical preparation process.

The CARS trial registry provides a documented example of volume accounting. Participants received 30 mL of Cerebrolysin intravenously once daily for 21 days, PMID 26564102 and registration 2007-000870-21. The registry specifies 70 mL of saline as diluent, producing 100 mL of final infusion solution. Thus, 30 mL of drug preparation plus 70 mL of diluent equaled 100 mL total. This describes the registered study procedure. [CARS trial registry results](https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000870-21/results). The distinction between diluent volume and final volume matters when reading a protocol. A statement that treatment was delivered in a given volume does not automatically mean that this volume was added to the drug. The arithmetic describes preparation volume only. It does not determine active-peptide concentration in the brain, biological potency, therapeutic equivalence or an infusion rate. It also does not establish that the protocol is appropriate for another population. They did not help verify the trial dose and converted a literature summary into procedural instructions.

BUYING NOTES

Cerebrolysin requires a formulation-specific quality assessment. A generic claim of peptide purity does not establish equivalence to the medicinal mixture used in clinical trials. A validated analytical fingerprint can help characterize a mixture when compared with appropriate specifications. A certificate of analysis is only as informative as its methods, reference standards, tested attributes and connection to the actual batch. A percentage alone does not establish composition, potency, sterility, endotoxin control or suitability for clinical use. Even an authentic laboratory report may address only the sample submitted to that laboratory. Batch identification, authorization details, intact packaging, expiry and documented distribution history are complementary evidence. They are not a visual authenticity test. Legitimate labeling can include puncturable vials, while counterfeit material can imitate ampoules and cartons. Animal-source controls and manufacturing consistency matter for a tissue-derived preparation. Their adequacy cannot be inferred from a label photograph, an advertised purity figure or a vendor's assertion that material is pharmaceutical grade. Conversely, the available sources do not establish that counterfeiting is more frequent than every other quality problem. The central question is whether the preparation and its documented quality correspond to the formulation studied and authorized. Clinical evidence does not transfer automatically to another hydrolysate, powder, compounded formulation or product using a similar name. This section describes verification limits and does not identify a supplier or purchasing route.

COMMON MISTAKES

- Calling Cerebrolysin a single peptide. It contains peptides and amino acids, but its clinical evidence concerns a mixture produced by a defined manufacturing process.
- Treating a reported volume as a personal dose recommendation. Population, route, frequency, duration and clinical context belong to the same study regimen.
- Assuming that the absence of a single active molecule makes mass measurements meaningless. Mixture mass can be measured without establishing the activity of individual constituents.
- Describing the 1998 infusion study as the entire healthy-human evidence base. An exploratory oral study in healthy older adults also exists, but neither establishes durable enhancement.
- Assuming that a lower-dose group beating placebo proves it beat every higher-dose group. A direct comparison between active groups requires its own statistical evidence.
- Equating EEG changes, increased neurogenesis or altered mouse amyloid markers with improved real-world cognition, recovery or longevity.
- Treating similar overall adverse-event rates as proof that nonfatal serious adverse events are unchanged. These are different outcomes.
- Using the tau paper without its expression of concern, or describing that notice as a retraction. Publication-status notices must be read with the original research.
- Confusing the amount of diluent with the final infusion volume.
- Assuming that an unlisted substance is cleared for sport. Substance classification and restrictions on the administration method are separate questions.
- Treating an ampoule, vial, certificate or familiar name as sufficient evidence of identity and quality. None establishes equivalence to the studied preparation by itself.

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DSIP

Delta sleep-inducing peptide

Nonapeptide

Module 4 · Mind & Longevity

Goals: Sleep

Route: SC or intranasal

A nonapeptide from early sleep research with inconsistent human insomnia findings, an unresolved biological target, and no established regimen for sleep or recovery.

WHAT IT IS

DSIP means delta sleep-inducing peptide. It is a linear nonapeptide with the sequence Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu and molecular weight approximately 849 daltons. A historical review dates its isolation from rabbit cerebral venous blood to 1977, by the Schoenenberger-Monnier group (PMID 16539679, PMID 6145137).

The name reflects an early experimental hypothesis about slow wave sleep. It does not establish that administered DSIP reliably increases restorative sleep in humans. Positive laboratory studies exist, but independent controlled insomnia studies found little clinically meaningful benefit (PMID 1299794, PMID 3583493).

The reviewed literature does not establish an endogenous precursor or a specific DSIP receptor. The 2006 review identifies these uncertainties explicitly. This is a limitation of the proposed biology, not proof that a synthetic peptide cannot have pharmacological effects (PMID 16539679).

Another distinction concerns DSIP-like immunoreactivity. This measures material recognized by an antibody, which need not consist exclusively of intact DSIP. Results from immunoassays, synthetic peptide administration, modified analogues and fusion proteins answer different questions. They should not be treated as interchangeable evidence for a single sleep mechanism.

MECHANISM

Direct target identification remains incomplete. In rat neurons, DSIP enhanced GABA-activated currents and altered NMDA-related responses. Changes in calcium uptake into cortical synaptosomes also suggested presynaptic effects. These findings support possible modulation of inhibitory and excitatory signaling, but do not establish a selective human receptor mechanism (PMID 17369935).

A rat immobilization experiment found reduced stress-induced c-Fos expression in part of the hypothalamic paraventricular nucleus. Dizocilpine and cycloheximide prevented this effect in different stress-resistance groups. The results implicate NMDA-related signaling and protein synthesis, without demonstrating direct NMDA antagonism or a human anxiolytic effect (PMID 22094385).

Animal experiments also support an indirect opioid-related pathway. Centrally administered DSIP produced antinociception that naloxone blocked, and the effect was absent in morphine-tolerant mice (PMID 2853064). A separate study found no binding to the opioid receptor subtypes tested. It instead demonstrated calcium-dependent release of immunoreactive Met-enkephalin from rat brainstem slices (PMID 2706459). Spinal adrenergic antagonists reduced antinociception in another mouse experiment, suggesting involvement of descending noradrenergic pathways (PMID 2713670). These experiments do not establish analgesic efficacy or predictable opioid interactions in humans.

Brain entry is supported by animal research. A radiolabeled DSIP derivative crossed rat blood-brain and dog blood-CSF barriers through an apparently noncompetitive process (PMID 6547363). Dog experiments linked CSF entry of DSIP and analogues to plasma exposure, half-life and lipophilicity (PMID 3768731). Earlier dog work identified reversible protein binding and suggested that free peptide crossed the barrier (PMID 6897451). These findings cannot quantify intact DSIP exposure in the human brain after subcutaneous or intranasal administration.

Human biomarker studies complicate a simple sleep-hormone explanation. Plasma DSIP-like immunoreactivity peaked in the afternoon and was lower during REM and slow wave sleep in one study (PMID 8175965). Another found a decline at sleep initiation during both evening sleep and morning recovery sleep (PMID 8745061). Neither establishes whether administering DSIP improves sleep. Circulating immunoreactivity may differ from local brain signaling and may include related molecules.

GILZ, also called the DSIP immunoreactor, has been discussed in circadian and metabolic research. That terminology does not identify GILZ as the precursor of DSIP or invalidate every older immunoassay result (PMID 19849801).

Some animal experiments describe nonmonotonic responses, meaning higher exposure did not consistently produce greater effects (PMID 6145137, PMID 6548967). Restraint-stress findings also varied with exposure and experimental conditions (PMID 26902351). These observations do not establish a universal bell-shaped response or a human therapeutic window.

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Grade C applies to the sleep and recovery claims: human studies exist, but their results are too inconsistent and methodologically limited to establish clinically meaningful benefit. This does not mean DSIP has only animal data. Several controlled human investigations reported improvements, while independent controlled studies found weak or clinically insignificant effects (PMID 6689058, PMID 1299794, PMID 3583493).

The 2006 review questioned whether DSIP had been adequately established as an endogenous sleep factor (PMID 16539679). A 2026 orthopaedic review discusses DSIP among proposed recovery agents, but contributes no new controlled DSIP efficacy data. Its broad discussion cannot establish recovery, hypertrophy or performance benefits (PMID 41490200).

The evidence supports an experimentally active compound with unresolved therapeutic relevance. It does not support a dependable sleep protocol, a proven combination strategy, or a claim that increasing slow wave sleep improves training outcomes through DSIP.

Human data. Positive sleep studies came predominantly from one research program. An early crossover study in six volunteers reported acute and delayed sleep changes after morning administration, without conventional sedation on its behavioral and EEG assessments (PMID 6895513). Another small study in chronic insomnia reported delayed sleep improvement (PMID 7028502). A 1983 publication summarized five double-blind investigations and reported better sleep and daytime functioning, with apparent effects accumulating over repeated administrations (PMID 6689058). An eighteen-patient laboratory study reported improved sleep after a week of treatment, with further improvement or persistence during the following week. Its abstract does not describe a placebo-controlled randomized design (PMID 3792404). A separate controlled study in fourteen chronic insomniacs reported improvements in sleep and daytime performance over seven treatment nights (PMID 3622582). An open study by Kaeser, involving seven patients, reported sustained improvement in six patients during subsequent follow-up. Its uncontrolled design cannot establish that DSIP caused the prolonged changes (PMID 6391926). Independent results were less convincing. Bes and colleagues studied sixteen chronic insomniacs using a double-blind matched-pairs parallel-group design. Apparent improvements in sleep efficiency and latency were weak and partly attributable to changes in the placebo group. Subjective sleep quality did not improve (PMID 1299794). Monti and colleagues used a double-blind crossover design. Changes mainly involved stage 2 sleep, without improvement in slow wave sleep. Baseline differences complicated the comparison, and the authors judged the clinical benefit limited (PMID 3583493). Human research continued beyond the early insomnia studies. A 2009 randomized anesthesia experiment included twenty-four patients. DSIP increased heart rate, reduced heart-rate variability and appeared to lighten isoflurane anesthesia on EEG-derived measures. This was an anesthesia experiment, not a treatment trial for insomnia, but it contradicts a uniformly hypnotic mechanism (PMID 19142086). Withdrawal reports included an initial sixty-seven-patient series and a later 107-patient series. Both reported substantial improvement, but lacked placebo controls and excluded some participants from evaluation. These reports may include overlapping experience and should not be added as independent evidence (PMID 6328354, PMID 6548969). A later open opioid-detoxification report exists, but its PubMed record has no abstract. Detailed outcomes were not verified here (PMID 9617990). A seven-patient pain pilot reported reductions in pain and accompanying depressive symptoms without a blinded control group (PMID 6548970). Small studies of DSIP-containing preparations in diabetes and retinopathy reported

Animal and mechanistic data. Sleep findings vary by species and experimental conditions. The early review describes different effects on delta and REM sleep, with nonmonotonic responses in some experiments (PMID 6145137). A comparative study found increased spindle-dominated light non-REM sleep in rabbits, preferential REM effects in cats, and reduced withdrawal jumping in morphine-dependent mice. Those endpoints are not equivalent to improved human slow wave sleep or recovery (PMID 6548967). Modified compounds require separate interpretation. A phosphorylated analogue improved sleep measures and spatial-memory performance in rats exposed to simulated high altitude (PMID 30107169). A DSIP-containing fusion protein enhanced pentobarbital-associated sleep in mice (PMID 28462721). Another fusion-peptide study examined neurotransmitters and behavior in a chemically induced mouse insomnia model (PMID 39444618). Neither fusion study establishes the activity of an ordinary DSIP preparation at comparable human exposure. Stress experiments reported changes in antioxidant enzymes, lipid peroxidation and hepatic measurements during cold, restraint or foot-shock stress. Results depended on the model and exposure. A rat focal-stroke study found improved motor recovery after a repeated intranasal course, without a statistically significant reduction in infarct volume (PMID 34500605). An earlier rat ischemia study reported behavioral and survival benefits (PMID 9762721). A separate investigation primarily supported the modified KND peptide during reperfusion, while reporting fatal outcomes in preliminary occlusion experiments. Plain DSIP and KND results must remain distinct (PMID 33918965). Rodent antinociception and reviews of epileptic or other neurological models broaden the pharmacology, but do not establish human treatment indications. Central administration in experimental animals differs substantially from peripheral administration in humans (PMID 2853064, PMID 8330074, PMID 8581045).

changes in symptoms or physiological measurements. They do not establish insomnia treatment, geroprotection or prevention of diabetic complications (PMID 15754961, PMID 25739189). An intranasal P300 report exists, but its metadata alone cannot establish the clinical significance or detailed study design (PMID 11763019). Observational findings in healthy volunteers, Cushing syndrome and suicidal patients concern DSIP-like immunoreactivity. They neither demonstrate therapeutic benefit from DSIP nor establish that administered DSIP causes depression, suicidality or sleep disruption (PMID 8175965, PMID 8745061, PMID 7700506, PMID 9606527).

REGULATORY STATUS AND SPORT

STATUS	DSIP is also called emideltide. FDA's 2026 evaluation states that neither the free base nor acetate is an FDA-approved drug component. It found no registrations in the countries searched. This is a bounded regulatory search, not proof about every jurisdiction. [FDA 2026 emideltide evaluation](https://www.fda.gov/media/193344/download). Published studies of regional DSIP-containing preparations document clinical investigation or use, not current marketing authorization (PMID 15754961, PMID 25739189). Research labeling, historical use and a substance identifier do not establish drug approval.
WADA	DSIP should be treated as prohibited at all times under S0 on the basis of its non-approved pharmacological status. The 2026 list does not name DSIP or emideltide individually. S0 covers pharmacological substances without current governmental approval for human therapeutic use when no subsequent section applies. This is an application of the category rule, not a DSIP-specific ruling quoted from WADA. Absence from the named examples does not establish permission. [WADA 2026 Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	The controlled insomnia studies reviewed used intravenous administration. Investigators emphasized slow administration in the early sleep research (PMID 6689058, PMID 6895513). No controlled human subcutaneous insomnia study was identified in this review. Animal subcutaneous findings do not establish equivalent human exposure or efficacy (PMID 6548967). Intranasal administration has human research precedent in retinopathy and a P300 report, but neither provides controlled evidence for treating insomnia by that route (PMID 25739189, PMID 11763019). The 2009 anesthesia experiment used intravenous boluses in a monitored clinical setting. That different procedure and endpoint should not be generalized into a sleep regimen (PMID 19142086).
HALF-LIFE	FDA's 2026 evaluation cites an approximately eight-minute plasma half-life, referencing the historical review PMID 11437870. The underlying human pharmacokinetic methods were not independently verified here. [FDA 2026 emideltide evaluation, page 50](https://www.fda.gov/media/193344/download). The dog studies establish that distribution and protein binding complicate interpretation of circulating DSIP-like material (PMID 3768731, PMID 6897451). A plasma disappearance estimate is not a validated subcutaneous half-life or a dosing interval. Early sleep reports described effects developing after approximately an hour and sometimes persisting much longer (PMID 6689058). Those clinical observations do not demonstrate that intact peptide remained present for the entire effect period.
TIMING	The early studies did not establish a consistent bedtime schedule. Some used morning administration and reported changes in subsequent sleep (PMID 6895513). A historical summary described both pre-sleep and repeated morning schedules, with different results from twice-daily administration (PMID 6391925). The independent parallel-group trial administered DSIP during the afternoon (PMID 1299794). Reported delayed effects do not identify an optimal timing window. Likewise, the circadian rhythm of plasma immunoreactivity cannot prescribe a treatment time. It is an observational biomarker pattern, not an administration study (PMID 8175965, PMID 8745061).
CYCLE LENGTH	Controlled sleep investigations were generally brief, including three treatment days and approximately one week of repeated treatment (PMID 1299794, PMID 3622582). One eighteen-patient study included a follow-up week after treatment (PMID 3792404). The seven-patient open series reported follow-up lasting months after a short administration series. Follow-up duration is not continuous drug exposure (PMID 6391926). The retinopathy study described two months of intranasal treatment, but its endpoint and formulation cannot establish a chronic insomnia regimen (PMID 25739189). The reviewed evidence does not establish cycling, washout periods, tolerance prevention or long-term safety for recurrent use.
TITRATION	No validated human insomnia titration algorithm was identified. The anesthesia study tested several exposure groups, but its findings cannot define a sleep-treatment window (PMID 19142086). Some animal experiments found nonmonotonic effects, while other outcomes varied differently with exposure (PMID 6548967, PMID 26902351, PMID 26470489). These data neither prove that escalation always reverses benefit nor identify a useful human ceiling. Repeated administration at a fixed experimental dose is different from dose escalation. The early reports of accumulating effects do not establish either practice as clinically appropriate (PMID 6689058).

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human, early crossover study in six healthy volunteers.	Approximately 21.2 mcg/kg, originally reported as 25 nmol/kg, administered by slow IV infusion on the active-treatment morning (PMID 6895513).	Slow IV infusion.	One active-treatment administration in the crossover experiment, given in the morning.	The dose, route and morning timing are stated in the abstract of PMID 6895513. The mcg conversion uses a molecular weight of approximately 849 daltons. This describes an experimental exposure, not a recommended dose. · PMID 6895513
Human, eighteen middle-aged and older patients with chronic insomnia.	Approximately 25.5 mcg/kg per IV administration, originally reported as 30 nmol/kg, with six administrations over one week (PMID 3792404).	IV.	Six administrations over one week.	Dose, route, frequency and study population are reported in PMID 3792404. This was not established as the highest human exposure or an optimal regimen. · PMID 3792404
Human, double-blind parallel-group insomnia study with sixteen participants.	Approximately 21.2 mcg/kg IV, originally reported as 25 nmol/kg, once each afternoon before three consecutive study nights (PMID 1299794).	IV.	Once daily for three consecutive days.	The abstract of PMID 1299794 specifies the dose and afternoon schedule. The investigators judged the therapeutic effects weak. · PMID 1299794
Human, double-blind crossover investigation in chronic insomnia.	Approximately 21.2 mcg/kg IV, originally reported as 25 nmol/kg, within a four-night DSIP/placebo crossover investigation (PMID 3583493).	IV.	Night-associated administration within the four-night crossover investigation. The retrieved abstract does not fully specify the treatment sequence.	PMID 3583493 reports the dose, route and four-night design. It does not justify interpreting every study night as an active DSIP dose. · PMID 3583493
Human, DSIP-containing preparation studied in diabetic retinopathy.	300 mcg of DSIP intranasally per day for two months, reported in the original abstract as 0.0003 g daily (PMID 25739189).	Intranasal.	Daily for two months. Division of the daily amount is not specified in the abstract.	PMID 25739189 reports this exposure for visual evoked-potential recovery after photostress. It was not a sleep study and does not validate the same amount by injection. · PMID 25739189
Human, randomized anesthesia experiment with twenty-four participants and three active exposure groups.	Approximately 21.2, 42.5 or 84.9 mcg/kg per IV bolus, originally 25, 50 or 100 nmol/kg. Administration occurred before and after anesthesia induction (PMID 19142086).	IV bolus in a monitored anesthesia study.	Two administrations during the experiment, one while awake and one after anesthesia induction.	Dose groups and administration sequence are reported in PMID 19142086. The study found physiological changes inconsistent with a simple hypnotic effect. These are not insomnia doses. · PMID 19142086
Animal, rat focal-stroke experiment using plain DSIP.	120 mcg/kg intranasally, once before arterial occlusion and then daily for seven days after reperfusion (PMID 34500605).	Intranasal.	Eight treatment days, including pretreatment and seven post-reperfusion days.	The abstract of PMID 34500605 reports this schedule. Motor recovery improved, but infarct-volume reduction was not statistically significant. No human-equivalent dose is inferred. · PMID 34500605
Animal, phosphorylated DSIP analogue during simulated high-altitude exposure.	10 mcg/kg of phosphorylated DSIP intraperitoneally once daily during the circadian active period (PMID 30107169).	Intraperitoneal.	Daily during hypobaric-hypoxia exposure.	PMID 30107169 reports the exposure. The administered compound was phosphorylated DSIP, so these figures do not establish a regimen for plain DSIP. · PMID 30107169
See the references and the safety section for what is documented.	100 to 300 mcg SC or intranasally once nightly before bed, commonly cited in non-clinical use; not validated in trials.	SC or intranasal, as described in informal use.	Nightly, sometimes described as a two-to-four-week course; this schedule is not validated in trials.	commonly cited in non-clinical use; not validated in trials. No controlled human sleep study supporting this amount, route and schedule was identified. Absolute amounts cannot establish exposure equivalence across routes. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

No combination is documented for this compound in the sources cited.
Use the avoid list and the protocol that includes it as the guide.

– Selank

No controlled DSIP combination study was identified. DSIP's rat GABA and NMDA findings do not demonstrate complementary anxiolysis with selank or improved human sleep. Overlapping mechanistic language cannot establish additive benefit, interaction safety or a suitable schedule (PMID 17369935).

– Epitalon

No validated combination benefit was identified. A circadian pattern in DSIP-like immunoreactivity does not show that DSIP corrects circadian phase, either alone or with epitalon. Module placement and shared longevity claims provide no pharmacological evidence (PMID 8175965).

– Ipamorelin

No direct combination evidence was identified. The hypothesis that DSIP protects sleep-related growth-hormone pulses has not been demonstrated. The independent insomnia studies do not establish reliable slow wave sleep enhancement, so a recovery rationale remains unsupported (PMID 3583493).

– CJC-1295

No direct combination evidence was identified. Changes in sleep efficiency or stage 2 sleep do not establish greater growth-hormone secretion, hypertrophy or recovery.

– GHRP-6

The reviewed DSIP studies do not establish an interaction with GHRP-6. Combining investigational agents also makes attribution of sleep changes and adverse effects more difficult.

– Hexarelin

No direct interaction study was identified. Rat stress-signaling findings cannot predict whether hexarelin opposes DSIP in humans. The concern is uncharacterized combined exposure, not a proven antagonistic interaction or a validated rule about cortisol (PMID 22094385).

– Melanotan II

No DSIP interaction study or validated separation interval was identified.

SAFETY

COMMON EFFECTS

Small early sleep studies reported generally good tolerability and sometimes improved daytime alertness. Their limited sample sizes cannot estimate adverse-event frequency for broader use (PMID 6895513, PMID 6689058, PMID 3622582). The withdrawal-series abstract mentions headaches, but does not provide the complete safety account (PMID 6548969). The 2009 anesthesia experiment found increased heart rate and reduced heart-rate variability. These are documented human physiological effects, although their significance outside anesthesia is uncertain (PMID 19142086). DSIP therefore cannot be described as physiologically inactive during waking or uniformly free of autonomic effects.

SERIOUS SIGNALS

FDA's review of PMID 6548969 identifies serious events omitted from its abstract summary: hypotension in two patients and recurrent discomfort with sweating and nausea in another. One repeat administration was followed by progressive hypotension. [FDA 2026 emideltide evaluation, pages 51 and 52] (<https://www.fda.gov/media/193344/download>). A preclinical paper reported complete mortality in preliminary experiments involving DSIP during myocardial occlusion in rats and KND during cerebral occlusion in mice. These are distinct compounds and models. The finding cannot establish a human incidence or a rule that all pre-ischemia DSIP exposure is fatal (PMID 33918965). Indeed, a different rat stroke study used pretreatment and reported improved motor recovery (PMID 34500605). Central-administration neurological syndromes and modulation of isolated rabbit-heart responses provide additional experimental signals, without quantifying human risk (PMID 8581045, PMID 2378944). FDA also identifies potential immunogenicity, peptide-impurity and characterization concerns for compounded emideltide. These remain insufficiently characterized for the proposed route. [FDA compounding safety assessment](<https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>).

CONTRAINDICATIONS

There is no approved DSIP prescribing label establishing a formal contraindication list. Pregnancy, breastfeeding and pediatric use lack an adequate benefit-risk basis in the reviewed clinical evidence. Cardiovascular disease,

symptomatic low blood pressure, cerebrovascular disease and seizure disorders warrant particular concern because relevant safety and interaction data are incomplete. Concurrent opioids, sedatives, anesthetics and treatment for substance dependence require clinical medication review. The opioid-related animal mechanism supports a possible interaction, not a proven interaction magnitude or a substitute withdrawal treatment (PMID 2706459). Human anesthesia findings directly support concern about unexpected interactions with anesthetic care (PMID 19142086). Anti-doping prohibition is a sporting eligibility issue, distinct from a medical contraindication. Persistent insomnia also requires assessment of its cause. The presence of sleep symptoms does not establish an indication for DSIP.

STOP RULES

Chest pain, fainting, severe breathlessness, new focal weakness, speech disturbance, sudden visual loss or a severe allergic reaction require urgent medical assessment. Further exposure should cease while a serious reaction is evaluated. New palpitations, marked dizziness, severe headache, confusion, agitation, worsening mood or excessive daytime sleepiness warrant prompt assessment. Suicidal thoughts require immediate support regardless of any suspected cause. The observational depression study does not establish that DSIP causes suicidality (PMID 9606527). Fever or spreading redness, warmth, swelling or pain following administration raises concern for infection or another local reaction. An apparently clear solution does not exclude contamination. Lack of perceived benefit does not justify escalation. No trial establishes a two-week self-experiment, a stopping threshold based on that duration, or a rescue strategy using higher exposure.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved standard vial presentation established by the cited trials. Label mass, actual peptide content, salt form and total powder mass are different measurements. A lyophilized cake's appearance can identify an obvious physical defect, but cannot establish identity, potency, sterility or an intact temperature history. A collapsed cake alone does not prove degradation, and an intact white cake does not prove suitable quality.

SOLVENT

The reviewed clinical evidence does not validate a universal home-reconstitution procedure. Compatibility depends on the exact chemical form, formulation, concentration and intended route. Bacteriostatic water is not interchangeable with every study vehicle, and preservative content does not establish a DSIP-specific usable lifetime. A research protocol requires a documented vehicle and validated handling procedure for the actual material. Solvent selection cannot be inferred from the peptide's short sequence alone.

STORAGE

No DSIP-specific storage duration for a home-prepared solution was established from the reviewed clinical evidence. Stability depends on chemical form, pH, concentration, excipients, container and temperature history. Microbiological usability and chemical stability are separate questions. Storage conditions require formulation-specific stability data. Refrigeration or a preservative cannot establish that an unidentified research preparation remains suitable over a given period. Visible discoloration, particles, cloudiness or a compromised closure indicate a quality concern, but absence of these findings is not proof of acceptable quality.

Hypothetical concentration arithmetic only: a verified peptide content of 5 mg in a final solution volume of 2 mL equals 2.5 mg/mL, or 2500 mcg/mL. This is a mathematical example, not a trial formulation, administered dose or preparation instruction.

The calculation uses final volume. It assumes complete dissolution, accurate peptide-content measurement and no relevant loss to the container. It says nothing about sterility, compatibility, degradation or biological activity. A label reporting total powder mass cannot automatically supply the peptide-content value in this calculation.

For a documented study comparison, PMID 6895513 reports approximately 21.2 mcg/kg by slow IV infusion on the active-treatment morning. That is a body-weight-adjusted experimental exposure, not a fixed amount transferable to another route. PMID 25739189 reports 300 mcg intranasally per day for two months in retinopathy research. Equal mass would not establish equal exposure if administered intravenously or subcutaneously.

A concentration calculation answers how much material is present per unit volume. It cannot answer whether that material has a useful dose, whether another route is equivalent, or whether the formulation matches a published study. Syringe-mark conversions and instructions for drawing an amount have therefore been removed.

BUYING NOTES

A certificate of analysis is evidence about a tested sample, not automatic proof about every container carrying the same product name. Useful documentation identifies the tested batch, laboratory, methods, dates and acceptance criteria. Traceability matters because a generic document cannot establish the characteristics of a particular lot.

Chromatographic purity, peptide identity, actual peptide content and microbiological quality answer different questions. A high HPLC area percentage does not establish sterility, low endotoxin, correct net content or absence of every impurity. No universal purity percentage establishes clinical suitability.

The approximate molecular weight of unmodified DSIP is 849 daltons, but mass-spectrometric interpretation depends on charge state, adducts and the analytical method (PMID 6145137). A raw spectral peak need not appear at the neutral molecular weight. A certificate without mass spectrometry is incomplete for that identification question, but is not automatically a fabricated certificate.

Chemical identity must also distinguish plain DSIP from phosphorylated DSIP, KND and fusion proteins. Those materials produced different experimental findings and cannot share an efficacy claim merely because their names contain DSIP (PMID 30107169, PMID 33918965, PMID 28462721, PMID 39444618).

Price, powder color and a research-use label cannot establish pharmaceutical quality. The relevant distinction is between documented analytical results and assumptions about an untested preparation. Neither a COA nor correct concentration arithmetic converts limited clinical evidence into an established treatment.

COMMON MISTAKES

- Treating the name as an efficacy finding. DSIP's historical association with delta sleep is a research hypothesis, and later controlled studies did not establish reliable clinical benefit (PMID 16539679, PMID 1299794, PMID 3583493).
- Calling every human study negative, or treating every positive report as confirmation. The record includes controlled positive findings, weak independent replications and uncontrolled series with substantial limitations.
- Treating animal brain entry as quantified human bioavailability. The cited distribution experiments involved animals, immunoassays and, in some cases, labeled derivatives (PMID 6547363, PMID 3768731).
- Equating an approximate plasma half-life with the duration of a clinical effect or a dosing interval. These measurements require different evidence and may describe different molecular material.
- Applying evidence from phosphorylated DSIP, KND or fusion proteins to plain DSIP. A chemical modification can alter distribution and activity, so the administered compound must remain explicit.
- Assuming that several unvalidated mechanisms create a validated combination. No controlled DSIP combination evidence was identified for the catalog pairings discussed here.
- Interpreting good tolerability in small sleep studies as absence of serious events across the literature. The withdrawal safety account includes hypotension, and the anesthesia study documents autonomic effects.
- Using an immunoreactivity association as proof of causation. Biomarker differences in sleep, Cushing syndrome or depression do not establish the effects of administering synthetic DSIP.

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Epitalon

Epithalon, Ala-Glu-Asp-Gly

Synthetic pineal tetrapeptide

Module 4 · Mind & Longevity

Goals: Longevity, Sleep

Route: SC or intranasal

A synthetic pineal tetrapeptide with experimental telomere and circadian effects, but no established human longevity or sleep benefit.

WHAT IT IS

Epitalon, also called Epithalon or AEDG, consists of four amino acids: Ala-Glu-Asp-Gly. It belongs in Module 4, Mind & Longevity, under Longevity and Sleep as research interests, not demonstrated clinical outcomes. It was developed through research on pineal peptide preparations.

Epitalon must be distinguished from Epithalamin, a pineal gland extract containing multiple components. Human survival findings attributed to that extract cannot establish the efficacy of synthetic AEDG. Likewise, experiments using human cells describe laboratory biology, not outcomes in people receiving treatment.

MECHANISM

No clinically validated, specific Epitalon receptor has been established. Agonism at the melatonin receptors MT1 or MT2 has not been established. Proposed pineal effects involve phosphorylated CREB and arylalkylamine N-acetyltransferase, AANAT, an enzyme involved in melatonin synthesis. Findings differ across experimental systems, including isolated pineal experiments without increased melatonin release, summarized in PMID 40141333. These observations do not establish a receptor-to-response pathway in humans.

The central longevity hypothesis concerns telomere maintenance. A 2003 experiment reported telomerase-component expression, telomerase activity and telomere elongation in cultured human fetal fibroblasts, PMID 12937682. A 2025 study reported increased hTERT expression and telomerase activity in normal cell cultures, PMID 40908429. Breast cancer cell lines showed increased alternative lengthening of telomeres, ALT, activity. These laboratory findings do not demonstrate organism rejuvenation, reduced mortality or a favorable balance between tissue maintenance and cancer risk. A published correction replaced incorrect figures in that study, PMID 41240216.

The circadian hypothesis has limited human biomarker support. AEDG research reported changes in CLOCK, CRY2 and CSNK1E expression in blood cells alongside urinary melatonin-metabolite changes, PMID 33280326. Blood-cell gene expression does not establish correction of the brain's circadian pacemaker or improved sleep architecture. Older rhesus-monkey experiments reported altered evening melatonin and cortisol rhythms, PMID 11550036. Proposed direct regulation of DNA or chromatin remains mechanistic research rather than a clinically established explanation.

EVIDENCE · GRADE C

Grade C applies to longevity and sleep outcomes: animal findings exist, but human evidence is too weak to establish these benefits. The individual cell-culture findings are grade D evidence. Araj et al., PMID 40141333, provide a narrative overview, not a human efficacy trial or a formal scoping review. The small human biomarker study does not establish lifespan extension, improved healthspan or insomnia treatment.

Human data. The AEDG circadian study has a 2020 Russian PubMed record, PMID 33280326, and a subsequent English publication discussed in FDA's assessment. Among 75 women evaluated, the low-melatonin subgroup included 20 receiving AEDG and 20 receiving placebo. FDA describes randomized allocation, unspecified blinding and no reported safety data. The short study measured urinary melatonin metabolites and blood-cell gene expression. Sleep outcomes were not measured; nonspecific reports of improved wellbeing lacked a described assessment method. A separate controlled clinical report examined retinitis pigmentosa, PMID 12195242. Its ophthalmic setting, local administration and reporting limitations prevent extrapolation to systemic longevity or sleep treatment. No convincing human lifespan-extension evidence for synthetic Epitalon was identified.

Animal and mechanistic data. In female Swiss-derived SHR mice, PMID 14501183, Epitalon did not increase mean lifespan or reduce total spontaneous tumor incidence. It increased survival among the longest-lived animals and reduced leukemia occurrence. Reporting only maximum lifespan would conceal the unchanged average-lifespan result. This experiment included female mice from one stock and does not establish human efficacy or cancer safety. Old-monkey hormone findings, PMID 11550036, support endocrine investigation but do not demonstrate better sleep or longer human life.

STATUS	Research compound without an established approved therapeutic indication or approved dosing label. FDA's 2026 assessment identifies no FDA-approved Epitalon product and no approvals in the other jurisdictions it reviewed. An orphan-drug designation is not marketing approval. Compounding availability does not establish approval, efficacy or pharmaceutical equivalence. The assessment is an advisory-committee briefing document, not itself a final compounding determination. Source: FDA Epitalon assessment, https://www.fda.gov/media/193345/download .
WADA	Prohibited at all times under the 2026 WADA S0 category for non-approved pharmacological substances. This classification applies the category rule to Epitalon's unapproved status; Epitalon is not individually named in that list. S0 covers pharmacological substances without governmental approval for human therapeutic use that are not addressed by subsequent categories. Absence from the named examples does not establish permission. Source: WADA 2026 Prohibited List, https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf .

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Subcutaneous administration appears in animal research and non-clinical use. Human reports include sublingual administration and specialized parabolbar administration near the eye. Intranasal exposure appears in preclinical research, but a validated human nasal formulation, bioavailability or effective regimen was not identified. Route changes cannot be treated as equivalent, and animal administration does not establish suitability for human use.
HALF-LIFE	A reliable human elimination half-life has not been established. FDA found no human pharmacokinetic data for the free base or acetate. Numerical half-lives repeated online should not determine timing or frequency. Biological changes lasting beyond exposure would also not establish prolonged circulation of intact peptide.
TIMING	No human comparison establishes bedtime, morning, fasting or training-related administration as superior. A circadian hypothesis alone cannot determine clock time. Sleep schedules, light exposure and shift work are major confounders when interpreting perceived changes. Timing claims require clinical outcomes, not only changes in melatonin-related biomarkers.
CYCLE LENGTH	Study durations belong to their specific endpoints and routes. The human sublingual course lasted 20 days, associated with PMID 33280326 and described in PMID 40141333. The mouse lifespan experiment repeated monthly courses, PMID 14501183. Neither validates annual cycling, indefinite maintenance or repeated systemic courses in adults.
TITRATION	No validated human escalation schedule, target exposure or maximum tolerated dose was identified. A subjective sleep response does not establish target engagement. Absence of immediate symptoms does not resolve long-term safety, and increasing exposure cannot be assumed to improve the intended outcome.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human circadian-biomarker study, not an insomnia or longevity efficacy trial	0.5 mg total per day, sublingually in two daily administrations for 20 days, associated with PMID 33280326 and detailed in FDA's assessment.	Sublingual spray.	Three sublingual sprays twice daily for 20 days, as described in FDA's assessment of the English publication associated with PMID 33280326.	PMID 33280326 identifies the Russian report. FDA's assessment supplies the spray schedule from the subsequent English publication; PMID 40141333 also reports the daily amount. The volume per spray was not described. This formulation cannot establish an equivalent injected or intranasal dose. · PMID 33280326
Human retinitis pigmentosa research	5 mcg per eye by parabolbar administration on each of 10 consecutive days, reported in the secondary review PMID 40141333 for PMID 12195242.	Parabolbar administration, a specialist ophthalmic procedure.	Daily administration for 10 consecutive days is described in PMID 40141333; the retrieved primary abstract does not specify the regimen.	Clinical report PMID 12195242. The numerical regimen was checked against secondary review PMID 40141333, not a retrieved primary methods section. It is not a systemic sleep or longevity regimen. · PMID 12195242
Female Swiss-derived SHR mouse lifespan experiment	1 mcg per mouse, approximately 30 to 40 mcg/kg, subcutaneously on each of five consecutive days every month, PMID 14501183.	Subcutaneous administration in 0.1 mL normal saline per mouse per dosing day, PMID 14501183.	Daily on five consecutive days each month, from three months of age until natural death, PMID 14501183.	Primary-study abstract, PMID 14501183. The per-kg range is the authors' mouse estimate, not a human-equivalent dose or a basis for direct body-weight scaling. · PMID 14501183
Human cell-culture telomere experiment	1 mcg/mL added directly to normal fibroblast and epithelial cell cultures daily for three weeks, PMID 40908429.	Direct addition to cell-culture medium, not administration to a person.	Daily treatment with daily medium renewal for three weeks, PMID 40908429.	A culture concentration cannot be converted into an injected dose without exposure and distribution data. · PMID 40908429

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Commonly circulated non-clinical systemic use	5 to 10 mg subcutaneously per day, commonly cited in non-clinical use; not validated in trials.	Subcutaneous.	Daily in non-clinical descriptions; neither an effective course length nor a tolerable cumulative exposure has been established.	Commonly cited in non-clinical use; not validated in trials. FDA's assessment documents online milligram-range claims. These are not approved labeling or evidence of a validated human subcutaneous regimen. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ DSIP	Conceptual overlap in sleep research only. No controlled human Epitalon-DSIP combination evidence was identified. Shared positioning around sleep does not establish additive benefit. Simultaneous exposure would obscure attribution of sleep changes or adverse effects.	- IGF-1 LR3	Precautionary concern about combining experimental telomere-maintenance effects with growth signaling. The cancer implications of this combination have not been established. This is a mechanistic concern, not a documented clinical drug interaction or quantified risk.
+ Thymalin	A proposed relationship between pineal and thymic aging creates a research hypothesis. Historical extract-combination findings do not validate synthetic Epitalon with Thymalin.	- FOXO4-DRI	Senescent-cell targeting and attempts to alter replicative limits affect different aspects of cell survival. Their combined effects cannot be predicted from separate experiments. No adequate human combination safety evidence was identified.

SAFETY

COMMON EFFECTS	A reliable Epitalon-specific adverse-event frequency profile is unavailable. Local discomfort, redness or irritation are plausible administration-related effects. Headache, sleep changes and fatigue cannot currently be assigned dependable incidence rates or causality. Reports of good tolerability from limited studies are not equivalent to systematic safety surveillance.
SERIOUS SIGNALS	Cancer-related uncertainty deserves attention because the 2025 cell study reported telomere extension and increased ALT activity in breast cancer cell lines, PMID 40908429. This does not prove that Epitalon causes cancer in humans. It does prevent presenting telomere maintenance as uniformly beneficial. Hypersensitivity, peptide aggregation, contamination and endotoxin are additional concerns with inadequately characterized preparations.
CONTRAINDICATIONS	No approved contraindication list exists. Pregnancy, breastfeeding, childhood, active cancer, unexplained masses and ongoing cancer treatment are settings where missing safety information is especially consequential. Renal or hepatic impairment has no validated dose adjustment. These are precautionary exclusions, not claims of formally established contraindications.
STOP RULES	Following exposure, breathing difficulty, facial swelling, fainting or a severe generalized rash require emergency assessment. Fever with spreading injection-site redness, new visual symptoms or persistent severe headache warrant prompt medical evaluation. Persistent sleep deterioration or other new symptoms warrant discontinuation and clinical review. These are general response criteria, not Epitalon-specific trial thresholds.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	There is no approved standard vial strength. The 10 mg starting quantity in the example below comes from laboratory stock preparation in PMID 40908429. It does not establish a commercial vial standard, actual peptide content or suitability for administration.
SOLVENT	Normal saline was used in the mouse study, PMID 14501183. Bacteriostatic water was used for a laboratory stock in PMID 40908429. Neither establishes a validated human injectable formulation. Bacteriostatic water cannot sterilize a contaminated powder, and laboratory solvent use does not establish clinical compatibility.
STORAGE	No validated universal storage period or beyond-use date exists for reconstituted Epitalon. Conditions require formulation-specific stability and microbiological data. Refrigeration or a preservative does not establish continued potency or sterility. Appearance alone cannot verify either, and a laboratory stock's handling conditions do not define clinical storage requirements.

Laboratory concentration example: PMID 40908429 reports 10 mg dissolved in 4 mL bacteriostatic water, producing a stated stock concentration of 2.5 mg/mL. That equals 2,500 mcg/mL. This stock supported cell-culture experiments; the normal-cell exposure was 1 mcg/mL added directly to culture medium daily for three weeks, PMID 40908429. Stock concentration and final culture concentration describe different stages of the experiment. Neither is a human dose, an injection volume or a clinical reconstitution standard. The arithmetic illustrates mass divided by volume without establishing sterility, compatibility, stability or suitability for administration.

A useful certificate of analysis distinguishes peptide identity, chromatographic purity and actual peptide content. A high purity percentage does not prove the container holds its labeled mass. Batch linkage, test date, laboratory traceability and analytical methods matter. Injectable-material assessment additionally requires sterility and endotoxin information, which a mass spectrum or chromatogram cannot supply. Salt form, water content and residual counterions can affect what a stated mass represents. None of these documents establishes clinical efficacy, regulatory approval or equivalence to a preparation used in published research.

COMMON MISTAKES

- Treating Epitalon and Epithalamin as interchangeable names for the same intervention.
- Calling experiments in human-derived cell cultures human clinical trials.
- Presenting maximum mouse lifespan gains while omitting the unchanged mean lifespan.
- Equating urinary melatonin-metabolite changes with proven insomnia relief.
- Scaling a mouse dose directly by human body weight or transferring a dose unchanged between routes.
- Assuming that an unnamed substance is permitted under WADA rules despite the S0 category.
- Using a purity certificate, clear solution or lack of immediate symptoms as proof of safety.

REFERENCES

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2. Khavinson VKh et al. Epithalon peptide induces telomerase activity and telomere elongation in human somatic cells.. *Bulletin of experimental biology and medicine*, 2003. PMID 12937682 DOI 10.1023/a:1025493705728 (Telomerase induction and telomere elongation in cultured human fetal fibroblasts, not human longevity outcomes.)
3. Al-Dulaimi S et al. Epitalon increases telomere length in human cell lines through telomerase upregulation or ALT activity.. *Biogerontology*, 2025. PMID 40908429 DOI 10.1007/s10522-025-10315-x (Cell-culture hTERT, telomerase and ALT findings, daily culture exposures and laboratory stock preparation. Does not establish a human therapeutic regimen.)
4. Al-Dulaimi S et al. Correction: Epitalon increases telomere length in human cell lines through telomerase upregulation or ALT activity.. *Biogerontology*, 2025. PMID 41240216 DOI 10.1007/s10522-025-10326-8 (Replaces incorrect Figures 1, 2 and 3 in the 2025 cell-culture study.)
5. Anisimov VN et al. Effect of Epitalon on biomarkers of aging, life span and spontaneous tumor incidence in female Swiss-derived SHR mice.. *Biogerontology*, 2003. PMID 14501183 DOI 10.1023/a:1025114230714 (Mouse dose and monthly schedule, unchanged mean lifespan, survival among the longest-lived animals and tumor endpoints.)
6. Goncharova ND et al. Regulatory effect of Epithalon on production of melatonin and cortisol in old monkeys.. *Bulletin of experimental biology and medicine*, 2001. PMID 11550036 DOI 10.1023/a:1017928925177 (Old rhesus-monkey melatonin and cortisol findings underlying the circadian research rationale.)
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MOTS-c

Mitochondrial open reading frame of the 12S rRNA-c

Mitochondrial-derived peptide

Module 4 · Mind & Longevity

Goals: Longevity, Fat loss

Route: SC

WADA prohibited

A mitochondrial-derived signaling peptide with metabolic and physical-function findings in mice, but no established human benefit for fat loss or longevity.

WHAT IT IS

MOTS-c means mitochondrial open reading frame of the 12S rRNA-c. It is a 16-amino-acid mitochondrial-derived peptide first described in the cited 2015 publication. Its coding sequence lies within the mitochondrial 12S ribosomal RNA region. Endogenous MOTS-c has been detected in tissues and circulation. Synthetic MOTS-c is used experimentally to investigate metabolic regulation. PMID 25738459.

Module 4, Mind & Longevity. Goal tags: Longevity and Fat loss. These describe research interests, not demonstrated human outcomes. Measuring naturally occurring MOTS-c, administering native synthetic MOTS-c, and testing the modified analog CB4211 are distinct evidence categories. Results from one do not automatically establish efficacy, safety, or dosing for another.

MECHANISM

The foundational model links MOTS-c to folate metabolism, de novo purine synthesis, and cellular energy sensing. Cell experiments found disruption of the folate cycle and associated purine synthesis, with accumulation of AICAR. This intermediate can activate AMP-activated protein kinase, AMPK. AMPK helps coordinate glucose uptake, fuel utilization, and responses to energy stress. This pathway has experimental support. However, the initial molecular interaction through which MOTS-c changes folate metabolism remains incompletely defined. AMPK is a downstream kinase, not an established MOTS-c receptor. PMID 25738459.

Skeletal muscle appears to be an important target tissue. Mouse experiments support improved insulin responsiveness and altered muscle glucose metabolism. These findings suggest effects on metabolic flexibility, the ability to adjust fuel use to changing demands. They do not establish direct activation of the insulin receptor or clinically meaningful human fat loss. The cited studies do not establish a validated cell-surface receptor that fully explains native MOTS-c activity. PMIDs 25738459 and 33473109.

A second mechanism involves communication from mitochondria to the nucleus. Under metabolic stress, MOTS-c translocated into the nucleus in an AMPK-dependent manner and regulated stress-responsive gene expression. Experiments implicated antioxidant response elements and interactions with transcription factors including NFE2L2, also called NRF2. This supports an intracellular stress-response role alongside proposed circulating signaling functions. Most direct evidence for this mechanism comes from cell systems. PMID 29983246.

Animal work also connects MOTS-c with muscle gene programs involved in metabolism, proteostasis, and adaptation to exercise. These observations support hypotheses about preserving function with aging. They do not demonstrate reversal of biological aging, prevention of dementia, or extension of human lifespan. The contributions of extracellular signaling, cellular uptake, and nuclear activity after human administration remain unresolved. The review by Kong and colleagues summarizes these translational gaps. PMIDs 33473109 and 36824008.

EVIDENCE · GRADE C

Grade C applies to administered native MOTS-c for fat loss and longevity. Animal intervention data exist, while human evidence does not establish these treatment claims. Mechanistic plausibility is stronger than clinical validation. The cited review discusses therapeutic potential and translational gaps, rather than demonstrating treatment efficacy. Human biomarker studies do not justify grade B for administered MOTS-c. PMID 36824008.

Human data. Reynolds and colleagues measured endogenous MOTS-c responses to exercise in human muscle and blood. Participants were not given MOTS-c. This supports exercise-responsive biology without establishing a treatment effect. Du and colleagues studied 40 obese children and adolescents and 57 controls. Lower circulating concentrations were evident particularly in obese males. This observational pediatric result cannot establish causality, an adult deficiency diagnosis, or a replacement threshold. PMIDs 33473109 and 29691953. The modified analog

Animal and mechanistic data. Lee and colleagues reported protection against diet-induced obesity and insulin resistance in mice. Reynolds and colleagues reported improved physical performance in young and older mice and preservation of several late-life functional measures. However, the overall survival comparison was not statistically significant, $P = 0.23$. These findings support research on function during aging, not a demonstrated lifespan extension. PMIDs 25738459 and 33473109. The late-life intermittent phase followed earlier daily treatment in the

CB4211 underwent a completed phase 1a/1b study, NCT03998514. Sponsor-reported findings included exploratory biomarker changes and injection-site reactions. These findings concern a different molecule and do not validate native MOTS-c. No corresponding PubMed treatment-results record was verified in this review. The retrieved evidence did not establish that administered native MOTS-c reduces human fat mass or extends lifespan. The FDA assessment also identified no clinical administration studies supporting the proposed uses. [FDA MOTS-c assessment](https://www.fda.gov/media/193347/download).

methods. It therefore cannot establish the independent effect of starting intermittent treatment in previously untreated old mice. Body composition, treadmill performance, and glucose handling are informative experimental outcomes. Species, route, exposure, and study design limit translation. Preventing weight gain during a controlled high-fat diet also differs from treating established human obesity. PMID 33473109.

REGULATORY STATUS AND SPORT

STATUS	Native MOTS-c is not an FDA-approved medicine and has no approved prescribing label. It remains investigational. The FDA briefing document evaluates proposed compounding uses; that evaluation does not confer approval. [FDA MOTS-c assessment](https://www.fda.gov/media/193347/download). The registry lists the modified analog study NCT03998514 as completed on April 19, 2021. Completion does not imply approval, demonstrated efficacy, or continuing active development. ClinicalTrials.gov, NCT03998514.
WADA	Prohibited at all times, in and out of competition. The 2026 WADA Prohibited List explicitly names MOTS-c in S4.4.1, AMPK activators, within hormone and metabolic modulators. Its listed classification is S4. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Subcutaneous administration appears in informal human-use descriptions and was used for the modified analog CB4211 in NCT03998514. The cited native MOTS-c mouse interventions used intraperitoneal administration. Subcutaneous use is therefore a reported practice, not a clinically validated route for native MOTS-c. Oral and intranasal bioavailability are not established by the cited evidence. PMIDs 25738459 and 33473109.
HALF-LIFE	A reliable clinical elimination half-life for administered native MOTS-c has not been established in the retrieved evidence. The FDA assessment did not identify clinical pharmacokinetic studies. Numbers without a defined species, formulation, route, sampling method, and assay cannot establish an administration interval. Peptide disappearance from blood and persistence of downstream signaling are different measurements.
TIMING	There is no validated human timing relative to meals, sleep, or training. An endogenous increase after exercise does not establish that administration before exercise improves results. Fasting has no demonstrated role in optimizing native MOTS-c exposure. Exercise-related biomarker timing and the timing of an administered intervention answer different questions.
CYCLE LENGTH	No validated human cycle, maintenance phase, or washout interval exists. Short animal experiments and prolonged mouse follow-up address different questions and cannot define a universal human cycle. The intermittent mouse phase followed daily treatment. The four-week CB4211 study concerns the modified analog only, as recorded in NCT03998514.
TITRATION	No evidence-based titration algorithm exists for native MOTS-c. Informal gradual escalation has not been shown to prevent immunogenicity, contamination-related harm, or delayed adverse effects. Subjective energy changes cannot establish a pharmacologically appropriate dose. Neither absence of immediate symptoms nor a biomarker change establishes an effective exposure.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved-label and human native-peptide context	No approved dose and no validated human therapeutic dose identified for native MOTS-c.	No approved route.	No approved or trial-validated schedule.	No native MOTS-c prescribing label exists. The cited human exercise and observational studies measured endogenous peptide rather than administering it. PMIDs 33473109 and 29691953.
Human investigation of the modified analog CB4211	A sponsor-reported analog dose exists, but no numeric dose is retained here without a verified PubMed treatment-results record or approved label.	Subcutaneous in registered study NCT03998514.	Once daily for four weeks in the registered phase 1b component.	ClinicalTrials.gov, NCT03998514, and its sponsor report describe an analog investigation. Neither establishes a native MOTS-c dose.
Mouse insulin-sensitivity experiments	5 mg/kg per administration, intraperitoneally once daily for seven days, reported by Lee and colleagues, PMID 25738459.	Intraperitoneal.	Once daily for seven days.	Primary mouse intervention study, PMID 25738459. The reported exposure is retained in animal mg/kg units and is not converted into a human regimen. · PMID 25738459

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Middle-aged and old mouse physical-performance experiments	15 mg/kg per administration, intraperitoneally once daily for two weeks, reported by Reynolds and colleagues, PMID 33473109.	Intraperitoneal.	Once daily for two weeks before the reported performance assessment.	Primary animal intervention study assessing physical capacity and muscle metabolism, PMID 33473109. This exposure does not establish a human equivalent. · PMID 33473109
Intermittent phase of a late-life mouse intervention	15 mg/kg per administration, intraperitoneally three times weekly from approximately 23.5 months of age, reported by Reynolds and colleagues, PMID 33473109.	Intraperitoneal.	Three times weekly during late-life follow-up, following an earlier daily-treatment phase.	The methods describe eight weeks of daily injections before transition to intermittent treatment, PMID 33473109. The intermittent phase was not the animals' first exposure. It does not validate a human maintenance cycle. · PMID 33473109
Informal non-clinical human-use descriptions	5 to 10 mg per administration, subcutaneously two to three times weekly, commonly cited in non-clinical use; not validated in trials.	Subcutaneous in informal descriptions.	Two to three times weekly in informal descriptions.	Commonly cited in non-clinical use; not validated in trials. This anecdotal convention has no established minimum effective dose, tolerable ceiling, or exposure-response relationship. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ SS-31	Hypothesis only: different mitochondrial targets provide a mechanistic rationale for research. No verified human combination trial establishes additive fat loss, improved function, tolerability, or an effective schedule. Mechanistic differences alone do not demonstrate synergy.	– IGF-1 LR3	Potential overlapping effects on glucose regulation create an unquantified interaction concern. Native MOTS-c lacks established human interaction data. IGF-related glucose lowering adds uncertainty when interpreting proposed complementary metabolic effects. This is a precaution based on pharmacology, not a demonstrated MOTS-c-specific interaction.
+ Humanin	Hypothesis only: humanin and MOTS-c belong to mitochondrial-derived signaling research, with potentially different stress-response roles. Shared biological context does not establish improved outcomes from combined administration. No validated human combination regimen was identified. Findings involving either peptide alone cannot determine the effects of their joint exposure.	– FOXO4-DRI	Combining experimental approaches to aging compounds uncertainty about tissue effects and delayed toxicity. No verified human evidence establishes the efficacy or compatibility of this pairing. Simultaneous exposure would also make adverse effects difficult to attribute. A shared longevity research theme does not demonstrate a useful combination.

SAFETY

COMMON EFFECTS	The incidence and pattern of adverse effects from administered native MOTS-c are unknown. Informal reports cannot establish frequency or causation. Injection-site reactions occurred in the sponsor-reported CB4211 trial, but those findings cannot be assigned directly to native MOTS-c. [Sponsor trial report filed with the SEC] (https://www.sec.gov/Archives/edgar/data/1522602/000121390021041377/ea145151ex99-2_cohbar.htm).
SERIOUS SIGNALS	Relevant concerns include immune reactions, peptide aggregation, impurities, and contamination. Glucose lowering is mechanistically plausible, especially alongside glucose-lowering treatment, but its magnitude in humans is unquantified. The FDA assessment emphasizes absent clinical safety data and potential immunogenicity. These are potential hazards, not established adverse-event rates. Cancer, reproductive, and chronic organ-safety risks remain insufficiently characterized.
CONTRAINDICATIONS	There is no approved label defining formal contraindications. Pregnancy, breastfeeding, childhood, active malignancy, significant renal or hepatic impairment, and prior severe peptide or excipient reactions require particular caution. These represent evidence gaps or reasons for specialist assessment, not established MOTS-c-specific contraindications. Concurrent glucose-lowering treatment creates an additional unresolved interaction concern.
STOP RULES	Systemic symptoms or persistent injection-site inflammation warrant withholding further exposure pending medical assessment. Breathing difficulty, facial swelling, fainting, severe confusion, or fever with spreading redness warrant urgent care. These are general clinical warning signs rather than a validated MOTS-c monitoring algorithm. Normal routine laboratory results do not establish long-term safety.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No approved vial presentation exists. A nominal 10 mg lyophilized vial appears below solely as a hypothetical arithmetic input, not a dose. Labeled mass does not establish peptide identity, measured content, sterility, or suitability for human administration. Free-base and salt labeling can also affect interpretation of reported content.

SOLVENT

Bacteriostatic water appears in informal preparation descriptions. A validated native MOTS-c formulation with established preservative compatibility and post-reconstitution stability was not identified. Solubility alone does not establish formulation suitability. The calculation below assumes a final solution volume without specifying a clinically validated solvent or preparation method.

STORAGE

No approved storage instructions or validated multidose beyond-use period were identified for native MOTS-c. Stability depends on formulation, temperature, oxidation, aggregation, container, and handling. Laboratory stability documentation applies only to its tested conditions. A clear solution does not prove sterility, potency, or absence of aggregates. Chemical stability and microbial suitability require separate evidence.

Hypothetical concentration arithmetic only: a sample containing exactly 10 mg in exactly 1 mL of final solution has a concentration of 10 mg/mL. This equals 10,000 mcg/mL. A 0.5 mL laboratory aliquot would contain 5 mg, calculated as 10 mg/mL multiplied by 0.5 mL. These are assumed sample quantities, not an administered dose, route, or frequency. Final solution volume may differ from the volume of solvent added. Syringe markings describe volume and cannot establish MOTS-c IU or biological potency. This example checks mass and volume conversion only. It does not validate peptide content, solvent compatibility, preparation, or a human administration protocol.

BUYING NOTES

A meaningful certificate of analysis separates sequence identity, chromatographic purity, actual peptide content, and relevant contaminant testing. Purity percentage alone cannot establish how much active peptide a vial contains. Sterility and endotoxin testing are separate from chemical purity. Documentation needs lot-specific methods and traceable sample identity to support its stated conclusions. The molecular form, including free base or salt, also matters when interpreting content. A research-use designation, clean chromatogram, or generic certificate does not establish clinical suitability, regulatory approval, or treatment efficacy.

COMMON MISTAKES

- Treating low endogenous MOTS-c as a diagnosed deficiency with a validated replacement target.
- Presenting human exercise-induced changes as evidence from an administered-peptide trial.
- Transferring the modified analog's dose, tolerability, or exploratory findings directly to native MOTS-c.
- Multiplying a mouse mg/kg dose by adult body weight and calling the result clinically appropriate.
- Describing improved mouse physical function or reduced fat accumulation as proven human longevity or obesity treatment.
- Presenting the late-life intermittent mouse phase as first exposure, or describing its nonsignificant overall survival comparison as established lifespan extension.
- Confusing syringe markings with mcg, mg, or biological IU, or assuming a vial label verifies actual content.
- Treating absent adverse-event data as evidence of safety or mechanistic overlap as proof of combination benefit.

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2. Kim KH et al. The Mitochondrial-Encoded Peptide MOTS-c Translocates to the Nucleus to Regulate Nuclear Gene Expression in Response to Metabolic Stress.. *Cell metabolism*, 2018. PMID 29983246 DOI 10.1016/j.cmet.2018.06.008 (AMPK-dependent nuclear translocation, antioxidant response elements, NRF2-related interactions, and stress-responsive gene regulation in experimental systems.)
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SS-31 (Elamipretide)

Elamipretide, Bendavia, MTP-131

Mitochondria-targeted tetrapeptide

Module 4 · Mind & Longevity

Goals: Longevity, Recovery

Route: SC

A mitochondria-targeted tetrapeptide with a narrow FDA-approved indication in Barth syndrome, while longevity and training-recovery benefits remain unproven.

WHAT IT IS

SS-31, also called elamipretide and MTP-131, is a synthetic aromatic-cationic tetrapeptide with the sequence D-Arg-2,6-dimethyl-Tyr-Lys-Phe-NH₂. It interacts with the inner mitochondrial membrane, where cells organize oxidative phosphorylation and produce ATP. PMID 39940712.

Module 4: Mind & Longevity. Goal tags: Longevity, Recovery. These tags describe research interests, not established benefits for healthy adults. Elamipretide has an FDA-approved pharmaceutical formulation for improving muscle strength in eligible patients with Barth syndrome. That approval does not establish equivalence between pharmaceutical elamipretide and material labeled SS-31 for laboratory research. PMID 41335372.

MECHANISM

The principal characterized target is cardiolipin, a phospholipid concentrated in the inner mitochondrial membrane. SS-31 is not primarily a conventional cell-surface receptor agonist. Its aromatic and positively charged residues support membrane association and interaction with cardiolipin. Biochemical experiments and animal studies support preservation of mitochondrial cristae, the membrane folds that organize respiratory-chain proteins and ATP synthesis. Cardiolipin binding is substantially better established than claims about slowing biological aging. PMID 23813215; PMID 39940712. One experimentally demonstrated mechanism involves the cardiolipin-cytochrome c interaction. During mitochondrial stress, cytochrome c can acquire peroxidase activity that promotes cardiolipin oxidation and membrane injury. SS-31 inhibited this activity in experimental systems and preserved cristae during renal ischemia in rats. This was associated with faster ATP recovery after reperfusion and less downstream cellular injury. These findings explain a plausible protective mechanism under energetic stress. They do not prove that additional ATP production improves performance in an already healthy person. PMID 23813215. Proposed downstream effects include improved oxidative-phosphorylation coupling, reduced mitochondrial reactive oxygen species, and changes in redox-sensitive cellular processes. In aged mouse muscle, functional improvement occurred without increased mitochondrial content. This supports improved mitochondrial function rather than simply more mitochondria. Responses depend on tissue and disease context. Mitochondrial rejuvenation describes an interpretation of experimental findings, not demonstrated human lifespan extension. PMID 30597195; PMID 39940712.

EVIDENCE · GRADE A

Grade A follows this product's definition because elamipretide is an approved drug and has multiple human randomized trials. This grade describes regulatory status and the evidence base, not consistent efficacy across indications. For healthy-adult longevity and training recovery, the evidence remains C: preclinical findings without convincing clinical validation of those outcomes. The human evidence includes a substantial negative randomized trial. Approval, study quality and benefit for a particular goal must be assessed separately.

Human data. MMPOWER-3 randomized 218 people with genetically confirmed primary mitochondrial myopathy. At 24 weeks, elamipretide did not improve either primary endpoint: six-minute walking distance or patient-reported fatigue. The walking-distance difference versus placebo was -3.2 meters, with a 95% confidence interval from -18.7 to 12.3 meters. This directly limits claims of broadly improved endurance or fatigue. It does not establish benefit or lack of benefit in every other population. PMID 37268435. The earlier 36-person MMPOWER study generated short-term signals, including a dose-response relationship. The highest-dose comparison in the unadjusted analysis narrowly missed conventional statistical significance, with $p = 0.053$. An adjusted post hoc analysis was positive, but did not establish durable benefit. The later negative phase 3 trial deserves greater weight when discussing primary mitochondrial myopathy. PMID 29500292. The Barth syndrome crossover study enrolled 12 participants and

Animal and mechanistic data. An eight-week study in aged female mice reported improved mitochondrial coupling, redox balance, muscle fatigue resistance and treadmill endurance. Young healthy muscle showed no apparent bioenergetic enhancement, an important limit on extrapolation to trained adults. The study also found that improved fatigue resistance did not restore the age-related decline in specific muscle force. PMID 30597195. Rat renal ischemia experiments support preservation of mitochondrial structure during injury. Ischemia-reperfusion injury is not equivalent to ordinary exercise stress. PMID 23813215. These studies assessed function and injury, not human lifespan extension.

missed both primary endpoints during its blinded phase. Improvements appeared during the small open-label extension. Expectation effects, repeated testing, attrition and lack of a concurrent control complicate interpretation. Accelerated approval subsequently relied on knee-extensor strength as an intermediate clinical endpoint. These disease-specific observations cannot establish improved recovery after resistance training or longer survival in healthy adults. PMID 33077895; PMID 41335372.

REGULATORY STATUS AND SPORT

STATUS	Elamipretide received FDA accelerated approval in September 2025 as FORZINITY. The indication is improved muscle strength in adults and pediatric patients with Barth syndrome weighing at least 30 kg. Approval relied on knee-extensor strength as an intermediate clinical endpoint. Continued approval may depend on verification of clinical benefit in a confirmatory trial. Longevity and routine training recovery are not approved indications. The first-approval review has a 2026 PubMed publication year and a December 2025 electronic publication date. PMID 41335372. Label source: [FORZINITY prescribing information] (https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=146bf34c-76f2-48db-ac07-fb29cce2cd75&type=display).
WADA	Neither SS-31 nor elamipretide is explicitly named in the 2026 Prohibited List, checked September 5, 2026. S0 concerns substances without current governmental approval for human therapeutic use. Because elamipretide has FDA approval, that absence-of-approval criterion no longer describes the compound. This is an interpretation of S0, not a compound-specific WADA ruling. Absence by name does not establish clearance under every class-based provision. No compound-specific determination was located in the official sources searched. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Subcutaneous administration is the approved route and the main route in longer clinical trials. Intravenous infusion was used in early clinical research. The approved formulation is not labeled for intravenous administration. These formulations and exposure patterns are not interchangeable. Oral or intranasal efficacy for longevity or training recovery is not established by the cited evidence.
HALF-LIFE	Approximately 3 to 4 hours in plasma, according to the clinical-development briefing hosted by FDA. Plasma elimination differs from the duration of tissue effects and does not establish a need for repeated daily administration. Renal impairment can alter exposure. Source: [FDA-hosted 2024 clinical-development briefing] (https://www.fda.gov/media/182553/download).
TIMING	Clinical protocols used regular daily administration or scheduled infusions. The approved label specifies administration at the same time each day. No convincing evidence establishes superior longevity or recovery outcomes from pre-workout, post-workout, fasting or bedtime administration. A pharmacokinetic peak should not be interpreted as an established performance window.
CYCLE LENGTH	Published exposures range from five days in early MMPOWER to 24 weeks in MMPOWER-3, with longer Barth syndrome extensions. PMID 29500292; PMID 37268435; PMID 33077895. These are study durations, not validated healthy-adult cycles. Evidence does not define an optimal on-off schedule, maintenance phase or repeat-course interval. A crossover washout serves trial design and does not establish a cycling strategy.
TITRATION	Fixed-dose clinical studies do not validate community escalation schedules. The early dose-ranging study assigned separate cohorts; it did not establish a self-directed titration schedule. PMID 29500292. Renal adjustment in the approved label addresses altered drug exposure, not tolerance-building. The cited studies do not establish a dose-response relationship for healthy-adult longevity or training recovery.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved Barth syndrome indication	40 mg subcutaneously once daily in patients weighing at least 30 kg; FORZINITY prescribing information.	Subcutaneous	Once daily	FORZINITY prescribing information, sections 2.1 and 2.2. For adults with eGFR below 30 mL/min who are not receiving dialysis, the label specifies 20 mg subcutaneously once daily. The label provides no established regimen for adults receiving dialysis or eligible pediatric patients with renal impairment.
MMPOWER-3, primary mitochondrial myopathy	40 mg subcutaneously once daily for 24 weeks; PMID 37268435.	Subcutaneous	Once daily	Randomized phase 3 trial with 218 participants. Both primary efficacy endpoints were negative. This regimen documents trial exposure, not a recommendation for healthy adults. · PMID 37268435

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Early MMPOWER dose-ranging trial	0.01, 0.1 or 0.25 mg/kg/hour intravenously for two hours once daily for five consecutive days; PMID 29500292.	Intravenous infusion	One two-hour infusion daily	Separate randomized dose cohorts in 36 adults with primary mitochondrial myopathy. The methods confirm consecutive escalating-dose cohorts. Infusion rates are not subcutaneous doses or evidence for individual dose escalation. · PMID 29500292
Barth syndrome crossover trial and initial open-label extension	40 mg subcutaneously once daily during each 12-week active-treatment period and during the open-label extension; PMID 33077895.	Subcutaneous	Once daily	Twelve participants entered the randomized crossover study, with a four-week washout between treatment periods. Ten entered the extension and eight reached 36 weeks. Neither blinded primary endpoint was met. · PMID 33077895
Aged-mouse skeletal muscle research	3 mg/kg/day by continuous subcutaneous osmotic-pump delivery for eight weeks; PMID 30597195.	Subcutaneous implanted osmotic pump	Continuous delivery	The full-text methods confirm subcutaneous pump implantation and replacement after four weeks. Dose is retained as reported per kilogram in mice. No human-equivalent dose is inferred; continuous exposure differs from a daily bolus. · PMID 30597195

STACKING

+ NAD+	Hypothesis only for this exact pairing. Aged-mouse research combined SS-31 with NMN, an NAD precursor, and reported complementary cardiac effects. That experiment did not test administered NAD itself. It cannot validate an SS-31 plus NAD regimen in humans, or establish human combination safety. PMID 32779818.	– BPC-157	The cited evidence does not establish an SS-31 combination regimen or recovery advantage. Adding another experimental agent makes adverse effects and changes in training tolerance harder to attribute. The concern is uncertainty, not a demonstrated specific toxic interaction.
+ MOTS-c	A proposed mitochondrial combination without supporting human combination data in the cited evidence. Shared interest in mitochondrial function does not establish additive benefit, suitable sequencing or compatibility.	– FOXO4-DRI	The cited evidence does not establish human combination safety or longevity benefit. Combining mitochondrial modulation with an experimental senolytic concept does not establish efficacy merely because both are discussed in aging research.

SAFETY

COMMON EFFECTS	Injection-site redness, pain, itching and induration dominate the clinical tolerability profile. In the small Barth crossover trial, all elamipretide recipients experienced injection-site redness; most events were mild or moderate. Local reactions also contributed to discontinuation during longer exposure. PMID 33077895. The FORZINITY label additionally describes eosinophil increases without associated clinical manifestations in the reported observations.
SERIOUS SIGNALS	The FORZINITY label reports serious hypersensitivity, sometimes requiring emergency treatment. Reactions can arise shortly after initiation or after months of exposure. Small trials cannot reliably exclude rare harms. Long-term safety in healthy adults remains insufficiently characterized.
CONTRAINDICATIONS	The labeled contraindication is serious hypersensitivity to elamipretide or formulation ingredients. Renal impairment requires prescribing review. Pregnancy and breastfeeding lack adequate human safety data. The benzyl-alcohol-containing formulation carries a neonatal toxicity warning and is not approved for neonates. These label-specific limitations do not establish the safety of an unapproved formulation.
STOP RULES	Breathing difficulty, facial swelling, widespread hives or collapse require stopping exposure and emergency assessment. The label excludes rechallenge after serious hypersensitivity. Persistent severe skin reactions or spreading redness with fever require medical review. These are adverse-event precautions, not a substitute for a monitored treatment plan.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	The FORZINITY prescribing information describes a ready-to-use 280 mg/3.5 mL solution, equivalent to 80 mg/mL. This is vial content and concentration, not a dose. The presentation is for single-patient use. It does not establish the composition, potency or handling requirements of a powder labeled SS-31.
SOLVENT	The approved formulation requires no reconstitution. Its label does not establish a solvent or preparation method for research powder. Bacteriostatic water does not establish compatibility, chemical stability, endotoxin control or sterility of such material. The label also excludes mixing with other medicines in the same syringe.
STORAGE	FORZINITY prescribing information specifies storage at 2 to 8 C without freezing. After first opening, the vial may remain refrigerated or be stored at 20 to 25 C. Disposal is required eight days after first opening. These formulation-specific conditions cannot be transferred to reconstituted research powder.

Label-based arithmetic only: the FORZINITY prescribing information reports 40 mg subcutaneously once daily for eligible patients and a concentration of 80 mg/mL. Dividing that labeled dose by the labeled concentration gives 0.5 mL. This demonstrates the relationship between mass, concentration and volume for the approved solution. It is not a powder-reconstitution procedure or a healthy-adult regimen. The labeled concentration refers to elamipretide content, which differs from the mass of its hydrochloride salt. Syringe volume markings do not independently identify peptide mass, and elamipretide is not dosed in IU. The calculation depends on a verified concentration; arithmetic cannot verify the contents of an unknown preparation.

BUYING NOTES

A certificate of analysis has limited scope. Chromatographic purity does not establish peptide identity, actual vial content, sterility, endotoxin burden or stability after preparation. Meaningful documentation links the tested lot to the material and distinguishes peptide content from salt mass. Different analytical questions require different validated tests; a single purity percentage cannot answer all of them. Research-only labeling and a familiar compound name do not establish pharmaceutical equivalence or suitability for human use.

COMMON MISTAKES

- Calling SS-31 entirely investigational despite its narrow FDA approval, or treating that approval as evidence for general longevity.
- Highlighting small positive studies while omitting the negative MMPOWER-3 primary endpoints or the exploratory nature of adjusted analyses.
- Treating mitochondrial biomarkers, exercise tolerance, post-training recovery and lifespan as interchangeable outcomes.
- Converting mouse mg/kg exposure directly into a human dose or equating continuous pump delivery with a daily bolus.
- Confusing syringe volume markings with mg or IU, transferring storage rules between formulations, or assuming bacteriostatic water sterilizes a powder.
- Interpreting absence from WADA's named examples as definitive clearance for competitive sport.

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Humanin

HNG (S14G-humanin)

Mitochondrial-derived peptide

Module 4 · Mind & Longevity

Goals: Longevity

Route: SC (research)

A mitochondrial-derived cytoprotective peptide with animal evidence for selected healthspan effects, but no established human treatment dose or demonstrated human longevity benefit.

WHAT IT IS

Humanin, abbreviated HN, is generally described as a 24-amino-acid mitochondrial-derived peptide. Its proposed coding sequence lies within the mitochondrial MT-RNR2 region. It participates in cellular stress responses and has been investigated in neurodegeneration, metabolic dysfunction, cardiovascular injury, and aging. Module placement: 4, Mind & Longevity. Primary goal category: Longevity. This category describes the research question, not an established treatment indication, PMID 37106758.

HNG means S14G-humanin, an analogue in which glycine replaces serine at position 14. It is not an exact alias for native Humanin. Much of the intervention literature uses this more potent analogue, with potency depending on the experimental assay. Native Humanin, HNG, and HNGF6A differ in sequence and experimental behavior. Their potency, pharmacokinetics, and reported doses are not interchangeable, PMID 23836030.

MECHANISM

Humanin has extracellular signaling actions and intracellular interactions with proteins controlling cell death. Neuronal experiments support receptor complexes involving ciliary neurotrophic factor receptor alpha, CNTFR-alpha, WSX-1, also called IL27RA, and gp130, also called IL6ST. Receptor knockdown and binding experiments support their involvement in protection against Alzheimer-related cellular insults. Downstream JAK/STAT signaling, particularly STAT3 activation, contributes to protection. The precise receptor organization and its importance across different human tissues remain incompletely established, PMID 19386761.

A separate extracellular pathway involves formyl peptide receptor 2, FPR2, historically called FPRL1, with context-dependent calcium and ERK signaling. These findings support proposed effects on inflammatory responses and cell survival, but receptor activation does not establish clinical benefit, PMID 37106758. Inside cells, Humanin binds BAX and inhibits its movement from the cytosol to mitochondrial membranes. This reduces mitochondrial cytochrome c release and subsequent apoptotic signaling in experimental systems. Biochemical and cell experiments directly support this interaction, PMID 12732850.

Downstream findings vary by model. HNG increased AMPK and endothelial nitric oxide synthase phosphorylation in mouse cardiac ischemia experiments, PMID 20651283. Humanin also interacts with IGFBP-3, influencing analogue clearance and the circulating IGF system in rodents, PMID 23836030. Reduced oxidative stress, altered autophagy, and metabolic responses are additional proposed contributors to healthspan effects, PMID 37106758. These findings do not establish that administering Humanin reverses biological aging. They also do not establish that inhibiting apoptosis benefits every tissue or disease state.

EVIDENCE · GRADE C

Grade C applies to therapeutic longevity claims: intervention evidence is predominantly animal-based, while human associations cannot establish treatment benefit. Individual receptor and protein-binding findings are mechanistic, grade D. The 2023 systematic review summarizes aging biology; it is not a human treatment trial, PMID 37106758. No published human therapeutic trial administering native Humanin or HNG was identified in the PubMed searches performed for this review. This is a bounded search finding, not proof that no unindexed or unpublished study exists.

Human data. Human studies include circulating peptide measurements, disease comparisons, and genetic associations. The cognitive-aging paper links a mitochondrial variant to Humanin levels and cognitive aging. Its administered-peptide experiments were in mice, PMID 30242290. Children of centenarians had higher circulating Humanin in another study, which cannot show that supplementation extends life, PMID 32575074. A 2025 randomized trial measured endogenous Humanin during exercise and astaxanthin interventions in women with type 2 diabetes, PMID 41249265. Humanin itself was not

Animal and mechanistic data. Humanin overexpression extended lifespan in worms through a daf-16/FOXO-dependent mechanism. In aged female mice, chronic HNG improved selected metabolic and inflammatory measures without significantly extending lifespan, PMID 32575074. Other experiments reported improved cognitive performance in aged mice and reduced cardiac injury after experimentally induced ischemia, PMIDs 30242290 and 20651283. These models address specific biological questions, not human longevity. Related publications examine overlapping chronic-treatment models, so publication counts do not necessarily

administered. Its randomized design therefore does not justify grade A for Humanin treatment or establish Humanin as the cause of observed changes.

represent independent intervention replications. Worm overexpression, mouse analogue treatment, and naturally occurring human peptide levels are distinct forms of evidence.

REGULATORY STATUS AND SPORT

STATUS	Research compound. No approved Humanin or HNG medicine, regulatory dosing label, or established clinical indication was identified in the reviewed sources. A research-use designation does not establish pharmaceutical quality or authorization for human treatment. This review does not constitute a jurisdiction-by-jurisdiction approval or legal-status determination.
WADA	Prohibited at all times as an unapproved pharmacological substance. S0 applies when a substance lacks governmental approval for human therapeutic use and is not addressed by another section. Humanin is not individually named in the 2026 list. Applying S0 here is a category-based interpretation, not a Humanin-specific WADA determination. Absence from the named examples does not establish permission. Source: [WADA 2026 Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Intraperitoneal administration predominates in the intervention studies summarized here. Intracardiac administration was also studied in acute mouse cardiac injury, PMID 20651283. The rodent pharmacokinetic paper discusses additional preclinical literature using intravenous, intracerebroventricular, and intranasal routes, PMID 23836030. Subcutaneous administration is not an established clinical route. No validated human subcutaneous regimen or human subcutaneous bioavailability study was identified in this review.
HALF-LIFE	No established human half-life. Following intraperitoneal HNG, the rodent study reported approximately 30 minutes in wild-type mice and an apparent value exceeding 4 hours in rats. Analogue identity and IGFBP-3 binding affected the measured profile, PMID 23836030. Rat sampling was sparse, and rat doses differ between the paper's methods and figure legends. These estimates describe experimental concentration profiles, not validated human elimination parameters. They cannot establish a human subcutaneous dosing interval, and plasma persistence is not equivalent to duration of biological activity.
TIMING	No evidence establishes morning, bedtime, fasting, or workout-related administration for people. Acute cardiac experiments timed treatment around induced ischemia or reperfusion, PMID 20651283. That design cannot support a daily wellness schedule. Exercise-associated changes in endogenous Humanin also do not establish when an administered peptide would be effective.
CYCLE LENGTH	No validated human cycle, maintenance schedule, or washout interval was identified. The prolonged mouse experiment describes an animal study duration, not a human cycling strategy, PMID 32575074. It does not establish a rationale for popular on-and-off patterns or show that intermittent human exposure improves tolerability.
TITRATION	No human dose-escalation study, maximum tolerated dose, exposure target, or dose-adjustment algorithm was identified. Animal efficacy cannot supply these missing parameters. Body-weight or body-surface-area conversion alone cannot establish a clinically acceptable human starting dose or account for analogue-specific exposure.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved-label and human therapeutic dosing	No approved-label dose or administered-Humanin therapeutic trial dose identified in this review.	No established human therapeutic route.	No established human frequency.	The cited human studies measured endogenous Humanin rather than administering it. The randomized exercise and astaxanthin study illustrates this distinction, PMID 41249265. · PMID 41249265
Aged female mice, longitudinal HNG healthspan experiment	HNG 4 mg/kg per administration, intraperitoneally twice weekly for 14 months, beginning at 18 months of age, PMID 32575074.	Intraperitoneal.	Twice weekly for 14 months, beginning at 18 months of age.	Primary animal study methods, PMID 32575074. The methods specify twice weekly, resolving the potentially ambiguous term bi-weekly used elsewhere in the paper. · PMID 32575074
Male mice, analogue pharmacokinetics	HNG or HNGF6A 2 mg/kg, given once intraperitoneally with subsequent serial sampling, PMID 23836030.	Intraperitoneal.	Single administration with serial sampling.	Primary pharmacokinetic experiment, PMID 23836030. Different analogues and mouse genotypes were compared; their exposures were not interchangeable. · PMID 23836030
Male mice, acute myocardial ischemia dose-response experiment	HNG 0.04, 0.2, 0.4, 1, or 2 mg/kg, given once intraperitoneally 1 hour before induced ischemia, PMID 20651283.	Intraperitoneal pretreatment.	One administration 1 hour before experimentally induced ischemia.	Primary animal study, PMID 20651283. These were separate experimental dose groups. The largest response occurred at the highest tested dose. · PMID 20651283

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Male mice, intervention at cardiac reperfusion	HNG 2 mg/kg, given once by intracardiac administration at reperfusion, PMID 20651283.	Intracardiac.	One administration at reperfusion.	Primary animal study methods, PMID 20651283. This experimental delivery method does not establish a practical human treatment route. · PMID 20651283
Non-clinical dosing claims	No numerical range included because a consistent, attributable range distinguishing native Humanin from HNG was not verified.	No verified human subcutaneous regimen.	Unvalidated and not established.	No traceable non-clinical dosing source was verified. An unvalidated-use tag alone would not establish the accuracy of a numerical range. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ MOTS-c	Hypothesis only: both belong to mitochondrial-derived peptide research, with overlapping metabolic and stress-response themes. This provides a rationale for comparative experiments. No Humanin plus MOTS-c treatment trial establishing additive benefit, optimal sequencing, or combination safety was identified in this review.	– FOXO4-DRI	Not an established longevity combination. Proposed senolytic effects of FOXO4-DRI and Humanin's antiapoptotic effects suggest possible functional opposition. This remains an untested mechanistic concern. Neither concurrent administration nor a spacing strategy has been validated for this combination.
+ SS-31	Hypothesis only: mitochondrial membrane and bioenergetic research could complement Humanin's proposed cytoprotective signaling. Different proposed targets do not prove synergy. No validated Humanin plus SS-31 regimen or combination longevity benefit was identified in this review.	– IGF-1 LR3	Complementary effects cannot be assumed. Humanin interacts with IGFBP-3 and alters circulating IGF-system measurements in rodents, PMID 23836030. An experimental IGF analogue adds endocrine and proliferative uncertainties. This is a mechanistic concern, not a demonstrated clinical drug interaction.

SAFETY

COMMON EFFECTS	Human adverse-event frequencies are unknown because adequate administered-peptide safety trials were not identified. A reliable list of common Humanin side effects therefore cannot be supplied. Local reactions, hypersensitivity, and contamination-related illness are general concerns with unvalidated injectable preparations, not established Humanin-specific incidence estimates.
SERIOUS SIGNALS	Antiapoptotic signaling raises a context-dependent concern about preserving cells that should undergo programmed death, including potentially malignant cells. The BAX experiments establish an antiapoptotic mechanism, not evidence that Humanin causes cancer, PMID 12732850. Long-term tumor effects, immunogenicity, reproductive safety, and organ toxicity remain insufficiently characterized for human administration. Rodent metabolic and IGF-axis findings also make endocrine interactions plausible, PMID 23836030.
CONTRAINDICATIONS	There is no approved label defining formal contraindications. Pregnancy, breastfeeding, childhood, active malignancy, cancer treatment, and substantial renal or hepatic disease lack adequate safety evidence. These are unresolved risk settings, not trial-established contraindications. Glucose-lowering treatment raises additional monitoring questions because Humanin affects metabolic pathways in experimental models.
STOP RULES	During supervised investigational exposure, breathing difficulty, facial swelling, fainting, severe confusion, or spreading redness with fever warrant stopping exposure and urgent medical assessment. Protocol-defined abnormalities in glucose or organ-function testing require investigator review. No validated Humanin-specific laboratory stopping thresholds exist.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No standardized pharmaceutical vial strength was identified. The hypothetical stock amount in the calculation below is an arithmetic assumption, not a verified typical presentation. Container labeling alone does not establish peptide identity, active content, or suitability for administration.
SOLVENT	No validated human formulation was identified. Bacteriostatic water compatibility, preservative tolerance, and post-reconstitution stability cannot be assumed. The cited mouse cardiac study dissolved HNG in saline, PMID 20651283. That experimental formulation does not establish a general diluent or preparation procedure for human use.
STORAGE	No universal refrigerated shelf life or beyond-use date can be assigned. Stability depends on sequence, concentration, buffer, preservative, container, and handling. Research material requires formulation-specific stability documentation. Storage conditions for frozen research plasma or tissue samples do not establish storage conditions for a peptide preparation. A clear solution does not establish identity, potency, sterility, or absence of endotoxin.

Arithmetic only: PMID 23836030 used HNG 2 mg/kg once intraperitoneally in mice. For a hypothetical 25 g mouse, that study exposure calculates as 2 mg/kg multiplied by 0.025 kg, equaling 0.05 mg or 50 mcg. The mouse weight is an illustrative assumption, not a reported individual animal measurement. Separately, a hypothetical stock containing 5 mg HNG in a final volume of 2 mL would contain 2.5 mg/mL, or 2,500 mcg/mL. Dividing the study-derived amount for that hypothetical mouse by this assumed concentration gives a nominal volume of 0.02 mL. The stock amount, final volume, and concentration are calculation inputs, not a documented study formulation. No solvent compatibility, sterility, stability, or dosing accuracy is established by this arithmetic. Peptide mass and liquid volume are different quantities; neither establishes biological potency in IU.

BUYING NOTES

A meaningful research COA identifies the exact sequence, distinguishes HN from HNG and HNGF6A, and ties results to the specific lot. Mass spectrometry addresses molecular identity. A chromatographic purity percentage alone does not establish peptide content or biological potency. Water content and counterions can affect the relationship between total powder mass and peptide mass. Sterility, endotoxin, residual solvents, and aggregation require separate assessment where relevant. Neither a research-use label nor a purity claim establishes suitability for human administration.

COMMON MISTAKES

- Calling HNG an interchangeable synonym for native Humanin and transferring its potency or dose without identifying the sequence.
- Reading a human biomarker study, genetic association, or exercise trial as evidence that administered Humanin works in people.
- Reporting mouse healthspan improvements as demonstrated mouse or human lifespan extension.
- Treating a rodent half-life as a human subcutaneous half-life, or assuming plasma clearance determines the entire biological effect.
- Converting animal mg/kg values into a personal dose without human pharmacokinetic and safety development.
- Assuming absence from the named examples in the WADA list means an unapproved pharmacological substance is permitted.

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FOXO4-DRI

Proxofim

D-retro-inverso FOXO4 peptide (senolytic)

Module 4 · Mind & Longevity

Goals: Longevity

Route: SC (research)

An experimental senolytic peptide targeting the FOXO4-p53 interaction, with animal evidence and no established human longevity benefit or dosing regimen.

WHAT IT IS

FOXO4-DRI is a synthetic, cell-penetrating D-retro-inverso peptide designed to interfere with a survival mechanism used by certain senescent cells. D-retro-inverso describes reversed sequence orientation combined with D-amino acids. This design aims to preserve relevant molecular interactions while increasing resistance to enzymatic degradation. It does not establish predictable human exposure or a standardized pharmaceutical formulation. PMID 28340339.

Placement: Module 4, Mind & Longevity. Goal: Longevity research. Its defining experimental action is senolysis, elimination of susceptible senescent cells through apoptosis. The evidence includes animal experiments, human cell cultures, and observations in human tissue. Human-derived experimental material does not establish safety or efficacy in people receiving the peptide.

MECHANISM

FOXO4-DRI targets an intracellular protein interaction rather than an established cell-surface receptor. FOXO4 is a forkhead transcription factor. Its interaction partner, p53, is a stress-response protein involved in cell-cycle arrest, apoptosis, and tumor suppression. In experimental senescence, FOXO4 helps retain p53 in a nuclear environment favoring survival. Disrupting that interaction can permit p53 redistribution and cell-intrinsic apoptosis. The foundational experiments demonstrated preferential killing of susceptible senescent cells under the conditions studied. They did not establish universal recognition of every harmful or aged cell. PMID 28340339.

Structural work identified the second transactivation domain of p53, TAD2, as a binding target. Both the FOXO4-derived sequence and the cationic cell-penetrating segment contribute to the interaction. Phosphorylation of p53 increased binding affinity for FOXO4 and FOXO4-DRI. This suggests that cellular stress state could influence molecular engagement. These findings do not establish human tissue targeting, effective exposure, or a therapeutic window. PMID 40593617.

Experimental downstream effects include mitochondrial apoptotic signaling and changes involving BAX and caspase activation. These findings should not be assumed to occur uniformly across tissues. Reduced senescence-associated secretory phenotype, or SASP, may follow removal of susceptible cells. Lower inflammatory markers do not prove direct blockade of an inflammatory receptor. PMIDs 28340339 and 41625068. A structured narrative review cautions that many antioxidant claims attributed to FOXO4 are extrapolated from other FOXO proteins. Whole-body rejuvenation, durable cognitive improvement, and lifespan extension in humans remain unestablished. PMID 42510573.

EVIDENCE · GRADE C

Grade C reflects animal efficacy evidence relevant to aging, with no established human longevity benefit. Cell-culture and molecular findings alone are grade D. The structured narrative review describes FOXO4-DRI as not clinically validated. It identifies pharmacokinetics, delivery, long-term toxicology, and p53-dependent tumor surveillance as unresolved. A review of preclinical findings does not upgrade them to evidence of clinical efficacy. PMID 42510573.

Human data. No published human treatment trial establishing safety, pharmacokinetics, or longevity benefit was identified in this PubMed search. Human-derived chondrocytes have been treated in culture. Senescence measures decreased, but standard pellet experiments did not show improved cartilage-forming potential. These are laboratory findings, not clinical joint-repair outcomes. Human testicular tissue observations investigated FOXO4 expression and localization, without treating men with FOXO4-DRI. Neither study establishes a human adverse-event rate or effective regimen. PMIDs 33996787 and 31959736.

Animal and mechanistic data. The original mouse work reported improvements in selected functional and tissue outcomes after senescent-cell targeting. Later studies reported changes in aged testicular function and vascular aging. The Leydig-cell study acknowledged that direct elimination of senescent Leydig cells in aged mice had not been demonstrated. These findings do not establish generalized lifespan extension. Another investigation found adverse pulmonary hemodynamic changes and pulmonary endothelial-cell loss in susceptible models, including animals receiving FOXO4-DRI. Benefit in one tissue does not establish benefit across the circulation. PMIDs 28340339, 31959736, 41625068, and 36515093.

STATUS	No approved FOXO4-DRI drug label or established clinical formulation was identified. The verified literature describes a preclinical compound without clinical validation. Its evidence includes animal experiments and human cell or tissue studies. Research labeling or commercial availability does not establish authorization for human therapeutic use. This status does not provide a validated manufacturing standard, human dosing schedule, or clinical monitoring framework. PMID 42510573.
WADA	Prohibited at all times under S0, based on its status as a non-approved pharmacological substance. This is an application of WADA's category definition, not an individually named FOXO4-DRI listing. S0 covers pharmacological substances without governmental approval for human therapeutic use that are not addressed by subsequent categories. Absence from the named examples does not establish permission. Source: [WADA 2026 Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	The verified dose examples below use intraperitoneal administration in mice. They establish the route used in those experiments, not a validated route for people. No human subcutaneous bioavailability or route-equivalence study was identified. Claims that subcutaneous administration is an established or usual human research route are unsupported by these sources. PMIDs 31959736 and 41625068.
HALF-LIFE	A reliable human plasma elimination half-life has not been established in the verified literature. D-amino-acid chemistry can improve proteolytic resistance, but it does not supply a numerical half-life. Plasma clearance, tissue persistence, intracellular target engagement, and the duration of cell-depletion effects are separate measurements. An intermittent animal schedule cannot determine any of them. Pharmacokinetic characterization remains a requirement for clinical translation. PMID 42510573.
TIMING	No evidence establishes an optimal relationship to meals, workouts, sleep, or fasting. Research schedules were selected for specific models and endpoints. Changes measured after treatment do not demonstrate that the compound remained in circulation throughout the observation period. A delayed tissue outcome cannot independently establish ongoing drug exposure.
CYCLE LENGTH	Documented experiments include a short intermittent course and longer repeated exposure, as specified in the cited dose entries. There is no established human cycle length, retreatment interval, or cumulative exposure limit. No validated human marker indicates when another course would be appropriate. These animal schedules should not be reframed as longevity maintenance protocols.
TITRATION	No human escalation scheme has been validated. Neither body-surface-area conversion nor proportional body-weight multiplication establishes an appropriate starting dose by itself. Translation would require exposure measurements, toxicology, formulation characterization, and a monitored clinical protocol. Apparent tolerance after an exposure would not establish the consequences of repeated exposure or tissue depletion.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Naturally aged mice, Leydig-cell senescence and testosterone secretion	5 mg/kg per administration, intraperitoneally every other day for three administrations, as reported in PMID 31959736.	Intraperitoneal, mouse experiment.	Every other day for three administrations; outcomes included assessment 30 days after treatment. PMID 31959736.	Zhang and colleagues, primary animal study. The published amount remains in mg/kg of mouse body weight and is not converted into a human dose. The experimental vehicle was phosphate-buffered saline. Source: [Primary study, results and methods](https://www.aging-us.com/article/102682/text). · PMID 31959736
Naturally aged mice, vascular aging	5 mg/kg per administration, intraperitoneally every two days for one month, as reported in PMID 41625068.	Intraperitoneal, mouse experiment.	Every two days during one month. PMID 41625068.	Hu and colleagues, natural-aging treatment arm. This schedule examined vascular outcomes and does not validate maintenance treatment for healthy adults. Source: [Primary study, section 2.1] (https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2025.1729166/full). · PMID 41625068
D-galactose-induced aging in mice, vascular outcomes	5 mg/kg per administration, intraperitoneally every two days for four weeks, as reported in PMID 41625068.	Intraperitoneal, mouse experiment.	Every two days for four weeks, beginning after four weeks of aging-model induction. PMID 41625068.	Hu and colleagues, induced-aging arm of the same publication, section 2.1. Aging-model induction continued during treatment. This is a separate experimental context, not an independent replication or a human dose-ranging study. · PMID 41625068
Approved labeling and human intervention trials	No approved label dose or verified human trial dose was identified.	No validated human route identified.	No validated human frequency identified.	The verified review describes preclinical activity without clinical validation. A numerical human regimen cannot be supplied from these findings. The PubMed search did not identify a human treatment trial supporting one. · PMID 42510573

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Informal non-clinical regimens	No dependable numerical range was verified. The tag commonly cited in non-clinical use; not validated in trials does not verify an otherwise unsupported number.	No informal route is treated as established by the verified literature.	No standardized or trial-validated human frequency identified.	No primary source supporting a reproducible informal regimen was verified. An unattributed schedule would not fulfill the requirement for traceable dose provenance.

STACKING

+ SS-31	No established synergy. Proposed overlap between mitochondrial research and senescence research does not demonstrate a beneficial combination. No verified FOXO4-DRI coadministration study supports additional efficacy, suitable sequencing, or tolerability for this pairing. Its inclusion represents an unanswered research question, not a documented stack.	– IGF-1 LR3	No established clinical interaction or validated combination protocol. Concerns about pairing growth-related signaling with an apoptosis-directed intervention remain hypothetical. The direction and magnitude of any interaction could depend on tissue and disease state.
+ MOTS-c	No established synergy. Shared interest in metabolism and aging does not establish compatible pharmacology or improved outcomes. No verified coadministration evidence supports this pairing. Changes in metabolic endpoints would not independently establish successful senolysis or show that combined exposure improves the benefit-risk balance.	– Humanin	No established clinical interaction. Proposed opposition between cytoprotection and senolysis is a mechanistic hypothesis that requires direct testing. No verified FOXO4-DRI coadministration study establishes whether this pairing changes target engagement, cell clearance, adverse effects, or functional outcomes.

SAFETY

COMMON EFFECTS	Human adverse-event frequencies are unknown, so no evidence-based list of common effects exists. Injectable preparations can carry risks of local inflammation, contamination-related illness, and hypersensitivity. These are general preparation-related concerns, not measured FOXO4-DRI event rates. Fatigue or flu-like symptoms are not validated indicators of successful senescent-cell clearance.
SERIOUS SIGNALS	A study including FOXO4-DRI reported pulmonary endothelial-cell loss and adverse pulmonary hemodynamic changes in susceptible animal models. This is a preclinical hazard signal, not a measured human event rate. PMID 36515093. Other unresolved concerns include tissue-dependent loss of useful senescent cells and effects on p53-dependent tumor surveillance. Long-term cancer safety has not been established. PMID 42510573.
CONTRAINDICATIONS	There is no approved label defining formal contraindications. Pregnancy, breastfeeding, childhood, pulmonary hypertension, active malignancy, and major organ disease lack an established safety basis. Pulmonary vascular disease is especially concerning given the animal signal. These are evidence limitations and risk considerations, not a complete clinical screening protocol. The absence of a listed condition would not establish suitability.
STOP RULES	Following exposure, new breathlessness, chest pain, fainting, facial or throat swelling, or marked deterioration warrants urgent medical assessment. Fever with a worsening injection site also requires prompt assessment. Further exposure should stop pending evaluation. Symptoms should not be interpreted as detoxification or proof that treatment is working.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No standardized clinical vial strength exists. The numerical example below assumes 5 mg of material solely for concentration arithmetic. That amount is an illustrative quantity, not a verified commercial presentation, human dose, or statement about the contents of any preparation.
SOLVENT	The mouse study in PMID 31959736 reported phosphate-buffered saline as its experimental vehicle. This does not establish a human reconstitution method or suitability for other routes. No validated human instructions or supporting compatibility data for bacteriostatic water were identified. Solvent identity, concentration, sterility, and stability require formulation-specific evidence.
STORAGE	No approved storage specification or validated human-use post-reconstitution beyond-use period was identified. Research storage depends on the actual formulation and stability data. A general refrigeration rule cannot establish how long dissolved peptide remains chemically intact or microbiologically suitable. The expiration date of a solvent likewise does not establish the stability of a peptide solution prepared with it.

Concentration arithmetic only, with hypothetical inputs: 5 mg of material in a final total volume of 2 mL equals 2.5 mg/mL, or 2500 mcg/mL. Final total volume is the relevant denominator; it is not automatically identical to the volume of solvent added. This calculation establishes only the relationship between assumed mass and final volume. It does not establish actual peptide content, solvent compatibility, sterility, stability, or an administration schedule. No human dose or administration volume follows from these inputs. The documented animal dose remains in the research-use entry with its route, frequency, and PMID. Syringe markings are device volume conventions and do not establish peptide biological activity or IU. A concentration result cannot resolve missing clinical pharmacology.

BUYING NOTES

Analytical documentation should distinguish identity, peptide content, purity, and microbiological quality. A chromatographic purity percentage does not prove the stated mass, correct stereochemistry, sterility, or low endotoxin burden. For this molecule, sequence orientation and D-amino-acid composition are particularly relevant. A certificate of analysis is more informative when it identifies the tested batch, laboratory, methods, and quantitative results. Identity and purity require methods capable of addressing the relevant analytical question. Even complete chemical characterization would not resolve the absence of human efficacy, dosing, and long-term safety data.

COMMON MISTAKES

- Treating experiments on human cells as evidence of acceptable tolerability in people receiving FOXO4-DRI.
- Calling subcutaneous administration an established human research route when the verified dose examples used intraperitoneal administration in mice.
- Converting mouse mg/kg directly into a personal dose without exposure measurements or toxicology data.
- Assuming a protease-resistant structure establishes a long human plasma half-life.
- Equating lower senescence markers with longer lifespan, better cognition, or guaranteed functional recovery.
- Describing all senescent cells as harmful despite tissue-dependent functions and the pulmonary vascular hazard signal.
- Interpreting absence from WADA's named examples as permission to use a non-approved pharmacological substance.
- Using concentration arithmetic as evidence that a preparation, solvent, storage period, or administration regimen has been validated.

REFERENCES

1. Baar MP et al. Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging.. *Cell*, 2017. PMID 28340339 DOI 10.1016/j.cell.2017.02.031 (Foundational FOXO4-p53 interference, senescent-cell apoptosis, and selected functional outcomes in mice.)
2. Zhang C et al. FOXO4-DRI alleviates age-related testosterone secretion insufficiency by targeting senescent Leydig cells in aged mice.. *Aging*, 2020. PMID 31959736 DOI 10.18632/aging.102682 (Human tissue observations, experimental Leydig-cell biology, and the cited mouse dosing regimen using phosphate-buffered saline.)
3. Huang Y et al. Senolytic Peptide FOXO4-DRI Selectively Removes Senescent Cells From in vitro Expanded Human Chondrocytes.. *Frontiers in bioengineering and biotechnology*, 2021. PMID 33996787 DOI 10.3389/fbioe.2021.677576 (Human cell-culture senolysis and the absence of improved chondrogenic potential in standard pellet experiments.)
4. Born E et al. Eliminating Senescent Cells Can Promote Pulmonary Hypertension Development and Progression.. *Circulation*, 2023. PMID 36515093 DOI 10.1161/CIRCULATIONAHA.122.058794 (Pulmonary vascular harm signal from senolytic interventions, including FOXO4-DRI in susceptible animal models.)
5. Bourgeois B et al. The disordered p53 transactivation domain is the target of FOXO4 and the senolytic compound FOXO4-DRI.. *Nature communications*, 2025. PMID 40593617 DOI 10.1038/s41467-025-60844-9 (Structural characterization of p53 TAD2 binding, cell-penetrating-segment involvement, and phosphorylation-dependent affinity.)
6. Hu Z et al. FOXO4-DRI regulates endothelial cell senescence via the P53 signaling pathway.. *Frontiers in bioengineering and biotechnology*, 2025. PMID 41625068 DOI 10.3389/fbioe.2025.1729166 (Vascular-aging experiments and repeated intraperitoneal schedules. Year follows PubMed pubdate; the electronic publication date is January 15, 2026.)
7. Mateescu DM et al. FOXO4 as a Redox-Sensitive Regulator of Antioxidant Defense and Cellular Senescence: Cysteine-Based Signaling, p53 Interaction, and Therapeutic Targeting.. *Antioxidants (Basel, Switzerland)*, 2026. PMID 42510573 DOI 10.3390/antiox15070842 (Structured narrative review documenting absent clinical validation, limits of FOXO-family extrapolation, and unresolved pharmacokinetic and safety requirements.)

NAD+

Nicotinamide adenine dinucleotide

Coenzyme (not a peptide; included because it is stacked with the mitochondrial peptides)

Module 4 · Mind & Longevity

Goals: Longevity

Route: SC, IV or oral precursors

An essential metabolic coenzyme with established cellular functions, but unproven longevity benefits from direct supplementation.

WHAT IT IS

NAD+ means nicotinamide adenine dinucleotide in its oxidized form. It is a coenzyme, not a peptide. NADH is its reduced counterpart. Nicotinamide riboside, NR, and nicotinamide mononucleotide, NMN, are precursors used to synthesize NAD+. These substances are related but are not interchangeable treatments.

Included in Module 4, Mind & Longevity, because NAD+ biology overlaps with mitochondrial peptide research. The relevant goal is longevity research, not demonstrated lifespan extension. Oral precursor trials provide considerably more human evidence than subcutaneous NAD+ use. Their findings cannot establish the effectiveness of compounded NAD+ injections. The compound, formulation, route, population and measured endpoint all matter when interpreting a study.

MECHANISM

NAD+ accepts electrons during glycolysis, fatty acid oxidation and the tricarboxylic acid cycle, becoming NADH. Mitochondrial NADH supplies electrons to respiratory complex I, supporting the proton gradient that drives ATP synthesis. These redox functions are established biochemistry. NAD+ availability and the NAD+/NADH ratio influence metabolism. Additional NAD+ does not necessarily increase ATP production when relevant cellular pools are already adequate.

NAD+ is also consumed by sirtuins, including SIRT1 and SIRT3, and poly(ADP-ribose) polymerases such as PARP1. NAD-cleaving enzymes include CD38 and SARM1. These systems participate in protein regulation, DNA damage responses, calcium signaling and axonal degeneration. SIRT1 interacts with PGC-1alpha and metabolic programs connected to AMPK. Restoring depleted NAD+ might affect these processes, but universal sirtuin activation, mitochondrial rejuvenation and human lifespan extension are not established treatment outcomes.

Nicotinamide salvage uses NAMPT and NMNAT enzymes. NR enters through nicotinamide riboside kinases and downstream NMN conversion. Extracellular NAD+ undergoes enzymatic processing before its components can be reused. It is not a conventional peptide receptor agonist. No validated receptor-mediated anti-aging mechanism has been established for injected NAD+. Plasma changes do not prove intact delivery into muscle, brain or mitochondrial NAD+ pools. Mechanistic background: PMID 33353981. Human infusion metabolism: PMID 31572171.

EVIDENCE · GRADE C

Grade C applies specifically to longevity claims for direct NAD+: human evidence is too weak to establish improved healthspan or lifespan. It does not mean that human studies are absent. A 2026 systematic review included 33 human interventions and 80 rodent studies, covering January 2010 through October 2025. Human oral precursor studies consistently changed NAD-related biomarkers, but clinical outcomes were heterogeneous, frequently null or endpoint-specific. No eligible IV or IM NAD+ outcome trials addressed anti-aging or wellness within that review's scope. This finding does not exclude disease-specific studies or later publications. PMID 41655607.

Human data. Grant studied 11 men, including eight receiving NAD+, primarily to characterize plasma and urinary metabolites. This was not an efficacy trial for fatigue, cognition or longevity. PMID 31572171. Martens randomized 30 participants in an oral NR crossover trial; 24 completed it. NAD-related measures increased, and short-term tolerability was assessed. Exploratory vascular findings did not establish clinical benefit. PMID 29599478. Yu randomized 180 patients with ischemic cardiomyopathy-related heart failure. The one-month ejection-fraction result favored NAD+, but the six-month clinical-event difference was not statistically significant. This single-center, disease-specific finding does not establish longevity benefits in healthy trainees. PMID 40954388. Reyna's retrospective comparison included six NAD+ recipients and documented substantial

Animal and mechanistic data. Mills reported that long-term oral NMN improved several metabolic and functional measures in aging male mice, including insulin sensitivity and activity. This was precursor treatment, not subcutaneous NAD+. The study did not establish human benefit or demonstrate lifespan extension. Animal effects vary with model, tissue, baseline NAD+ status and intervention. Reported animal dose units are retained below because an arithmetic human equivalent would not establish an effective human regimen. PMID 28068222.

infusion symptoms. Its design cannot establish comparative effectiveness or long-term safety. PMID 41704678.

REGULATORY STATUS AND SPORT

STATUS	United States: no FDA-approved NAD+ injectable label for longevity was identified in the reviewed sources. Compounded NAD+ preparations are not FDA-approved drugs. Availability does not establish approval, effectiveness or eligibility under every compounding provision. Particular oral precursors are marketed as dietary supplements, a separate regulatory category. Supplement marketing does not establish approval to treat disease or validate injectable preparations. Ingredient status also depends on jurisdiction. Compounded drugs do not undergo FDA premarket review for safety, effectiveness and quality. [FDA explanation of compounded-drug risks] (https://www.fda.gov/drugs/human-drug-compounding/understanding-risks-compounded-drugs).
WADA	NAD+ is not specifically named in the 2026 WADA Prohibited List. Absence from the named substances does not establish clearance of every formulation or accompanying ingredient. Method M2.2 prohibits IV infusions or injections totaling more than 100 mL per 12 hours, both in and out of competition. Exceptions cover administration legitimately received during hospital treatment, surgery or clinical diagnostic investigations. A wellness infusion can therefore involve a prohibited method regardless of the ingredient's status. [2026 WADA Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Direct NAD+ has been studied intravenously. Subcutaneous administration appears in non-clinical descriptions, but no controlled SC longevity trial was identified in the reviewed evidence. Oral NR and NMN are precursor interventions with different absorption and metabolism. Oral NAD+, NADH, NR and NMN cannot share a single evidence or dosing profile. Findings from one route do not establish equivalent exposure or benefit through another.
HALF-LIFE	No clinically validated terminal half-life supports a standard SC or IV longevity schedule. The Grant infusion study observed rapid removal or metabolism during the early infusion period, without establishing a conventional elimination half-life. Plasma NAD+, cellular NAD+ and downstream metabolites have different kinetics. A quoted short plasma half-life cannot define tissue exposure or duration of benefit. PMID 31572171.
TIMING	No controlled evidence establishes an optimal morning, evening, fasting or pre-workout schedule for direct NAD+. Study-specific meal restrictions and blood-sampling times served experimental control. They are not demonstrated requirements for benefit. The oral NR trial used morning and evening capsules with meals, but did not compare timing strategies. PMID 29599478.
CYCLE LENGTH	No validated longevity cycle, loading phase, maintenance interval or washout exists. Grant's single infusion, Yu's seven-day hospital regimen and Reyna's four-day retrospective series answer different questions. The six-week oral precursor phase also concerns a different intervention. These durations do not form a unified protocol. PMIDs 31572171, 40954388, 41704678 and 29599478.
TITRATION	No validated SC titration algorithm exists. IV tolerability may depend on delivery rate, but a rate change in response to symptoms does not establish overall safety. Symptoms do not prove cellular uptake, detoxification or treatment effectiveness. The reviewed studies do not establish a symptom-guided target dose, acceptable discomfort threshold or universal escalation schedule.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Direct NAD+, human metabolic pilot.	750 mg NAD+ by IV infusion over six hours, administered once, as reported in PMID 31572171.	IV infusion in normal saline.	One experimental infusion, PMID 31572171.	Grant 2019, eight treated participants and three controls. The empirically selected regimen characterized metabolism; it did not establish an effective longevity dose. · PMID 31572171
Direct NAD+, randomized heart failure trial.	10 mg NAD+ intravenously once daily for seven days alongside guideline-directed treatment, as reported in PMID 40954388.	Intravenous.	Daily for seven days, PMID 40954388.	Yu 2026, published online in 2025, studied 180 patients with ischemic cardiomyopathy-related heart failure. This was disease-specific research, not a healthy-adult protocol. · PMID 40954388
Direct NAD+, retrospective tolerability study.	500 mg NAD+ by IV infusion in 500 mL normal saline once daily for four consecutive days, as reported in PMID 41704678.	IV infusion.	Daily for four consecutive days, PMID 41704678.	Reyna 2026, six NAD+ recipients. This observational regimen does not establish a loading requirement. · PMID 41704678
Oral precursor, human randomized crossover trial.	500 mg NR orally twice daily for six weeks, as reported in PMID 29599478.	Oral nicotinamide riboside chloride capsules.	Twice daily during the six-week active phase, PMID 29599478.	Martens 2018. This is an NR dose, not an equivalent mass or schedule for direct NAD+. · PMID 29599478
Oral precursor, mouse aging study.	NMN at 100 or 300 mg/kg/day orally through drinking water for 12 months, as reported in PMID 28068222.	Oral, drinking water available ad libitum.	Daily exposure through drinking water, not a once-daily bolus, PMID 28068222.	Mills 2016, male C57BL/6N mice. Values retain the reported animal units; no human dose conversion is implied. · PMID 28068222

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Direct NAD+, non-clinical SC schedules.	25 to 100 mg NAD+ subcutaneously per administration, one to three times weekly, commonly cited in non-clinical use; not validated in trials.	Subcutaneous.	One to three times weekly, commonly cited in non-clinical use; not validated in trials.	Commonly cited in non-clinical use; not validated in trials. No primary clinical source validates this range, its frequency or its applicability to a particular formulation. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ SS-31	Theoretical complementarity only: mitochondrial membrane biology and NAD-dependent metabolism offer different proposed targets. No combination trial was identified among the verified references. Neither additive longevity benefit nor an effective combined regimen is established. Mechanistic plausibility alone cannot determine whether the combination improves outcomes.	– Semaglutide	FDA notes that some compounded semaglutide preparations contain added NAD. The safety and effectiveness of these combinations have not been established. This is an evidence gap, not proof of a specific pharmacokinetic interaction. [FDA compounded-semaglutide alert] (https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded).
+ MOTS-c	Proposed overlap in metabolic stress responses provides a mechanistic hypothesis, not evidence of synergy. No human NAD+ plus MOTS-c trial was identified among the verified references. Overlapping pathways could produce redundant, additive or unexpected effects; the available evidence does not distinguish these possibilities.	– FOXO4-DRI	No established combination safety or efficacy was identified among the verified references. Claims that NAD+ improves or undermines experimental senolytic effects remain speculative. Uncertainty about combined tissue effects does not constitute a documented drug interaction, and no validated sequencing or dosing strategy follows from it.

SAFETY

COMMON EFFECTS	Reyna reported abdominal cramping, nausea, vomiting, diarrhea, increased heart rate and chest pressure during NAD+ infusions. The small, selected sample cannot establish population incidence. PMID 41704678. Local pain and irritation are possible with injections, but reliable NAD+-specific SC frequency estimates were not identified. Oral precursor tolerability cannot be transferred to injectables.
SERIOUS SIGNALS	FDA received reports of severe chills, shaking, vomiting and fatigue after NAD+ injectables, sometimes requiring medical treatment. The agency described reactions consistent with excessive endotoxin exposure and highlighted unsuitable food-grade ingredients. These reports do not establish that NAD+ itself caused every reaction. Infection, hypersensitivity and infusion complications remain relevant. [FDA sterile-compounding alert] (https://www.fda.gov/drugs/human-drug-compounding/fda-reminds-compounders-use-ingredients-suitable-sterile-compounding).
CONTRAINDICATIONS	There is no FDA-approved NAD+ longevity label defining a complete contraindication list. Pregnancy, breastfeeding, significant hepatic or renal disease and active cancer are evidence gaps requiring individualized clinical assessment. These are precautionary categories, not a verified list of absolute NAD+-specific contraindications. Hypersensitivity to formulation components is a separate concern. NAD metabolism supports both normal tissue and tumor biology, but mechanistic concerns do not prove supplementation causes cancer. PMID 34964015.
STOP RULES	Chest pain, breathing difficulty, fainting, severe palpitations, rigors, fever, persistent vomiting or spreading injection-site inflammation warrant stopping administration and urgent medical assessment. These symptoms should not be normalized as detoxification or evidence of treatment effectiveness. Severe symptoms remain clinically relevant even when similar symptoms have appeared in a published infusion study.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No standardized FDA-approved NAD+ longevity vial exists. Reyna described 500 mg lyophilized preparations for IV administration, PMID 41704678. Compounded strengths, excipients and ready-to-use solutions vary.
SOLVENT	PMID 41704678 describes bacteriostatic-water reconstitution followed by saline dilution, without a universal reconstitution volume. Solvent suitability is formulation-specific. Bacteriostatic water does not remove endotoxin.
STORAGE	Storage temperature, light protection and beyond-use date depend on formulation-specific stability and sterility information. No universal refrigerated shelf life was established by these studies. Chemical stability and microbial integrity are separate questions. A clear appearance does not demonstrate potency, sterility or absence of endotoxin, and a raw-material certificate cannot establish a finished preparation's usable storage period.

Hypothetical concentration arithmetic only: a 500 mg preparation with a final solution volume of 5 mL would contain 100 mg/mL. The preparation mass matches the IV preparation described in PMID 41704678; the final volume is an assumption, not that study's reconstitution instruction. A 0.50 mL aliquot would contain one tenth of the

preparation's total mass. Neither the aliquot nor the assumed concentration represents a validated SC or IV dose, frequency or preparation method. On a U-100 insulin syringe, 100 marked units represent 1 mL, so 0.50 mL corresponds to 50 marked units. These markings express volume, not NAD+ IU or potency. Correct arithmetic cannot establish solvent compatibility, sterility, clinical appropriateness or formulation stability.

BUYING NOTES

Identity, assay and purity are separate from sterile-product suitability. A relevant certificate of analysis identifies the exact material, lot, analytical method and test date. Injectable evaluation additionally involves finished-product sterility, bacterial endotoxins, particulates, concentration and traceability. A raw-material purity percentage or research-use designation does not establish suitability for human administration. Documentation is meaningful only when it corresponds to the actual material and finished preparation being evaluated.

COMMON MISTAKES

- Calling NAD+ a peptide or treating NAD+, NADH, NR and NMN as interchangeable.
- Interpreting a higher blood NAD-related biomarker as proof of better cognition, training recovery or longevity.
- Transferring an oral precursor trial or mouse dose directly to SC NAD+.
- Treating infusion discomfort as evidence that treatment is working.
- Confusing U-100 syringe markings with mg or biological IU.
- Assuming absence from named WADA substances removes the separate IV-method restriction.

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PT-141

Bremelanotide, Vyleesi

Melanocortin MC4/MC3 receptor agonist

Module 4 · Mind & Longevity

Goals: Libido

Route: SC as needed

Bremelanotide is a centrally acting melanocortin agonist with modest demonstrated benefits for sexual desire and related distress in premenopausal women with HSDD.

WHAT IT IS

PT-141, also called bremelanotide, is a synthetic cyclic heptapeptide related to alpha-melanocyte-stimulating hormone, alpha-MSH. Its approved prescription formulation is Vyleesi. In this system it belongs in Module 4, Mind & Longevity, under Libido. That placement does not imply evidence for cognition or longevity.

It influences neural pathways involved in sexual motivation and response. Its approved indication is acquired, generalized hypoactive sexual desire disorder, HSDD, in premenopausal women. Approval does not establish effectiveness for ordinary libido fluctuations, exercise-related fatigue, testosterone deficiency, or sexual performance enhancement. Distressing low desire requires assessment of its cause before the trial evidence can be applied.

MECHANISM

Bremelanotide activates melanocortin receptors, which are G protein-coupled receptors. Their canonical signaling involves Gs, adenylyl cyclase, increased cyclic AMP, and downstream protein kinase A signaling. Calling PT-141 an MC4R/MC3R agonist is reasonable shorthand, but it is not selective for those receptors. The Vyleesi prescribing information identifies MC1R and MC4R as the most relevant binding targets at therapeutic exposure. MC1R activation in melanocytes promotes pigmentation and explains an important adverse effect.

MC4R-expressing neurons occur throughout the central nervous system, including networks relevant to motivation and autonomic sexual responses. Early PT-141 experiments demonstrated hypothalamic neuronal activation using c-Fos and anatomical overlap with pathways connected to penile tissue. These findings support a central mechanism, but neither c-Fos expression nor an erection establishes increased subjective desire. The contribution of MC3R to the clinical response remains less clearly established than the broader melanocortin hypothesis. PMID 12851303 supports these early experimental observations.

Central melanocortin signaling provides a biological rationale for effects on sexual responses. It does not establish a complete causal pathway for improvement in human HSDD. The prescribing information explicitly states that this clinical mechanism remains unknown. PT-141 has not been shown to restore deficient sex hormones or permanently reset libido. Desire, genital response, nausea, pigmentation, and blood-pressure effects involve overlapping but distinct biological processes.

EVIDENCE · GRADE A

Grade A applies specifically to the approved HSDD indication because bremelanotide has regulatory approval and two randomized phase 3 trials. It does not imply a large average benefit or strong evidence across sexes and diagnoses. Early erectile-response studies in men support a narrower grade B conclusion. General libido optimization, longevity, and peptide-combination claims are not established by the verified evidence.

Human data. The two 24-week RECONNECT trials randomized 1,267 premenopausal women. The safety population included 1,247 participants, and the primary efficacy population included 1,202. Compared with placebo, pooled differences were 0.35 points for the Female Sexual Function Index desire domain and minus 0.33 points for distress about low desire. Both differences were statistically significant. The prespecified satisfying-sexual-events endpoint did not significantly improve. These are modest average changes in patient-reported outcomes, not evidence that every encounter improves, PMID 31599840. The phase 2 dose-finding trial found improvements in sexual-function measures and satisfying sexual events, PMID 27181790. Its event-count result does not override the negative prespecified event-count endpoint in phase 3. A 52-week open-label extension enrolled 684 participants, of whom 272

Animal and mechanistic data. In hormonally primed, ovariectomized female rats, PT-141 increased sexual solicitation without broadly increasing locomotion, lordosis, or measured sexual reward, PMID 15226502. Other early experiments reported erections in rats and nonhuman primates, plus hypothalamic neuronal activation in rats, PMID 12851303. These findings support biological plausibility but cannot establish human satisfaction, relationship outcomes, or an effective human dose by body-weight conversion. Animal behavioral results remain grade C evidence when considered separately from the human HSDD trials.

completed it. Reported benefit persisted among participants, but the absence of a control group and substantial attrition limit conclusions about durability, PMID 31599847. Extension eligibility also selected participants who completed the core phase without serious adverse events. The pivotal program was industry funded, and participants were predominantly White. Earlier intranasal studies in men measured erectile rigidity under laboratory conditions. They do not establish broad treatment of male low desire, PMID 14963471.

REGULATORY STATUS AND SPORT

STATUS	The United States FDA approved Vyleesi in 2019 for acquired, generalized HSDD in premenopausal women. Low desire must cause marked distress or interpersonal difficulty and must not result from another condition, relationship problems, or medication effects. It is not approved for men, postmenopausal women, or sexual performance enhancement. Approval applies to the specified prescription formulation, not every material labeled PT-141. The prescribing information reviewed was revised in March 2024. Source: [Vyleesi prescribing information] (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f1d0c1b5-2f39-4bad-a6a4-0066e3ad5dcf).
WADA	Bremelanotide and PT-141 are not explicitly named on the 2026 WADA Prohibited List. Its approval for human therapeutic use means S0 does not apply merely because it is a peptide. No applicable prohibition was identified in this review. This is an interpretation of the published list, not substance-specific clearance from an anti-doping authority. Absence from the named examples alone cannot establish permission because some categories include unnamed substances. The exact medicine and current rules require confirmation through the relevant anti-doping organization. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Subcutaneous administration is the approved route. Intranasal administration was investigated during development, including erectile-response studies in men, PMID 14963471. Intranasal and subcutaneous quantities are not interchangeable because absorption differs. The verified prescribing information and studies do not establish an approved oral PT-141 regimen.
HALF-LIFE	The Vyleesi label reports a mean terminal half-life of approximately 2.7 hours after subcutaneous administration, with a range of 1.9 to 4.0 hours. Median peak plasma concentration occurs at approximately one hour. Early intranasal research reported mean half-lives of 1.85 to 2.09 hours, PMID 14963471. Plasma half-life does not establish the duration of benefit or justify repeat administration.
TIMING	The label's pre-activity timing is reported above. It also states that the optimal administration window and duration of efficacy are not fully characterized. Trial assessments over weeks cannot establish a guaranteed onset or duration after one exposure. Laboratory erectile-response timing in men is a different endpoint from subjective desire in women.
CYCLE LENGTH	There is no established bodybuilding-style cycle. Controlled efficacy trials lasted 24 weeks, with a subsequent 52-week open-label extension, PMIDs 31599840 and 31599847. The Vyleesi label specifies discontinuation after eight weeks without symptom improvement. Study duration does not establish a universal duration of treatment or a repeated cycling schedule.
TITRATION	The approved product uses a fixed dose and has no labeled titration ladder. Phase 2 dose groups do not validate stepwise escalation. Escalation to overcome nonresponse can increase exposure-related adverse effects without establishing additional benefit. The verified evidence does not provide a titration protocol for men or general libido enhancement.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved United States HSDD regimen	1.75 mg subcutaneously per as-needed administration, supplied in 0.3 mL, according to the Vyleesi prescribing information.	Subcutaneous, abdomen or thigh, according to the Vyleesi prescribing information.	The Vyleesi label specifies as-needed administration at least 45 minutes before anticipated sexual activity. It limits administration to once within 24 hours and does not recommend more than eight administrations monthly.	Vyleesi United States prescribing information, sections 2 and 3. This describes the authorized regimen, not a recommendation for the reader.
Phase 2 randomized dose-finding trial in premenopausal women	0.75 mg, 1.25 mg, or 1.75 mg subcutaneously per as-needed administration in separate randomized groups, PMID 27181790.	Subcutaneous, anterior thigh or abdomen, PMID 27181790.	After in-clinic testing, the study used 12 weeks of as-needed administration approximately 45 minutes before anticipated sexual activity, PMID 27181790. Study limits were once daily and 16 administrations per four weeks. These historical limits differ from the approved label.	Clayton and colleagues, randomized placebo-controlled dose-finding trial, PMID 27181790. Parallel dose groups do not establish an individual escalation schedule. · PMID 27181790

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CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Historical intranasal alcohol-interaction study described in the regulatory label	20 mg intranasally as a single experimental administration per relevant crossover period, according to Vyleesi prescribing information, section 12.2.	Intranasal research formulation, according to Vyleesi prescribing information, section 12.2.	Single experimental administration per relevant period in a controlled crossover study involving healthy men and women. Source: Vyleesi prescribing information, section 12.2.	Vyleesi United States prescribing information, section 12.2, Alcohol Interaction. This was not an approved libido regimen or the male erectile-response study cited elsewhere.
Female-rat sexual-solicitation experiments	50, 100, or 200 mcg/kg subcutaneously once before each behavioral test, PMID 15226502.	Subcutaneous, dissolved in saline, PMID 15226502.	One administration five minutes before each behavioral test, PMID 15226502.	Pfaus and colleagues, hormonally primed female-rat experiments, PMID 15226502. Full-text methods confirm the amounts, route, and timing. No human-equivalent dose is inferred. · PMID 15226502
Informal non-clinical use descriptions	0.5 to 2 mg subcutaneously per as-needed administration, commonly cited in non-clinical use; not validated in trials as a general-purpose regimen.	Subcutaneous in informal descriptions, commonly cited in non-clinical use; not validated in trials.	Intermittent, as needed, commonly cited in non-clinical use; not validated in trials. No standardized or validated frequency accompanies this informal range.	Commonly cited in non-clinical use; not validated in trials. This range is not a male dosing standard, a titration protocol, or an extension of regulatory approval. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ Kisspeptin-10	Hypothesis only, not demonstrated synergy. The verified bremelanotide references do not test this combination or establish an additive benefit. Proposed overlap in reproductive and sexual-response pathways is insufficient to predict clinical outcomes. No combination dose, frequency, or safety profile is established by the cited evidence.	– Melanotan II	Overlapping melanocortin agonism creates a plausible concern about additional nausea, pigmentation, and autonomic effects. This is a pharmacologic inference, not a quantified clinical interaction. The verified evidence establishes neither incremental benefit nor an acceptable combined exposure.
+ Oxytocin	Hypothesis only, not demonstrated synergy. The verified bremelanotide references do not establish that adding oxytocin improves desire, distress, or sexual satisfaction. Separate biological roles cannot establish combination efficacy. Context, route, and adverse effects would require direct evaluation in a combination trial.	– Semaglutide	Potentially overlapping gastrointestinal effects and delayed gastric emptying warrant clinical review. This is a pharmacologic inference, not a demonstrated contraindication specific to the pair. The verified bremelanotide evidence does not establish combination tolerability, efficacy, or effects on oral medication absorption.

SAFETY

COMMON EFFECTS	Nausea, flushing, headache, local injection reactions, and vomiting are prominent tolerability problems. In the pivotal program, nausea affected approximately 40% of treated participants. Adverse effects caused substantially more discontinuations than placebo. Nausea may lessen with subsequent exposures but is not evidence that the drug is working, PMID 31599840.
SERIOUS SIGNALS	Transient blood-pressure elevation and heart-rate reduction require attention, including in otherwise active adults. Ambulatory monitoring documented these effects, PMID 27977473. Focal hyperpigmentation may persist after discontinuation. The Vyleesi label warns that delayed gastric emptying can alter oral-drug absorption. It specifically advises avoiding concurrent oral naltrexone intended for alcohol or opioid addiction because reduced exposure could compromise treatment. Persistent vomiting can cause dehydration.
CONTRAINDICATIONS	The Vyleesi label contraindicates use with uncontrolled hypertension or known cardiovascular disease. It also discourages use in people at high cardiovascular risk. Suspected pregnancy warrants discontinuation because animal findings indicate potential fetal harm. The label calls for effective contraception during treatment. Human lactation data are absent. Severe renal impairment requires caution; severe hepatic impairment has not been evaluated and also requires caution. Fitness level does not substitute for blood-pressure assessment, medication review, or evaluation of the cause of low desire.
STOP RULES	Chest pain, fainting, or severe headache with neurological symptoms require urgent assessment. A prolonged painful erection also requires urgent assessment, although it is not established here as a common bremelanotide adverse effect. Persistent or severe nausea, vomiting, new pigmentation, or significant blood-pressure elevation

warrant discontinuation assessment and clinical review. Suspected pregnancy and lack of improvement after eight weeks are specific discontinuation criteria in the Vyleesi label.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	The approved presentation is a ready-to-use, single-dose autoinjector and requires no reconstitution. There is no regulator-established standard PT-141 powder vial. A powder's stated mass does not establish its identity, actual peptide content, sterility, or equivalence to the approved formulation.
SOLVENT	The approved formulation contains sterile water, glycerin, and pH-adjusting ingredients, according to the Vyleesi label. It does not require added diluent. Bacteriostatic water does not reproduce the approved formulation or establish a powder's sterility, stability, compatibility, or suitability for administration.
STORAGE	The Vyleesi label specifies storage at or below 25 degrees Celsius, protection from light, and no freezing. Those instructions apply to its original formulation and container. They do not establish a storage duration for reconstituted powder. Bacteriostatic water alone cannot justify a beyond-use date.

For concentration arithmetic, the Vyleesi label supplies 1.75 mg in 0.3 mL for one subcutaneous as-needed administration. Dividing the labeled mass by the labeled volume gives approximately 5.83 mg/mL, equivalent to approximately 5,833 mcg/mL. Multiplying that concentration by the original volume recovers the labeled mass. These calculations describe the approved solution, not a powder preparation or a method for altering its device. Mass, concentration, and liquid volume are different quantities. A syringe scale represents volume only when interpreted with that syringe's calibration; it does not define peptide biological activity in IU. A correct calculation cannot validate identity, sterility, or formulation equivalence. No reconstitution recipe or storage period for a research powder is established by this arithmetic.

BUYING NOTES

A certificate of analysis is useful only when it is authentic, batch matched, and clear about the methods and material tested. Chromatographic purity alone does not establish vial content, identity, sterility, endotoxin levels, or clinical equivalence. Relevant distinctions include peptide identity, actual content, salt form, impurities, and validated handling. A laboratory result applies to the sample tested and depends on sampling and chain of custody. A PT-141 label on a powder does not confer the approval held by the prescription formulation.

COMMON MISTAKES

- Applying grade A evidence to all libido goals, both sexes, or peptide combinations instead of the studied HSDD population.
- Treating improved desire scores as proof of more satisfying sexual events, despite the negative prespecified phase 3 event-count endpoint.
- Converting historical intranasal quantities directly into subcutaneous quantities.
- Using an animal dose per kilogram as a human dosing rule.
- Confusing syringe volume scales, peptide mass, and biological IU.
- Assuming nausea or skin darkening signals greater therapeutic benefit.
- Increasing exposure before assessing medication effects, relationship factors, sleep, mood, or endocrine causes of low desire.
- Treating the absence of an identified WADA prohibition as proof of product quality or medical suitability.

REFERENCES

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2. Clayton AH et al. Bremelanotide for female sexual dysfunctions in premenopausal women: a randomized, placebo-controlled dose-finding trial.. *Women's health (London, England)*, 2016. PMID 27181790 DOI 10.2217/whe-2016-0018 (Subcutaneous phase 2 dose groups, as-needed administration, historical frequency limits, and sexual-function outcomes.)
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5. Pfau JG et al. Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist.. *Proceedings of the National Academy of Sciences of the United States of America*, 2004. PMID 15226502 DOI 10.1073/pnas.0400491101 (Female-rat sexual-solicitation findings, animal doses per kilogram, subcutaneous route, and pretest timing.)
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7. Molinoff PB et al. PT-141: a melanocortin agonist for the treatment of sexual dysfunction.. *Annals of the New York Academy of Sciences*, 2003. [PMID 12851303 DOI 10.1111/j.1749-6632.2003.tb03167.x](#) (Early MC3R/MC4R pharmacology, hypothalamic neuronal activation, animal erectile responses, and central-mechanism rationale.)

Melanotan II

MT-2

Non-selective melanocortin agonist

Module 4 · Mind & Longevity

Goals: Skin, Libido

Route: SC

An unapproved, non-selective melanocortin agonist with small human studies showing pigmentation and erectile responses, unresolved long-term safety, and serious adverse-event reports.

WHAT IT IS

Melanotan II, also called MT-2 or MT-II, is a synthetic cyclic heptapeptide modeled on alpha-melanocyte-stimulating hormone, alpha-MSH. Its constrained structure produces activity across several melanocortin receptors. Module 4 placement and the goals Skin and Libido describe research interests, not established clinical indications.

Human development began with experimental pigmentation studies, followed by investigations of spontaneous erections and sexual desire. These outcomes require separate interpretation. Darker pigmentation does not establish healthier skin, and an erectile response does not establish a durable treatment for low desire. MT-2 has no approved prescribing label identified in the reviewed sources. There is no established benefit-risk profile or approved formulation for routine tanning or sexual-function treatment.

MECHANISM

MT-2 stimulates multiple melanocortin receptors. The cited review emphasizes MC1R, MC3R and MC4R, with receptor activation increasing intracellular cyclic AMP. Non-selective activity does not mean equal effects across receptor subtypes or tissues. Receptor affinity alone cannot predict the balance between pigmentation, erectile responses and adverse effects in a particular person.

MC1R signaling promotes melanin production in melanocytes, providing a biological explanation for pigmentation changes. The three-person pigmentation pilot documented visible changes in two participants, PMID 8637402. It did not establish prevention of UV injury, skin cancer or photoaging. A pigmentation endpoint cannot substitute for clinical evidence of photoprotection. The trial also does not establish that stimulation of existing pigmented lesions has a favorable long-term risk profile.

Central MC4R signaling is implicated in erectile responses, while MC3R contributions remain incompletely resolved. Proposed interactions with oxytocinergic pathways remain mechanistic observations. These pathways are discussed in PMID 17584130. [King review](https://pmc.ncbi.nlm.nih.gov/articles/PMC2694735/).

Rat experiments suggest central and peripheral neural involvement, depending on administration route, PMID 16360286. They do not support a simple direct relaxing effect on cavernosal smooth muscle. Appetite suppression occurred in human research, PMID 9679884, but the cited studies do not establish MT-2 as a weight-management treatment.

EVIDENCE · GRADE B

Grade B reflects small, short human studies with physiological endpoints. Placebo-controlled crossover experiments provide preliminary human evidence but do not establish reliable long-term efficacy or safety. Evidence is strongest for transient erectile responses and preliminary pigmentation changes. Claims involving longevity, skin rejuvenation, sustained libido improvement or clinically meaningful fat loss are unsupported by the cited research. The evidence includes early clinical trials, mechanistic research and case reports. It does not establish a validated consumer protocol or quantify uncommon adverse events.

Human data. The pigmentation pilot included three healthy men; two showed increased pigmentation after the dosing period, PMID 8637402. A crossover trial in ten men with psychogenic erectile dysfunction reported erections in eight participants and longer objectively measured rigidity than placebo, PMID 9679884. Another crossover trial enrolled ten men with organic erectile risk factors, PMID 11018622. Erections were reported after 12 of 19 MT-2 administrations versus 1 of 21 placebo administrations. These administration counts are not independent patient counts. Sexual desire increased on a questionnaire in the latter study. This acute questionnaire result does not establish durable libido improvement, effectiveness in healthy adults or effectiveness in women.

Animal and mechanistic data. Rat experiments support central and peripheral neural involvement in erection, with effects depending on administration route and experimental conditions, PMID 16360286. These studies help identify pathways but cannot establish a human dose, an exposure ceiling or a useful peptide combination. Anesthetized animal experiments also cannot establish patient satisfaction, sustained sexual-function improvement or tolerability during repeated human exposure. The cited animal findings do not resolve the long-term consequences of melanocyte stimulation.

STATUS	No approval for MT-2 human therapeutic use was identified in the reviewed sources, and no approved MT-2 label supplies a dose. Australia's TGA states that melanotan tanning products are unapproved, supply without a prescription is illegal, and public advertising is prohibited. [TGA melanotan warning] (https://www.tga.gov.au/news/blog/dont-risk-using-tanning-products-containing-melanotan). The UK MHRA states that unauthorized medicines cannot be sold, supplied or advertised. Its April 2024 explanation notes that classification depends on formulation and claims. That distinction does not establish approval or product quality. [MHRA regulatory explanation] (https://assets.publishing.service.gov.uk/media/669fbd3aa3c2a28abb50d55a/Final_Redaction_FOI_24_274.pdf). These sources describe jurisdiction-specific restrictions, not identical rules worldwide.
WADA	Prohibited at all times under S0, Non-Approved Substances. This classification applies the 2026 S0 rule to MT-2's unapproved pharmacological status; MT-2 is not individually named in that section. S0 covers pharmacological substances without governmental approval for human therapeutic use when other sections do not address them. Absence from named examples does not establish permission. The 2026 List took effect on January 1, 2026. [WADA 2026 Prohibited List, S0](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Subcutaneous, SC, administration is documented in the early human trials. Animal research also used intravenous and targeted central administration. Intranasal products appear in regulatory warnings, but the cited human trials do not establish their bioavailability, dose equivalence or safety. A nasal formulation cannot inherit the exposure assumptions of SC research. Formulation, delivered amount and route all affect interpretation of exposure.
HALF-LIFE	A reliable human elimination half-life could not be established from the retrieved sources. Common online half-life figures should not be presented as verified pharmacokinetics. Erectile effects and nausea lasting hours, and pigmentation lasting longer, are pharmacodynamic observations. Their duration does not measure circulating drug elimination or establish an interval that prevents accumulation or adverse effects.
TIMING	Human erectile studies monitored participants for six hours after administration, PMIDs 9679884 and 11018622. The pigmentation pilot assessed changes after dosing ended, PMID 8637402. These observations do not establish optimal timing relative to training, meals, sexual activity or sleep. No validated timing strategy separates desired pigmentation from systemic adverse effects.
CYCLE LENGTH	No evidence-based consumer cycle is established. The pigmentation pilot used a two-week treatment period, PMID 8637402. Erectile studies examined acute responses across treatment sessions, PMIDs 9679884 and 11018622. Neither design validates repeated seasonal courses, continuous maintenance or a recovery interval that eliminates risk. Follow-up suitable for detecting delayed skin outcomes was not established by these trials.
TITRATION	The pigmentation pilot used supervised escalation, PMID 8637402, but this does not establish a transferable self-titration algorithm. Nausea, yawning and pigmentation are not validated biomarkers of acceptable exposure. Lack of an immediate visible response does not establish that another administration is appropriate. Reducing acute symptoms would not resolve uncertainty about delayed adverse effects.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human phase I pigmentation pilot, three healthy men.	PMID 8637402 reports 0.01 mg/kg SC initially, escalating to 0.025 or 0.03 mg/kg per active administration, on alternating treatment weekdays.	Subcutaneous.	Five active administrations across two weeks. MT-2 and saline alternated on Monday through Friday treatment days, PMID 8637402.	Dorr RT, 1996, PMID 8637402. Historical supervised escalation in a three-person pilot, not an approved tanning regimen. · PMID 8637402
Human psychogenic erectile dysfunction crossover study.	PMID 9679884 highlights 0.025 mg/kg per experimental administration in its conclusions; SC administration is described in review PMID 17584130.	Subcutaneous, as described in review PMID 17584130.	Acute treatment sessions with six-hour monitoring. The reported dose does not define a daily treatment schedule.	Wessells H, 1998, PMID 9679884. The abstract highlights this dose but does not provide the complete dose schedule. · PMID 9679884
Human erectile dysfunction with organic risk factors.	0.025 mg/kg SC per study administration, scheduled twice across crossover sessions, reported in PMID 11018622.	Subcutaneous.	MT-2 and vehicle were each scheduled twice, with six-hour monitoring after each administration, PMID 11018622.	Wessells H, 2000, PMID 11018622. Severe nausea occurred after four of nineteen reported active administrations. · PMID 11018622
Acute erection experiments in anesthetized rats.	0.1, 0.3 and 1 mg/kg intravenously per acute experimental administration, reported in PMID 16360286.	Intravenous.	Acute experimental administrations, not a chronic daily regimen, PMID 16360286.	Giuliano F, 2006, PMID 16360286. Values retain the animal study's original mg/kg units. These findings do not establish human-equivalent doses. · PMID 16360286

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Informal cosmetic tanning use outside clinical research.	250 to 500 mcg SC once daily is commonly cited in non-clinical use; not validated in trials.	Subcutaneous.	Once daily in informal accounts, without a validated duration or maintenance schedule.	Commonly cited in non-clinical use; not validated in trials. This range has no verified primary source among the cited records or approved label. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ Oxytocin	Mechanistic overlap only. Oxytocinergic and melanocortin pathways may interact in central erectile control, as discussed in PMID 17584130. No validated human MT-2 plus oxytocin regimen or additive clinical benefit was identified in the reviewed evidence. A pathway interaction does not establish the effects of administering both compounds.	– PT-141	Overlapping melanocortin agonism creates a plausible concern for additive nausea and prolonged erections. Shared pharmacology is discussed in PMID 17584130. The combination has no established benefit-risk profile in the reviewed evidence. This is a mechanism-based caution, not a demonstrated interaction rate.
		– Semaglutide	Potential overlapping nausea, vomiting and appetite suppression could worsen poor intake or dehydration. This is a pharmacological inference, not a documented MT-2 interaction trial. MT-2 has no demonstrated complementary weight-management benefit, and the reviewed evidence does not establish combination tolerability.

SAFETY

COMMON EFFECTS	Early trials reported nausea, yawning, stretching, reduced appetite, spontaneous erections, sleepiness and fatigue, PMIDs 8637402, 9679884 and 11018622. Flushing, headache and vomiting also appear in the TGA warning cited under regulatory status. Pigmentation changes can involve freckles and existing moles rather than an even cosmetic change. The small study populations cannot provide reliable adverse-event rates for widespread or prolonged use.
SERIOUS SIGNALS	Ischemic priapism requiring surgery is documented in PMID 33460908. Renal infarction and previous reports of rhabdomyolysis or renal failure are discussed in PMID 31953620. A melanoma case followed MT-2 exposure together with sunbed use, PMID 24355990. These reports identify safety signals; they do not establish incidence or prove causation. Concurrent UV exposure and uncertain product composition complicate interpretation. Conversely, uncertain causation does not establish that repeated exposure lacks these risks.
CONTRAINDICATIONS	There is no approved MT-2 contraindication list. Risk-based concerns include previous melanoma, suspicious or changing pigmented lesions, strong familial melanoma risk, previous priapism, or conditions predisposing to priapism. Significant kidney disease and unstable cardiovascular disease also warrant particular concern. Pregnancy, breastfeeding and pediatric exposure lack adequate safety evidence. These are precautionary clinical considerations, not trial-validated exclusions or label-derived rules. Their absence does not establish eligibility for use.
STOP RULES	An erection lasting four hours requires emergency assessment, sooner if painful. Severe flank pain, markedly reduced urine, or dark urine with muscle pain warrant urgent care. Chest pain, fainting, severe headache, or signs of a severe allergic reaction also warrant urgent assessment. New or changing skin lesions require prompt clinical assessment. Further exposure should stop while significant adverse effects are evaluated.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No approved standard vial presentation was identified. A hypothetical 10 mg labeled vial is used only for the concentration example below. Labeled mass does not establish actual peptide content, identity, sterility or suitability for administration. Commercial availability of a presentation does not validate its formulation.
SOLVENT	Bacteriostatic water appears in informal preparation practices, but no approved MT-2 label validates a specific diluent, preservative compatibility or post-reconstitution shelf life. Adding a bacteriostatic solvent does not sterilize contaminated powder. The concentration example below does not validate a solvent or provide preparation instructions.
STORAGE	No regulator-approved storage instructions were identified for MT-2 vials. Refrigeration, light protection or freezing cannot be assigned a validated duration without formulation-specific stability data. Chemical stability and microbiological safety are separate questions. A clear solution and an intact-looking vial do not demonstrate either. A storage claim requires evidence for the actual formulation, container and conditions.

Concentration arithmetic only: a hypothetical 10 mg of material in a final volume of 2 mL gives 5 mg/mL, equivalent to 5000 mcg/mL. These are assumed inputs, not an approved formulation or dose. Final volume and volume of solvent added are not automatically identical. The calculation does not verify the material's identity, actual

content, dissolution or sterility.

For comparison with a published study, PMID 11018622 reports 0.025 mg/kg SC per session, with two active sessions scheduled. At a hypothetical body mass of 80 kg, that study exposure calculates to 2 mg SC per session. This is an illustrative derivation from PMID 11018622, not a reported participant's dose or a recommendation. The clinical study does not validate the hypothetical vial, solvent or concentration. Syringe markings indicate a device's volume calibration; they do not establish peptide potency or an IU conversion.

BUYING NOTES

A certificate of analysis requires separate interpretation of identity, measured peptide content, chromatographic purity, related impurities, sterility and bacterial endotoxins. A high HPLC purity percentage alone does not establish the labeled mass, microbiological quality or clinical suitability. Batch matching, laboratory traceability, methods and testing dates determine what a document can substantiate. Tests not performed cannot be inferred from a purity result. Documentation cannot convert an unapproved substance into an approved medicine. Research-use labeling does not establish safety for human exposure.

COMMON MISTAKES

- Treating stronger pigmentation as proof of skin protection or a reason to increase UV exposure.
- Confusing erections, sexual desire and durable sexual-function improvement, which are different outcomes.
- Reading administration-level response counts as though each represented a different participant.
- Copying an animal mg/kg dose into a human calculator without accounting for species, route and exposure differences.
- Calling hypothesized peptide pairings proven synergies, including GHK-Cu pairings unsupported by the reviewed evidence.
- Treating syringe markings as peptide potency units, or assuming that absence from WADA's named examples means permission.

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Kisspeptin-10

Metastin 45-54

KISS1R agonist, upstream of GnRH

Module 4 · Mind & Longevity

Goals: Libido

Route: SC or IV (research)

An investigational KISS1R agonist that stimulates reproductive hormone signaling, with human endocrine evidence but no established Kisspeptin-10 treatment benefit for low libido.

WHAT IT IS

Kisspeptin-10, also called KP-10 or Metastin 45-54, is the biologically active, amidated ten-amino-acid C-terminal fragment of kisspeptin. Its human sequence is YNWSFGLRF-NH₂. It activates the kisspeptin receptor, KISS1R, historically called GPR54, upstream of gonadotropin-releasing hormone, GnRH.

Module 4, Mind & Longevity. Goal: Libido, classified as investigational. Its strongest direct human evidence concerns luteinizing hormone, LH, follicle-stimulating hormone, FSH, and testosterone responses. The prominent sexual-desire trials used Kisspeptin-54, a different molecular form. Shared receptor activity does not establish interchangeable dosing, brain effects, or clinical outcomes.

MECHANISM

Kisspeptin-10 binds KISS1R, a G protein-coupled receptor expressed on GnRH neurons. KISS1R activates Gq/11 and phospholipase C, which splits PIP₂ into IP₃ and diacylglycerol. IP₃ mobilizes intracellular calcium, while diacylglycerol activates protein kinase C. Downstream signaling includes ERK1/2 activation and neuronal depolarization. These pathways explain receptor activation; their presence alone does not demonstrate a therapeutic libido effect.

GnRH then activates pituitary GnRH receptors, increasing LH and FSH secretion. LH stimulates testicular testosterone production; ovarian responses depend on follicular development and the prevailing hormonal environment. Human studies establish downstream hormone responses, usually measuring circulating LH rather than GnRH directly. Kisspeptin therefore depends on a sufficiently responsive hypothalamic-pituitary-gonadal axis. It cannot be assumed to overcome primary gonadal failure.

Endogenous kisspeptin participates in the KNDy network with neurokinin B and dynorphin, linking reproductive pulses to sex-steroid feedback. Repeated receptor stimulation can also recruit desensitization mechanisms. Extra-hypothalamic kisspeptin signaling provides a rationale for sexual-processing research. Translating that biology into a durable KP-10 libido treatment remains unproven. Patel and colleagues review reproductive signaling and emerging therapeutic applications, PMID 37467734. Attenuated hormone responses during prolonged exposure do not, by themselves, identify the precise site or mechanism of desensitization.

EVIDENCE · GRADE C

Grade C applies to the stated libido goal for Kisspeptin-10: available human evidence is too indirect to establish that claim. Its reproductive hormone effects warrant grade B because small, short human studies demonstrate endocrine activity. Endocrine responses are surrogate outcomes and do not establish improved sexual function. Trials involving Kisspeptin-54 do not upgrade KP-10 to grade A for libido.

Human data. George and colleagues demonstrated acute LH stimulation, increased LH pulse frequency, and increased testosterone during KP-10 infusion. Key experiments included four to six participants, PMID 21632807. Jayasena and colleagues found responses differed between men and women and across menstrual phases, PMID 21976724. A direct comparison found broadly similar gonadotropin responses to intravenous KP-10 and KP-54 at the tested exposures. It did not assess libido, PMID 26089302. A 2026 randomized, single-blinded, placebo-controlled study recruited 15 healthy men across small substudies, PMID 42549827. Intermittent subcutaneous infusion sustained gonadotropin stimulation over 12 days. After five days of continuous infusion, gonadotropin concentrations were similar to vehicle, while testosterone remained elevated. These findings demonstrate endocrine activity and exposure-dependent attenuation. They do not establish improved

Animal and mechanistic data. A dog toxicology study found no overt treatment-related toxicity after 14 days of daily intravenous KP-10 followed by a recovery period. LH responses were generally smaller on day 14 than day 1, PMID 34126799. This supports limited short-term nonclinical tolerability. It does not establish long-term human reproductive safety, cancer safety, or libido efficacy. Animal exposure levels do not define an appropriate human regimen.

sexual satisfaction or long-term treatment efficacy. Separate crossover trials had 32 male and 32 female completers with hypoactive sexual desire disorder. Both used KP-54. They found changes in sexual brain processing; the male study also found increased stimulus-associated penile tumescence and selected behavioral improvements. Acute laboratory findings do not establish lasting improvements in everyday sexual function, PMIDs 36735255 and 36287566. No cited trial establishes KP-10 efficacy for hypoactive sexual desire disorder.

REGULATORY STATUS AND SPORT

STATUS	Investigational in reproductive endocrinology. No FDA-approved Kisspeptin-10 therapeutic product or approved dosing label was identified in this review. FDA identifies potential immunogenicity, peptide-impurity, and active-ingredient characterization concerns for compounded KP-10. It also describes insufficient safety information for the proposed routes. Compounding availability does not establish approval, effectiveness, or equivalence to trial material. [FDA assessment of bulk substances with potential safety risks](https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks).
WADA	The 2026 WADA Prohibited List explicitly includes kisspeptin and its agonist analogues under S2.2.1, testosterone-stimulating peptides in males. Kisspeptin-10 falls within this category and is prohibited in males at all times, in and out of competition. The named subsection is male-specific. That wording does not establish unrestricted permission for other athletes, formulations, or administration methods. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Intravenous bolus and infusion are documented human research routes. Subcutaneous bolus and pump infusion have also been investigated. The 2026 subcutaneous study provides additional endocrine evidence for pump administration. Pump-controlled exposure differs from an intermittent bolus, even when nominal total amounts match. Oral bioavailability and a standardized intranasal KP-10 libido regimen are not established by these references.
HALF-LIFE	Approximately four minutes after stopping intravenous infusion, estimated from disappearance of circulating kisspeptin immunoreactivity in humans, PMID 21976724. Hormone responses can persist longer than measurable peptide exposure. This estimate is not a validated subcutaneous absorption half-life and does not establish a repeat-dosing interval. [Jayasena human pharmacokinetic study] (https://pmc.ncbi.nlm.nih.gov/articles/PMC3232613/).
TIMING	Research timing follows blood-sampling schedules, infusion duration, and reproductive physiology. Menstrual phase materially affected responses in PMID 21976724. No cited KP-10 trial establishes an optimal interval before sexual activity, exercise, meals, or sleep. A brief plasma half-life alone cannot identify an effective behavioral treatment window.
CYCLE LENGTH	There is no validated libido cycle. The 12-day human subcutaneous experiment, PMID 42549827, defines an observation period rather than a recommended cycle. It does not establish the safety of repeated cycles, continuous months of exposure, or a necessary washout period. Preserved endocrine responsiveness over that interval does not establish durable symptom relief.
TITRATION	No clinically validated titration algorithm exists. Greater exposure did not consistently produce a larger acute response, PMID 21632807. Hormonal context and exposure pattern matter. Loss of response cannot automatically be interpreted as insufficient dose or evidence that escalation will help. The small infusion studies do not define individual treatment targets.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Acute endocrine response in healthy men	0.01 to 3.0 mcg/kg by a single intravenous bolus per experimental visit, PMID 21632807. Within that study, 1 mcg/kg produced the strongest LH response; a single intravenous bolus of 3 mcg/kg produced a smaller response.	Intravenous bolus	Once per experimental visit, not a daily treatment schedule.	George and colleagues, dose-ranging human physiology study, PMID 21632807. Endpoints were hormone responses, not libido improvement. · PMID 21632807
Sustained endocrine stimulation in healthy men	4 mcg/kg/hour by continuous intravenous infusion for 22.5 hours, PMID 21632807. A separate experiment used 1.5 mcg/kg/hour by continuous intravenous infusion, PMID 21632807.	Intravenous infusion	Continuous during the respective monitored experiment.	George and colleagues, PMID 21632807. Infusion increased LH and testosterone; the lower-rate experiment permitted assessment of LH pulsatility. · PMID 21632807

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Subcutaneous bolus in women during the follicular phase	2, 4, 8, 16, or 32 nmol/kg by a single subcutaneous bolus per experimental visit, PMID 21976724. Circulating peptide increased without a significant gonadotropin response in this setting.	Subcutaneous bolus	Once per study visit.	Jayasena and colleagues, PMID 21976724. Original molar units are retained to preserve the reported exposure. Mass conversion requires an explicitly defined molecular mass and material basis. · PMID 21976724
Chronic subcutaneous infusion in healthy men	180 nmol/hour by continuous subcutaneous infusion for five days, PMID 42549827. A separate substudy used 150 nmol/hour by subcutaneous infusion for eight hours daily over 12 days, PMID 42549827.	Subcutaneous pump infusion	Continuous for five days in one substudy; eight hours on and 16 hours off daily in another.	Yeung and colleagues, randomized, single-blinded, placebo-controlled endocrine study, PMID 42549827. These experimental schedules do not establish a libido protocol. · PMID 42549827
Dog repeat-dose toxicology	30, 100, or 1000 mcg/kg by intravenous administration once daily for 14 days, PMID 34126799. These equal 0.03, 0.1, or 1 mg/kg, respectively, for the same intravenous daily animal exposures.	Intravenous	Once daily for 14 days, followed by a 14-day recovery observation.	Terse and colleagues, PMID 34126799. The mg/kg values are mass-unit conversions of the reported animal doses, not human-equivalent doses. · PMID 34126799
Acute subcutaneous infusion in healthy men	1.25 to 10.0 nmol/kg/hour by continuous subcutaneous infusion over an eight-hour experimental session, PMID 42549827.	Subcutaneous pump infusion	Continuous for eight hours during the acute dose-response experiment.	Yeung and colleagues, PMID 42549827. This substudy assessed LH, FSH, and testosterone responses. The reported range describes research exposure, not a validated libido dose or titration schedule. · PMID 42549827

STACKING

+ PT-141	Hypothetical mechanistic complementarity only: melanocortin signaling and KISS1R signaling involve different aspects of sexual and reproductive physiology. No cited human trial tested KP-10 with PT-141. Additional benefit, optimal timing, and combination safety are unknown.	– Melanotan II	An unsupported sexual-function combination. Exposure to multiple agents complicates attribution of effects and adverse reactions. No cited KP-10 combination trial establishes a favorable benefit-risk balance. This is a precaution about an unstudied combination, not a proven direct drug interaction.
+ Oxytocin	Overlap in social-affective and reproductive signaling provides a broad research hypothesis. No cited controlled human study demonstrates a KP-10 plus oxytocin libido benefit. Biological overlap is not evidence of clinical synergy or a basis for a combined protocol.		

SAFETY

COMMON EFFECTS

A reliable frequency table of common KP-10 adverse effects is unavailable. Small monitored studies cannot exclude uncommon reactions. The clearest reproducible effects are changes in LH, FSH, and sometimes testosterone. Local discomfort is a general parenteral-administration risk rather than a quantified KP-10-specific incidence. Hormone changes alone do not establish either clinical benefit or harm.

SERIOUS SIGNALS

Important uncertainties include immune reactions to peptide material or impurities, contamination-related infection, and unintended reproductive endocrine changes. These are potential risks, not established event rates. Attenuation during prolonged exposure raises a pharmacodynamic concern. The short dog study does not resolve chronic toxicity or human fertility outcomes. Available evidence cannot reliably estimate rare serious-event rates.

CONTRAINDICATIONS

There is no approved label defining formal contraindications. Pregnancy, breastfeeding, childhood, hormone-sensitive malignancy, and unexplained reproductive endocrine abnormalities require specialist assessment because therapeutic safety is unestablished. Primary gonadal failure and defective KISS1R signaling can also limit the expected mechanism. These are precautions and mechanistic limitations, not trial-proven contraindication categories.

STOP RULES

During supervised research, suspected hypersensitivity, breathing difficulty, fainting, severe headache, or visual disturbance warrant stopping exposure and urgent medical evaluation. Fever with an inflamed administration site or significant reproductive symptoms also warrants prompt assessment. Pregnancy or clinically important hormone abnormalities require protocol review. These are general clinical safeguards, not a validated KP-10 monitoring algorithm.

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RECONSTITUTION AND STORAGE

TYPICAL VIAL	No approved vial strength or standardized presentation exists. A hypothetical 5 mg quantity of lyophilized material is used below solely to explain concentration arithmetic. It is not a verified content claim, pharmaceutical specification, or administered dose. Nominal vial mass may differ from actual peptide content.
SOLVENT	The human infusion study used saline containing a gelatin-based carrier, PMID 21976724. That formulation does not validate arbitrary diluents or presentations. No universal solvent can be assigned from these references. Compatibility, preservative suitability, container adsorption, and stability require formulation-specific evidence. A concentration calculation cannot determine whether bacteriostatic water or another diluent is appropriate.
STORAGE	No universal storage interval can be assigned to reconstituted KP-10. Stability depends on formulation, pH, temperature, container adsorption, and preservative compatibility. A generic refrigerated shelf-life claim is not supported by these trials. Research material requires formulation-specific stability and handling documentation. Visual clarity alone cannot establish chemical stability, peptide content, or sterility.

Arithmetic example only, with no administration route or frequency assigned: a hypothetical 5 mg of actual peptide in 2 mL final solution equals 2.5 mg/mL. This is equivalent to 2500 mcg/mL. At that hypothetical concentration, a 0.04 mL analytical aliquot contains 100 mcg. The aliquot is a calculation example, not a study dose or proposed exposure. Final solution volume, rather than the volume of solvent added alone, determines the denominator. Syringe markings describe volume and do not establish IU of kisspeptin activity. Actual peptide content, formulation compatibility, sterility, and measurement accuracy remain separate questions. This calculation establishes neither a preparation method nor a clinically appropriate dose.

BUYING NOTES

The relevant quality questions are identity, actual peptide content, purity, sterility, endotoxin burden, and stability. Chromatographic purity alone does not establish the amount of active peptide or suitability for human administration. A meaningful certificate of analysis, COA, connects the tested sample to the exact lot and reports methods and results. Mass spectrometry can help distinguish KP-10 from KP-54 and modified analogues. Salt, water, and counterion content can affect nominal mass. Separate assays may be needed for content, sterility, and endotoxins. No COA establishes clinical efficacy or equivalence to material used in a trial.

COMMON MISTAKES

- Treating the KP-54 sexual-desire trials as direct evidence for KP-10.
- Equating higher LH or testosterone with a demonstrated improvement in libido.
- Applying results from healthy men to every menstrual phase or endocrine diagnosis.
- Replacing a pump infusion with a bolus because the nominal total amount matches.
- Reading nmol/kg, mcg/kg, and mcg/kg/hour as interchangeable quantities.
- Assuming more exposure always means greater stimulation or better results.
- Treating syringe markings as biological IU of kisspeptin.
- Describing kisspeptin as permitted in male athletes despite its explicit WADA listing.

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2. Jayasena CN et al. The effects of kisspeptin-10 on reproductive hormone release show sexual dimorphism in humans.. *The Journal of clinical endocrinology and metabolism*, 2011. PMID 21976724 DOI 10.1210/jc.2011-1408 (Sex and menstrual-phase differences, subcutaneous bolus exposures, protocol-specific infusion preparation, and approximately four-minute disappearance half-life after intravenous infusion.)
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applications.)

Oxytocin

Pitocin, Syntocinon

Neurohypophysial nonapeptide

Module 4 · Mind & Longevity

Goals: Libido

Route: Intranasal

A neurohypophysial nonapeptide with established obstetric uses, but inconsistent human evidence for improving libido through intranasal administration.

WHAT IT IS

Oxytocin is a nine-amino-acid peptide synthesized mainly in the hypothalamic paraventricular and supraoptic nuclei. It is released into circulation through the posterior pituitary and also acts within the brain. Synthetic oxytocin is used in approved injectable medicines. Approved indications, formulations, and availability differ between countries.

Module 4, Mind & Longevity. Goal: Libido. This placement reflects research into sexual experience, social processing, and partner interaction. It does not establish oxytocin as a treatment for low desire. Intranasal administration is the usual route in behavioral research. Intravenous and intramuscular administration have established obstetric applications. These routes cannot be treated as interchangeable, and evidence for one indication does not establish efficacy for another.

MECHANISM

Oxytocin binds the oxytocin receptor, OXTR, a G protein-coupled receptor. Its best-established signaling involves Gq/11 activation, phospholipase C, inositol trisphosphate, diacylglycerol, and increased intracellular calcium. In uterine smooth muscle, calcium-dependent myosin light-chain kinase supports contraction. In mammary tissue, contraction of myoepithelial cells produces milk ejection. Receptor expression and responsiveness depend on tissue and hormonal state, particularly pregnancy and estrogen exposure. These peripheral actions are established physiology, summarized by Gimpl and Fahrenholz, PMID 11274341.

Central OXTR signaling influences hypothalamic, limbic, and reward networks. Depending on the cellular setting, signaling can also involve Gi/o and MAPK pathways. Animal experiments connect oxytocin with dopamine, nitric oxide, sexual reflexes, and social behavior. In male rats, centrally administered oxytocin increased penile erection and hypothalamic nitric oxide metabolites. Morphine prevented these responses, and naloxone reversed that inhibition, PMID 9151298. This supports a neural mechanism in that model. It does not establish that nasal oxytocin reliably increases human desire.

Proposed intranasal pathways include transport associated with olfactory and trigeminal structures, systemic absorption, and stimulation of endogenous oxytocin release. Their relative contributions remain unresolved. A small human study found increased cerebrospinal fluid concentrations after nasal administration, PMID 24310737. Cerebrospinal fluid concentration does not directly measure receptor occupancy in sexual motivation circuits. Oxytocin can also interact with vasopressin receptors under some experimental conditions. Its behavioral effects depend on context and baseline characteristics. Stronger social salience or altered orgasm experience should not be equated with increased libido.

EVIDENCE · GRADE C

Grade C applies specifically to the claimed libido benefit. Human studies exist, but their results are too weak or inconsistent to support reliable efficacy. Approved obstetric uses separately qualify as grade A. The 2024 narrative review by Dale and colleagues integrates substantial animal and mechanistic research, PMID 39224135. Neither that review nor the trials below establishes a dependable treatment for low desire. The grade describes support for this claim, not the absence of human research.

Human data. A randomized, double-blind crossover trial included 30 premenopausal and postmenopausal women with sexual dysfunction. Oxytocin and placebo both improved questionnaire scores, without a statistically significant treatment advantage, PMID 26151620. This directly addresses the clinical claim. Improvement over baseline cannot be attributed to oxytocin when the placebo group improves similarly. In 29 healthy heterosexual couples, acute intranasal oxytocin did not improve sexual drive, arousal, erection, or lubrication. Some analyses found small to moderate improvements in orgasm intensity, post-intercourse contentment, and selected partner interactions, PMID 24503174. These exploratory findings concern specific experiences. They do not demonstrate treatment efficacy in

Animal and mechanistic data. Rodent studies provide mechanistic support for effects on erection, social interaction, and reward signaling. Direct brain administration in erection experiments differs fundamentally from human nasal delivery, PMID 9151298. Another rat study found increased social interaction and nucleus accumbens dopamine, with reduced activity and temperature at higher exposures, PMID 30120410. That study investigated social behavior and pharmacology, not human sexual dysfunction. Social investigation in rats is not equivalent to human libido. Species, route, and outcome differences prevent direct dose or efficacy translation.

people with persistent low desire. Small samples, subjective outcomes, multiple comparisons, and limited replication restrict confidence. Neither trial establishes a dependable long-term benefit or an optimal regimen.

REGULATORY STATUS AND SPORT

STATUS	FDA-approved injectable oxytocin has obstetric indications, including medically indicated labor induction or augmentation and control of postpartum bleeding. These indications do not include libido. Intranasal libido formulations are not FDA-approved for that purpose; compounded preparations do not inherit approval from the active ingredient. Source: [Pitocin prescribing information](https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dddcdcc3-cd4d-4573-98ac-9468bea23a8b).
WADA	Oxytocin is not named in the 2026 WADA Prohibited List, effective January 1, 2026. Its established human therapeutic approval also distinguishes it from substances prohibited under S0 solely because they lack such approval. Interpretation of the current list: oxytocin itself is not prohibited. This does not establish the status of every mixture or administration method. Source: [2026 WADA Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Intranasal spray dominates human behavioral and libido research. Approved obstetric formulations use intravenous infusion or intramuscular injection. The cited animal experiments include subcutaneous and intracerebroventricular administration. Exposure from one route cannot be inferred from an equal numerical amount delivered by another. Nasal deposition and the delivery device also affect interpretation of a reported exposure.
HALF-LIFE	The Pitocin prescribing information reports a plasma half-life of approximately 1 to 6 minutes. This is not an intranasal behavioral half-life. In PMID 24310737, plasma concentrations peaked at approximately 15 minutes. Cerebrospinal fluid concentrations showed a significant increase at 75 minutes. The study included 11 oxytocin recipients and four placebo recipients. It did not establish a complete central elimination curve or a duration of libido benefit. Plasma concentrations also did not correlate with cerebrospinal fluid concentrations in that small sample.
TIMING	Research timing depends on the endpoint. The women's trial used administration within 50 minutes before intercourse, PMID 26151620. The pharmacokinetic study found different blood and cerebrospinal fluid time courses, PMID 24310737. Neither establishes an optimal timing window for libido. Absence of an immediate sensation does not demonstrate inadequate exposure. A sampling time associated with a concentration change is not proof of peak clinical efficacy.
CYCLE LENGTH	No validated libido cycle exists. The women's crossover study used two 8-week treatment periods separated by a 2-week washout, PMID 26151620. Those durations describe the experiment. They do not establish a maintenance schedule, tolerance reset, or acceptable indefinite exposure. The absence of superiority over placebo remains relevant regardless of the treatment duration.
TITRATION	No evidence-based libido titration schedule is established. Increasing exposure until a subjective effect appears has not been validated. Variable nasal deposition, different devices, and contextual effects make subjective responses unreliable guides to dose escalation. The documented trials do not define a minimum effective libido dose or a maximum appropriate exposure for unsupervised use.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved obstetric use, postpartum uterine bleeding	10 IU, corresponding to 1 mL, intramuscularly once after placental delivery, as reported in the Pitocin prescribing information.	Intramuscular	Single administration after placental delivery in the labeled clinical setting.	Pitocin prescribing information, Control of Postpartum Uterine Bleeding. This is an obstetric exposure, without an established application to libido.
Human trial in women with sexual dysfunction	32 IU intranasally per sexual occasion, within 50 minutes before intercourse, during an 8-week treatment period, PMID 26151620.	Intranasal	On demand before intercourse, rather than a fixed daily schedule; each crossover treatment period lasted 8 weeks, PMID 26151620.	Muin and colleagues randomized crossover trial, PMID 26151620. Oxytocin did not outperform placebo. The regimen describes trial exposure, not a recommended schedule. · PMID 26151620
Human study of sexual experience and partner interaction	24 IU intranasally as a single acute administration for an experimental sexual encounter, PMID 24503174.	Intranasal	Single acute administration associated with the experimental encounter.	Behnia and colleagues study in 29 healthy couples, PMID 24503174. Selected orgasm and interaction outcomes changed, while sexual drive and arousal did not. · PMID 24503174
Human pharmacokinetic investigation	24 IU intranasally once, delivered as three sprays per nostril containing 4 IU per spray, PMID 24310737.	Intranasal	One administration during the sampling session.	Striepens and colleagues study of plasma and cerebrospinal fluid concentrations, PMID 24310737. The retrieved methods confirm the spray amount and number of actuations. · PMID 24310737

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CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Non-clinical libido protocols	No independently verified non-clinical dose range was established from the sources reviewed.	Intranasal in the claims being assessed.	No validated frequency or repeat-dose ceiling for non-clinical libido use was established by the cited studies.	No numerical non-clinical range is assigned. The sourced human exposures are documented separately above and do not establish an effective libido protocol. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

+ PT-141	Hypothesized complementarity only: melanocortin signaling and oxytocin signaling affect different aspects of sexual processing. The cited evidence does not establish a controlled human combination benefit. Efficacy of either agent alone cannot establish additive benefit or combination safety.	– Melanotan II	An unsupported experimental libido combination. The cited oxytocin evidence provides no reliable interaction, efficacy, or safety data for this pairing. The concern is uncertainty and difficulty attributing adverse effects. A specific harmful drug interaction has not been demonstrated by these sources.
+ Kisspeptin-10	A research hypothesis links reproductive signaling and sexual motivation with oxytocin-related social processing. The cited evidence does not establish an oxytocin plus kisspeptin libido protocol.	– Selank	Claims that adding an anxiolytic peptide makes oxytocin more effective or predictable lack supporting combination trials in the cited evidence. Simultaneous exposure would obscure whether changes in anxiety, mood, or sexual experience came from either substance. This is an evidence gap, not a documented pharmacological contraindication.

SAFETY

COMMON EFFECTS	No consistent excess of adverse effects over placebo was identified in a systematic review of 38 randomized trials involving 1,529 participants, PMID 21429671. Participants were predominantly male, and exposure was generally short. These findings do not establish that adverse effects never occur or define reliable frequencies for individual symptoms. The review also identified adverse-reaction case reports involving misuse or longer exposure. Its findings do not establish long-term safety or the quality of compounded formulations.
SERIOUS SIGNALS	The Pitocin label reports water intoxication with seizures or coma, arrhythmias, anaphylaxis, and uterine overstimulation or rupture. These primarily concern parenteral obstetric exposure. Their incidence cannot be transferred to nasal research. Antidiuretic activity makes prolonged exposure with excessive fluid intake concerning.
CONTRAINDICATIONS	Hypersensitivity is a labeled contraindication. Pregnancy makes experimental libido use inappropriate because of uterine effects. Existing hyponatremia, impaired water excretion, significant cardiovascular disease, or medications affecting fluid balance require clinical assessment. These are precautions for this experimental context, not a validated nasal contraindication list. No approved intranasal libido label defines a complete set of contraindications. Obstetric practice has additional contraindications based on maternal and fetal circumstances.
STOP RULES	Severe headache with confusion, repeated vomiting, seizure, fainting, chest pain, breathing difficulty, or facial swelling warrants discontinuation and urgent medical assessment. Uterine cramping or bleeding when pregnancy is possible also warrants urgent assessment. Persistent nasal irritation or substantial adverse mood changes warrants reassessment before further exposure. These are precautionary stop signals, not proof that oxytocin caused a particular symptom.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	Behavioral studies used prepared nasal spray. A lyophilized research vial labeled in mg is not equivalent to that formulation. Injectable presentations also differ from nasal preparations in concentration, excipients, packaging, and intended delivery. The presentation alone cannot establish the amount reaching systemic circulation or central compartments.
SOLVENT	The documented human pharmacokinetic study used a manufactured nasal preparation rather than powder reconstituted with bacteriostatic water, PMID 24310737. Bacteriostatic water alone does not establish suitable nasal pH, osmolality, preservation, stability, or delivered spray volume. The study does not validate transferring an injectable preparation into a nasal device.
STORAGE	Storage and the period allowed after opening depend on the exact formulation and container. A generic nasal refrigeration rule or shelf life cannot be assigned from these studies. The Pitocin injection label specifies 20 to 25 degrees Celsius for its presentation, without establishing nasal storage conditions.

In PMID 24310737, a single 24 IU intranasal administration used a preparation delivering 4 IU per spray. The study arithmetic was 24 IU divided by 4 IU per spray, giving six sprays total, distributed as three per nostril. This reproduces the documented exposure and device arithmetic. It does not establish a powder-to-solution compounding recipe or equivalence between different pumps. The retrieved methods do not establish a vial-mg-to-mL

BUYING NOTES

Relevant quality documentation identifies the formulation, biological potency, lot, expiry, storage conditions, excipients, and delivered amount per actuation. A purity chromatogram alone does not establish identity, potency, microbial quality, or pump performance. A certificate of analysis should match the actual lot and disclose test methods. Research-use labeling does not establish suitability for human administration. Chemical purity also does not demonstrate therapeutic equivalence, reproducible nasal delivery, or clinical efficacy. Documentation of one ingredient cannot substitute for characterization of the finished formulation.

COMMON MISTAKES

- Treating obstetric approval as evidence that nasal oxytocin is effective for low desire.
- Combining desire, arousal, erection, lubrication, orgasm, and relationship satisfaction into one outcome when the trials found different effects across them.
- Attributing improvement from baseline to oxytocin despite similar improvement with placebo.
- Assuming a brief plasma half-life means all central effects end within minutes or that frequent redosing is justified.
- Confusing oxytocin IU, peptide mass, syringe volume markings, and nasal actuations.
- Translating animal brain injections or body-weight-based exposures into human nasal doses.
- Calling a proposed peptide pairing a demonstrated synergy when the cited evidence does not establish a controlled combination benefit.

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Argireline

Acetyl hexapeptide-8, Acetyl hexapeptide-3

SNAP-25 mimetic cosmetic peptide

Module 4 · Mind & Longevity

Goals: Skin

Route: Topical

A topical SNAP-25 mimetic cosmetic peptide with limited, inconsistent human evidence for improving the appearance of expression lines.

WHAT IT IS

Argireline is acetyl hexapeptide-8, also called acetyl hexapeptide-8 amide. Acetyl hexapeptide-3 is an older name used in its literature. The synthetic, six-amino-acid sequence is Ac-Glu-Glu-Met-Gln-Arg-Arg-NH₂, commonly abbreviated Ac-EEMQRR-NH₂, PMID 18498523. Its molecular mass is approximately 889 Da, PMID 40196949.

Module 4, Mind & Longevity. Goal: Skin. Its relevant application is cosmetic wrinkle appearance, rather than demonstrated systemic longevity. Conventional use involves formulated topical creams or serums. Cosmetic ingredient status does not establish approval as an injectable medicine or validate claims about muscle relaxation.

MECHANISM

Argireline was designed to resemble part of the N-terminal region of SNAP-25, a component of the SNARE machinery supporting intracellular vesicle fusion. SNAP-25 works with syntaxin and synaptobrevin/VAMP to support calcium-dependent neurotransmitter release. Experimental work reported interference with SNARE complex formation or stability and reduced neurotransmitter secretion, PMID 18498523. This is an intracellular protein-interaction mechanism, rather than established agonism or antagonism at a cell-surface receptor.

The proposed cosmetic pathway involves reduced presynaptic acetylcholine release, followed by less muscle activation and reduced expression-related contraction. That sequence requires sufficient intact peptide to reach the appropriate nerve terminal and intracellular machinery. Ordinary topical application has not convincingly demonstrated that entire sequence in human facial muscles. Argireline is not an enzyme that cleaves SNAP-25.

Delivery is a major limitation. Its hydrophilicity and molecular size impede passive transport through the stratum corneum. In excised human and guinea pig skin, most applied peptide remained removable from the surface, PMID 24754410. None was detected in the dermis or underlying receptor fluid under the tested conditions. Superficial effects or formulation moisturization could contribute to observed smoothing, but this remains an interpretation rather than a demonstrated mechanism. Mouse collagen findings do not establish a human collagen-receptor target or a clinically verified dermal remodeling pathway.

EVIDENCE · GRADE C

C applies to a reliable, peptide-specific wrinkle-reduction claim. Human studies exist, but small samples, short follow-up, inconsistent findings and formulation differences leave that claim weakly supported. Individual short human trials fit the product's B category by design. Their existence does not establish consistent efficacy across formulations or predictable facial muscle relaxation. Lum's 2025 literature review included 10 studies and 312 participants, predominantly women, PMID 40196949. It found possible cosmetic improvement but uncertain significance, inconsistent measurement methods and difficulty separating peptide effects from other ingredients. The review is an evidence synthesis, not itself a human intervention trial.

Human data. The initial human cosmetic study reported wrinkle-depth reductions up to 30% after 30 days, PMID 18498523. This is a reported maximum, not an expected individual result. A randomized study of 60 Chinese participants allocated treatment and placebo 3:1 over four weeks, PMID 23417317. Its 48.9% figure described subjective anti-wrinkle efficacy, not a 48.9% reduction in wrinkle depth. Skin-replica roughness measures also improved in the active group. A later double-blind, split-face study of 19 women found no significant added wrinkle benefit over the same hyaluronic-acid serum without Argireline, PMID 38024099. The between-side wrinkle-score comparison had a p value of 0.829. A separate 24-patient blepharospasm pilot found a nonsignificant trend toward extending background treatment benefit, PMID 23146065.

Animal and mechanistic data. In D-galactose-aged mice, topical treatment over six weeks improved reported skin histology, increased type I collagen staining and decreased type III collagen staining, PMID 23464592. These were histological findings in an induced-aging model. They cannot establish clinical rejuvenation, human collagen remodeling or lasting wrinkle prevention. Excised guinea pig skin in the penetration experiment was an ex vivo preparation, not a living-animal efficacy trial, PMID 24754410.

That medical adjunct study does not establish cosmetic wrinkle efficacy. These findings do not demonstrate predictable facial muscle relaxation from conventional topical formulations.

REGULATORY STATUS AND SPORT

STATUS	A topical cosmetic ingredient, without an approved therapeutic drug label or injectable indication identified in the reviewed sources. Experimental medical or delivery research does not establish marketing approval. In the United States, cosmetic products generally do not undergo FDA premarket approval. Disease-treatment or structure/function claims can make a product a drug. [FDA wrinkle-product guidance] (https://www.fda.gov/cosmetics/cosmetic-products/wrinkle-treatments-and-other-anti-aging-products). The 2025 cosmetic safety assessment supported topical cosmetic use at ingredient concentrations up to 0.005%, PMID 40673537. Data above that concentration were insufficient for a safety determination. This concentration assessment is not a drug label, dosing schedule or universal legal concentration limit.
WADA	Argireline and acetyl hexapeptide-8 are not specifically named in the 2026 WADA Prohibited List. Absence from named examples does not establish permission. S0 prohibits pharmacological substances lacking governmental approval for human therapeutic use when they are not addressed by another section. This prohibition applies at all times. Cosmetic availability alone does not resolve whether S0 applies to a particular substance and use. No compound-specific clearance was established by this review; status remains unresolved rather than confirmed permitted. [2026 WADA Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES	Topical application to intact skin is the conventional cosmetic route. Published delivery experiments do not establish interchangeable exposure between ordinary creams, barrier-disrupting devices and injection. No validated systemic self-administration protocol was identified in the reviewed literature. The eyelid study involved a monitored medical protocol and does not establish unrestricted suitability of cosmetic formulas for eyelid application.
HALF-LIFE	No clinically established human plasma half-life or validated residence time at facial nerve terminals was identified for conventional topical use. Formulation shelf life, local persistence and systemic elimination half-life are different measurements. Application frequency in a study does not establish pharmacokinetic half-life.
TIMING	Morning and evening application appears in the split-face study schedule, PMID 38024099. No relationship to meals, exercise, sleep or hormonal timing was established in the reviewed studies. Cosmetic endpoints were usually assessed after weeks, not immediately after application. Study timing describes observation conditions rather than an optimized regimen.
CYCLE LENGTH	The Chinese and split-face wrinkle studies lasted four weeks, PMIDs 23417317 and 38024099. Their duration does not establish an optimal Argireline cycle. Persistence after discontinuation, long-term peptide-specific benefit and benefits of cycling remain inadequately characterized. Repeated use of multi-ingredient formulas cannot isolate the contribution of Argireline.
TITRATION	No validated dose-escalation schedule was identified. Increasing concentration to overcome poor penetration is unsupported. Higher nominal ingredient percentages may represent different stock solutions rather than greater pure-peptide exposure. The cosmetic safety assessment does not provide a titration protocol.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Initial human cosmetic study	An oil-in-water emulsion described as containing 10% Argireline was applied topically over 30 days, PMID 18498523. Application frequency was not specified in the retrieved primary abstract. The nominal percentage cannot reliably establish pure-peptide concentration without clarification of the ingredient preparation.	Topical facial skin, PMID 18498523	Treatment over 30 days; daily application frequency not specified in the retrieved primary abstract, PMID 18498523.	Primary study abstract, PMID 18498523. It reports the nominal formulation percentage and study duration, but does not resolve ingredient-solution versus pure-peptide content. · PMID 18498523
Randomized Chinese periorbital wrinkle study	Argireline or placebo was applied topically to periorbital wrinkles twice daily for four weeks, PMID 23417317. The retrieved primary abstract does not specify concentration, formulation mass per application or absorbed peptide dose. A numerical concentration is therefore not assigned here.	Topical periorbital skin, PMID 23417317	Twice daily for four weeks, PMID 23417317.	Primary randomized trial abstract, PMID 23417317. · PMID 23417317

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Investigational blepharospasm adjunct	A 0.005% acetyl hexapeptide-8 emulsion was applied topically to eyelids twice daily, starting after scheduled background treatment, PMID 23146065. One dispenser actuation supplied each application. The retrieved methods did not specify the dispensed mass or peptide mass per application.	Topical eyelid skin under a monitored research protocol, PMID 23146065	Twice daily during follow-up, beginning the day after background treatment, PMID 23146065.	Primary full-text methods, PMID 23146065. This was investigational medical use, not an approved label or a cosmetic self-treatment protocol. · PMID 23146065
Ex vivo penetration experiment	An emulsion reported as containing 10% acetyl hexapeptide-8 was applied topically once at 2 mg of formulation per square centimeter, PMID 24754410. Exposure lasted 24 hours. This is formulation loading, not absorbed peptide dose; the abstract does not resolve the ingredient-stock concentration basis.	Topical application to excised human and hairless guinea pig skin, PMID 24754410	Single application, assessed after 24 hours, PMID 24754410.	Primary penetration-study abstract, PMID 24754410. The loading describes an isolated-skin experiment and cannot establish a human systemic dose. · PMID 24754410
Mouse skin-aging experiment	Topical Argireline was applied twice daily for six weeks, PMID 23464592. The retrieved primary abstract does not report concentration, application mass or mg/kg. No numerical peptide dose or human-equivalent conversion can therefore be supplied reliably.	Topical mouse skin, PMID 23464592	Twice daily for six weeks, PMID 23464592.	Primary animal-study abstract, PMID 23464592. Missing exposure data remain missing rather than being inferred from human formulations. · PMID 23464592
Double-blind split-face serum study	A hyaluronic-acid serum with Argireline was applied topically to one facial side twice daily for four weeks, PMID 38024099. The other side received the corresponding serum without Argireline. The retrieved abstract does not specify peptide concentration or mass per application.	Topical facial skin, particularly around the eyes, PMID 38024099	Once each morning and evening for four weeks, PMID 38024099.	Primary split-face study abstract, PMID 38024099. The design documents formulation comparison and frequency, but does not establish an effective peptide dose. · PMID 38024099

STACKING

No combination is documented for this compound in the sources cited. Use the avoid list and the protocol that includes it as the guide.	– Argireline	Layering several Argireline-containing formulas makes total exposure harder to interpret without demonstrated additional benefit. Different nominal percentages may describe different stock solutions. This is an exposure-interpretation concern, not an established drug interaction.
	– LL-37	No controlled Argireline plus LL-37 trial was identified in the reviewed evidence. Combination efficacy, tolerability and formulation compatibility remain unestablished.

SAFETY

COMMON EFFECTS	Small topical studies reported limited adverse events, but cannot establish reliable event frequencies. Redness, stinging, itching or contact dermatitis may arise from the complete formula. The blepharospasm study described transient eyelid heaviness and mild noninfectious blepharitis in both active and placebo groups, PMID 23146065. Investigators associated those symptoms with the thick cream vehicle rather than demonstrating peptide-specific toxicity.
SERIOUS SIGNALS	No consistent serious systemic toxicity signal emerged from the small topical trials. Rare reactions, prolonged exposure and enhanced-delivery formulations remain insufficiently characterized. The 2025 assessment supported topical cosmetic ingredient concentrations up to 0.005%, with insufficient data above that concentration, PMID 40673537. This is a cosmetic concentration assessment without a prescribed application frequency, not a validated maximum daily dose.
CONTRAINDICATIONS	No approved prescribing label defining formal contraindications was identified. Known allergy to the ingredient or vehicle is a reason to avoid exposure. Pregnancy, breastfeeding, damaged skin and invasive delivery lack adequate dedicated safety evidence in the reviewed sources. Findings from intact skin cannot establish tolerability after barrier disruption or exposure of the eye itself.
STOP RULES	Persistent burning, worsening rash or eyelid inflammation are reasons to discontinue exposure and obtain clinical advice. Facial swelling, breathing difficulty, significant eye pain, vision changes or new weakness warrant prompt

medical assessment. These are general clinical warning signs, not established frequencies or characteristic adverse reactions to Argireline.

RECONSTITUTION AND STORAGE

TYPICAL VIAL	Not applicable to routine cosmetic use. The relevant presentation is a finished, preserved serum or cream with documented active content. Research powder mass alone does not define a usable topical preparation. A clinical formulation also depends on its vehicle, preservation, packaging and application characteristics.
SOLVENT	Studies used complete emulsions or serum vehicles. Bacteriostatic water alone does not reproduce their preservation, viscosity, pH, skin delivery or stability. The reviewed studies do not establish a general home-reconstitution method or an interchangeable solvent system.
STORAGE	Storage conditions and expiry depend on the finished formulation and packaging. No universal refrigerated shelf life or post-reconstitution period is established for all Argireline formulations. Preservative integrity and stability data matter independently of peptide identity. Storage assumptions from another peptide or vehicle do not validate this preparation.

The blepharospasm study used a prepared 0.005% topical emulsion in dispensers, applied twice daily, PMID 23146065. For concentration arithmetic only, assuming that study percentage means weight/weight gives 5 mg of peptide per 100 g of finished emulsion. The same hypothetical conversion gives 0.05 mg, or 50 mcg, per gram, calculated from the concentration reported in PMID 23146065. These are conditional mass-balance equivalents, not separately studied doses. The calculation does not reconstruct the vehicle or establish the amount delivered by the study dispenser. Without verified percentage basis, density and dispenser output, neither mg/mL nor peptide mass per application can be established. Syringe-unit conversions are inapplicable to this topical example.

BUYING NOTES

Relevant quality information includes exact ingredient identity, pure-peptide assay, percentage basis and finished-formula composition. A certificate of analysis reporting chromatographic purity does not establish concentration in the final cream, preservation, stability or clinical efficacy. A nominal ingredient-solution percentage is uninterpretable without the stock concentration. Documentation for the raw ingredient also does not establish finished-product quality. Cosmetic documentation does not establish suitability for invasive administration.

COMMON MISTAKES

- Treating a percentage of diluted ingredient solution as the same percentage of pure peptide.
- Presenting the Chinese study's 48.9% subjective efficacy figure as percentage wrinkle-depth reduction.
- Assuming a plausible SNARE mechanism proves that an ordinary cream reaches facial motor nerve terminals.
- Attributing improvement from a multi-ingredient serum entirely to Argireline or presenting hypothetical pairings as demonstrated synergy.
- Converting missing animal exposure data into a fabricated mg/kg dose or confusing formulation loading with absorbed peptide mass.
- Interpreting cosmetic safety assessment, ingredient listing or absence from WADA's named examples as blanket regulatory approval.

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The long game.

Mind, sleep, mitochondria and the compounds with real data.

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MODULE 5 OF 5 · UU LIFE PEPTIDES 2.0

PROTOCOL ROOM

The 14 ready-to-apply protocols. Fourteen complete protocols with week-by-week schedules, titration steps, monitoring, stop rules and exit plans, each built from the cards in modules two to four.

Module 5

UU LIFE PEPTIDES 2.0

Verified references

Educational and informational reference for adults. Not medical advice. Reported doses with provenance not a prescription. Many compounds described are not approved for human use and several are prohibited in sport. Decisions about any compound belong to you and a licensed clinician.

A UU LIFE PRODUCT · UU.LIFE

The 14 protocols

01	Tendon & Ligament Repair Recovery · Beginner · 8 weeks	BPC-157, TB-500
02	Post-Injury Recovery Accelerator Recovery · Intermediate · 6 weeks	BPC-157, TB-500, CJC-1295, Ipamorelin
03	Gut Repair Gut · Beginner · 8 weeks	BPC-157, KPV
04	Clean Bulk (GH Axis) Hypertrophy · Beginner · 12 weeks	CJC-1295, Ipamorelin
05	Advanced Hypertrophy Hypertrophy · Advanced · 10 weeks	CJC-1295, Ipamorelin, IGF-1 LR3
06	Fat Loss with Muscle Preservation (Incretin Class) Fat loss · Intermediate · 16 weeks	Semaglutide, Tirzepatide
07	Non-Incretin Recomposition Fat loss · Intermediate · 12 weeks	AOD-9604, HGH Fragment 176-191
08	Metabolic and Mitochondrial Reset Longevity · Intermediate · 8 weeks	MOTS-c, SS-31
09	Deep Sleep and Nightly Recovery Sleep · Beginner · 6 weeks	DSIP, Epitalon
10	Cognitive Focus Nootropics · Beginner · 4 weeks	Semax, Selank
11	Neuro-Regeneration Nootropics · Advanced · 8 weeks	Cerebrolysin, Semax
12	Longevity Maintenance Longevity · Intermediate · 10 weeks	Epitalon, Thymalin
13	Libido and Sexual Response Libido · Beginner · 4 weeks	PT-141, Kisspeptin-10
14	Skin, Hair and Connective Tissue Skin · Beginner · 12 weeks	GHK-Cu, Argireline

Every protocol follows the hierarchy from Module 1: inflammation and immunity, then energy, nervous system and sleep, then metabolism, then tissue and anabolic stimulus. Pre-checks, monitoring, stop rules and an exit plan are part of the protocol, not an appendix.

UU LIFE

Tendon & Ligament Repair: Evidence and Rehabilitation Review

BEGINNER · 8 WEEKS · CORE: BPC-157, TB-500 · SUPPORT: GHK-CU

An eight-week framework for understanding experimental repair peptides, tracking rehabilitation and recognizing when reassessment is needed. BPC-157, TB-500 and GHK-Cu have no established human regimen for tendon or ligament repair in the cited evidence. The reported exposures describe research, not reader recommendations. Eight weeks is a review period, not a promised healing deadline.

WHO IT IS FOR

Adults who train and have a clinically assessed tendon or ligament injury, an appropriate rehabilitation plan and an interest in evaluating peptide claims. Beginner describes the educational level, not suitability for experimental exposure. This framework supports discussions with a sports medicine clinician or physiotherapist.

WHO SHOULD NOT RUN IT

People with an undiagnosed acute injury, suspected rupture, infection, unstable joint or postoperative restrictions requiring a surgeon's plan. Pregnancy, breastfeeding, active cancer, major organ disease and copper-handling disorders fall outside any established suitability assessment for these experimental exposures. Specialist review cannot establish their safety. Under the current WADA Prohibited List, BPC-157 is prohibited at all times under S0. Thymosin beta-4 and its derivatives, including TB-500, are prohibited at all times under S2. Source: [WADA Prohibited List] (<https://www.wada-ama.org/en/prohibited-list>).

THE LOGIC

This framework organizes clinical questions and evidence review. It is not a validated sequence of peptide administration. Initial assessment distinguishes expected injury responses from infection, inflammatory disease or excessive irritability. Suppressing inflammation does not automatically improve healing. Energy availability, sleep, psychological demands and relevant metabolic problems are assessed alongside the injury. They are not postponed into separate treatment stages. Rehabilitation loading remains injury-specific and follows clinical restrictions.

BPC-157 appears first because its preclinical literature includes tendon and tendon-to-bone injury models. Its repair evidence is grade C: animal findings and human evidence too weak to establish structural healing. The retrospective knee-pain report, PMID 34324435, cannot demonstrate tendon regeneration, ligament stability or faster return to sport. The systematic review, PMID 40756949, found predominantly preclinical evidence; its search ended in June 2024.

TB-500 follows as a separate evidence question. A short human trial examined recombinant thymosin beta-4, not a validated TB-500 tendon-repair treatment. It does not establish the identity, dose or efficacy of preparations described as TB-500. TB-500-specific human tendon repair remains grade D, reflecting indirect mechanistic reasoning and unsupported extrapolation. The cited evidence does not establish benefit from adding it to BPC-157.

GHK-Cu is an optional evidence topic because a rat ACL reconstruction study reported temporary improvements in selected mechanical outcomes. This is grade C evidence for that animal model. The order reflects relevance and uncertainty, not demonstrated synergy or a reason to escalate treatment.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
BPC-157	Primary evidence review for experimental tendon repair. Grade C for repair; limited human pain observations do not establish tissue restoration.	PMID 18594781 reported BPC-157 10 mcg/kg by intraperitoneal administration once daily in rats after Achilles tendon-to-bone transection. This animal exposure does not establish a human dose or support conversion into a personal regimen. The animal exposure and early functional endpoints were verified in the abstract of PMID 18594781. PMID 34324435 describes uncontrolled human knee-pain observations without a structural-healing endpoint. PMID 40756949 documents the predominantly preclinical orthopedic evidence base.	Intraperitoneal in PMID 18594781. This does not establish equivalence with oral, subcutaneous or intra-articular human administration. · Once daily in PMID 18594781; no validated frequency for human tendon or ligament repair.	In PMID 18594781, treatment began 30 minutes after surgery. This establishes no timing advantage relative to human training, meals or sleep.	PMID 18594781 assessed early recovery on postoperative days 1 through 4. It does not support eight active treatment weeks.	No validated human titration steps for this indication. Neither low-dose initiation nor escalation for persistent pain has demonstrated benefit in the cited evidence.
TB-500	Secondary evidence review. Grade D for TB-500-specific human tendon repair; recombinant thymosin beta-4 findings provide indirect context only.	No validated TB-500 dose for human tendon repair is established by the cited studies. PMID 34346165 reported recombinant human thymosin beta-4 at 0.5, 2.0 or 5.0 mcg/kg intravenously once daily for 10 days. These were separate healthy-volunteer cohorts. These different-agent study exposures are not TB-500 doses. PMID 34346165 supports grade B evidence for short-term tolerability and pharmacokinetics of the studied recombinant thymosin beta-4 preparation. It does not establish long-term safety, TB-500 interchangeability or tendon healing. Source: [Wang et al., phase I study] (https://pubmed.ncbi.nlm.nih.gov/34346165/).	Intravenous for recombinant thymosin beta-4 in PMID 34346165. No route conversion to TB-500 is established. · Once daily for the related molecule in PMID 34346165. No validated TB-500 repair frequency.	No demonstrated relationship to training, food or sleep. Healthy-volunteer pharmacokinetics do not establish an effective rehabilitation schedule.	PMID 34346165 used a 10-day repeated-dose period. It provides no evidence-based TB-500 treatment duration for this framework.	Separate research cohorts are not personal titration steps. No validated loading, maintenance or escalation sequence exists for this repair claim.
GHK-Cu	Optional review of experimental matrix remodeling. Grade C for rat ACL graft healing; human tendon and ligament benefit remains unestablished.	PMID 25731775 reported GHK-Cu solutions at 0.3 or 3 mg/mL by intra-articular administration once weekly for four weeks in rats after ACL reconstruction. These are solution concentrations, not administered mass or human doses. The retrieved abstract does not specify administration volume. PMID 25731775 reported early laxity and stiffness findings that were absent at the later assessment. Ultimate load did not significantly improve. Source: [Fu et al., rat ACL reconstruction study] (https://pubmed.ncbi.nlm.nih.gov/25731775/).	Intra-articular in PMID 25731775. Topical exposure does not establish delivery to an injured tendon or ligament. · Once weekly for four administrations in PMID 25731775; no validated human repair frequency.	PMID 25731775 began treatment during postoperative week 2. No human training, food or bedtime advantage is established.	Postoperative weeks 2 through 5 in PMID 25731775. These research weeks do not establish a human treatment window.	Two fixed concentration groups were compared. They provide no human titration steps or rationale for escalation.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1	Confirm diagnosis, restrictions and a clinician-selected functional test. Record baseline symptoms and establish tolerable rehabilitation. Review BPC-157 evidence and distinguish animal exposures from human treatment.	Rest pain, swelling, instability and loss of function. Acute rupture or infection signs require assessment before progression.
2	Review nutrition, energy availability and sleep consistency. Repeat the same functional test under comparable conditions. Keep rehabilitation within the agreed symptom response.	Next-morning stiffness, swelling or reduced function after exercise. Persistent worsening indicates that load or diagnosis needs review.

WEEK	ACTIONS	WATCH
3	Progress one rehabilitation variable only when permitted by the treating clinician and current response. Review the distinction between TB-500 and recombinant thymosin beta-4.	Pain relief without corresponding strength or function improvement. Reduced pain alone does not establish stronger tissue.
4	Complete a midpoint review of pain, function, adherence and activity exposure. Reassess the diagnosis if progress is absent. Consider relevant metabolic testing when history supports it.	Increasing night pain, recurrent joint giving-way or inability to tolerate previously manageable activity.
5	Review the limited GHK-Cu evidence. Continue the rehabilitation plan and document every treatment change so that symptom trends remain interpretable.	Attributing ordinary recovery to an added compound. Animal improvements in stiffness do not establish human return-to-sport readiness.
6	Repeat objective testing with the clinician or physiotherapist. Introduce greater task demands only when appropriate for the specific injury and recovery stage.	Compensatory movement, reduced control, delayed swelling or a decline in the standardized functional test.
7	Assess whether gains persist across repeated sessions and ordinary daily activity. Prepare the week-eight review and identify unresolved restrictions.	Dependence on increasing analgesia to complete activity, repeated flares or inability to sustain the current workload.
8	Compare outcomes with baseline and set the next rehabilitation phase. Any experimental exposure requires clinician-directed review rather than automatic extension.	Persistent weakness, laxity, swelling or plateau. These findings justify reassessment rather than an assumed need for more peptides.

PRE-CHECKS

- Document injury location, onset, mechanism, diagnosis, prior surgery and current restrictions. Examination determines whether imaging would change management.
- Record pain at rest and during one standardized task, morning stiffness duration, swelling, range of motion and a clinically appropriate functional or strength measure.
- Record available baseline blood pressure, resting heart rate, body weight and usual activity level. These measurements provide context but cannot establish experimental peptide suitability.
- Record sleep duration, sleep quality, recent weight loss, dietary restriction, smoking, alcohol and rehabilitation capacity.
- Review diabetes, inflammatory disease, cancer, kidney or liver disease, allergies, pregnancy potential and copper-handling disorders. Review medicines, including corticosteroids, fluoroquinolones and anticoagulants.
- Fasting glucose or HbA1c may be relevant with diabetes risk, known dysglycemia or unexplained delayed healing. CBC, renal function and liver tests depend on clinical history and planned care. Routine hormone, inflammatory-marker or copper panels are not universal prerequisites. Normal results do not establish peptide safety, and validated contraindication or interaction profiles are unavailable for these experimental repair uses.

STOP RULES

- Stop loading the affected structure and obtain urgent assessment after a sudden pop with new weakness, deformity, inability to bear weight or abrupt loss of function.
- Seek same-day assessment for a hot, red, rapidly swelling joint, fever or spreading redness, particularly after any invasive procedure.
- Stop suspected experimental exposure and seek emergency care for breathing difficulty, facial or tongue swelling, fainting or chest pain.
- New unilateral calf swelling requires urgent assessment. Sudden breathlessness, progressive weakness or a cold, pale limb requires emergency assessment.
- Pause progression and contact the treating clinician for recurrent instability, worsening night pain or persistent next-day deterioration. New systemic symptoms, including jaundice, require prompt medical assessment.

EXPECTED TIMELINE

Symptoms may change over the first few weeks with appropriate load management. Structural recovery depends on the injury and cannot be inferred from pain alone. Week 4 is an organizational reassessment point; week 8 is an outcome review. Neither is a validated peptide-treatment milestone. Major tears and reconstructed ligaments may require substantially longer rehabilitation. None of the cited studies establishes a human peptide-assisted healing deadline.

COMMON MISTAKES

- Treating an educational eight-week framework as a validated eight-week drug cycle.
- Converting animal doses or solution concentrations into personal human doses.
- Assuming recombinant thymosin beta-4 and preparations described as TB-500 are clinically interchangeable.
- Using less pain as permission to resume unrestricted loading.
- Adding multiple compounds while changing training, making outcomes difficult to interpret.
- Extending experimental exposure instead of reassessing a stalled recovery.

TRACKER FIELDS

Injury site and diagnosis · Current clinical restrictions · Rest pain 0 to 10 · Standardized task name · Task pain 0 to 10 · Next morning stiffness minutes · Swelling measure and method · Range of motion degrees · Functional test name result and units · Rehabilitation sessions completed · Exercise load sets and repetitions · Activity exposure minutes · Next day symptom response · Average sleep hours · Sleep quality 0 to 10 · Body weight kg · Waist cm if measured · Resting heart rate bpm if indicated · Blood pressure mmHg if indicated · Medication and treatment changes · Experimental exposure if any compound dose route frequency dates and provenance · Adverse symptoms and onset · Laboratory results if indicated · Clinician review and next step

REFERENCES

1. Krivic A et al. Modulation of early functional recovery of Achilles tendon to bone unit after transection by BPC 157 and methylprednisolone.. *Inflammation research : official journal of the European Histamine Research Society ... [et al.]*, 2008. PMID 18594781 DOI 10.1007/s00011-007-7056-8 (Grade C. Rat tendon-to-bone injury experiment supporting the reported BPC-157 exposure and early functional findings. It does not establish human dosing, mature collagen healing or durable repair.)

2. Lee E et al. Intra-Articular Injection of BPC 157 for Multiple Types of Knee Pain.. *Alternative therapies in health and medicine*, 2021. PMID 34324435 (Grade C for tendon and ligament repair. Small uncontrolled retrospective human knee-pain report. It lacks demonstrated structural healing, standardized functional assessment and reliable evidence of combination superiority.)

MONITORING

- Weekly: compare standardized task pain, next-morning stiffness, swelling, range of motion and the selected functional measure with baseline.
- Record rehabilitation sessions, exercise load, repetitions, activity exposure and next-day response. Interpret improvement alongside changes in workload.
- Track sleep and weight trend when relevant to recovery. Blood pressure and resting heart rate monitoring follow clinical needs. Waist measurement is optional general context, not a tendon-healing endpoint.
- Record all treatment changes and adverse symptoms. Laboratory follow-up addresses clinical indications, abnormal baseline findings or symptoms. No validated laboratory panel can rule out harms from these experimental exposures.

EXIT PLAN

At week 8, reassess the diagnosis, function, strength, swelling and tolerance of meaningful activity. Continue rehabilitation according to tissue capacity and clinical restrictions. There is no validated washout duration, taper or repeat-cycle interval for this proposed combination. If experimental exposure occurred, document the last exposure and arrange clinician review of discontinuation and follow-up. Reassess symptoms and function after discontinuation; this observation period cannot confirm drug clearance or establish treatment causality. Persistent deficits may warrant repeat examination or imaging when it would change care.

3. Wang X et al. A first-in-human, randomized, double-blind, single- and multiple-dose, phase I study of recombinant human thymosin β 4 in healthy Chinese volunteers.. *Journal of cellular and molecular medicine*, 2021. PMID 34346165 DOI 10.1111/j.cmm.16693 (Grade B for short-term human tolerability and pharmacokinetics of the specific recombinant thymosin beta-4 preparation. This small phase I trial does not validate TB-500 dosing, long-term safety or tendon repair.)
4. Fu SC et al. Tripeptide-copper complex GHK-Cu (II) transiently improved healing outcome in a rat model of ACL reconstruction.. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*, 2015. PMID 25731775 DOI 10.1002/jor.22831 (Grade C. Supports the reported rat solution concentrations and schedule. Selected early mechanical benefits were absent at the later assessment; ultimate load did not significantly improve.)
5. Vasireddi N et al. Emerging Use of BPC-157 in Orthopaedic Sports Medicine: A Systematic Review.. *HSS journal : the musculoskeletal journal of Hospital for Special Surgery*, 2025. PMID 40756949 DOI 10.1177/15563316251355551 (Supports grade C for the BPC-157 repair claim: predominantly preclinical findings and weak human orthopedic evidence. Its search ended in June 2024. It does not establish a validated human repair regimen or a complete account of subsequently published evidence.)

Post-Injury Recovery Evidence and Rehabilitation Review

INTERMEDIATE · 6 WEEKS · CORE: BPC-157, TB-500, CJC-1295, IPAMORELIN

A six-week framework for evaluating recovery, understanding four experimental compounds, and tracking rehabilitation. No controlled human study in the verified evidence establishes that this combination accelerates musculoskeletal healing. Reported exposures describe research or non-clinical conventions, not recommended doses. Six weeks defines the assessment period, not a validated drug course or return-to-sport deadline.

WHO IT IS FOR

Adults who train, have a diagnosed musculoskeletal injury and an established rehabilitation plan, and want to assess peptide claims with a clinician. Intermediate refers to the interpretation required. Animal healing findings, human hormone responses, symptom relief, and restored tissue capacity are different outcomes.

WHO SHOULD NOT RUN IT

Unsuitable as a self-directed drug cycle, treatment for an undiagnosed injury, or substitute for surgery or rehabilitation. Pregnancy and breastfeeding lack adequate safety evidence. Active cancer, pituitary disease, uncontrolled diabetes, and unexplained swelling make experimental exposure especially inappropriate without specialist assessment. These concerns are not a complete, validated contraindication list. All four compounds are prohibited at all times: BPC-157 under S0, CJC-1295 and ipamorelin under S2.2.4, and TB-500 under S2.3. Source: [2026 WADA Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

THE LOGIC

The following order organizes the evidence review. It is not a validated biological hierarchy or sequence for administering peptides. Clinical assessment first identifies infection, inflammatory disease, postoperative complications, and excessive mechanical loading. Normal inflammation participates in repair; suppressing every inflammatory signal is not a recovery goal. BPC-157 enters this discussion because animal studies report effects on inflammatory signaling, vascular responses, and tendon repair. These findings do not establish human immune protection or faster healing.

Energy availability, pain management, sleep, and rehabilitation are assessed together. Underfeeding during injury, particularly during an aggressive fat-loss phase, can complicate rehabilitation. Neurological symptoms require appropriate examination. None of the four compounds has persuasive human evidence in the verified sources for correcting these recovery limitations after musculoskeletal injury.

Metabolic and endocrine history matter when interpreting growth hormone stimulation. CJC-1295 and ipamorelin affect the growth hormone axis. Glucose control, edema, and relevant endocrine disease therefore warrant attention. CJC-1295 appears first in the endocrine evidence review because its human trials documented sustained GH and IGF-1 responses. Those surrogate outcomes do not demonstrate tissue repair. Adding another secretagogue has no established injury-healing advantage.

Appropriate tissue loading follows the injury-specific rehabilitation plan throughout recovery, rather than waiting until other steps are complete. TB-500 belongs in the tissue-repair discussion, but evidence concerning full-length thymosin beta-4 cannot automatically be assigned to its fragment. Component order does not imply administration order. The verified studies do not validate sequential administration, simultaneous stacking, or six-week exposure to these four compounds. The schedule therefore specifies rehabilitation actions and assessment points without assigning active drug weeks. The broader evidence limitations are also discussed in PMID 41966639.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
BPC-157	Experimental tissue-repair candidate. Grade C for musculoskeletal recovery: animal findings and weak retrospective human pain evidence do not establish structural healing or a reliable human safety profile.	PMID 16583442 reported BPC-157 10 mcg/kg intraperitoneally once daily in rats after Achilles tendon detachment. This animal exposure is not an established human dose. Primary animal study, PMID 16583442. Systematic review PMID 40756949 included 35 preclinical studies and one retrospective clinical study, with searches through June 3, 2024.	Intraperitoneal in PMID 16583442. This experiment does not validate human subcutaneous, oral, or intra-articular administration. · Once daily in the rat experiment, PMID 16583442.	In PMID 16583442, treatment began 30 minutes after surgery. No validated human timing relative to training, meals, or sleep is established.	Animal outcomes were assessed through day 21 in PMID 16583442. Human active weeks within this six-week framework are not established.	No validated human starting dose, escalation interval, loading phase, or taper exists for musculoskeletal recovery. Animal dose groups do not constitute individual titration.
TB-500	Proposed tissue-remodeling candidate. Grade D for the TB-500 fragment's claimed human injury benefit. Actin-binding biology provides a rationale, not demonstrated clinical efficacy.	TB-500 2 mg subcutaneously twice weekly is commonly cited in non-clinical use; not validated in trials. This convention has no established efficacy or safety for human injury recovery. The dose is explicitly non-clinical. PMID 22962027 identified an acetylated thymosin beta-4 fragment in material labeled TB-500. It supports molecular identity, not dosing or healing efficacy. Full-length thymosin beta-4 is a different molecule; the name alone does not establish the contents of another preparation.	Subcutaneous describes the non-clinical convention only. The cited analytical paper does not establish a therapeutic route. · Twice weekly is commonly cited in non-clinical use; not validated in trials.	No validated relationship to rehabilitation sessions, food, or bedtime exists.	No evidence-based six-week course or active-week allocation exists.	No validated loading, maintenance, escalation, or tapering method exists. Lack of improvement does not establish a reason to increase exposure.
CJC-1295	Long-acting GHRH analog with human evidence of GH and IGF-1 elevation. Grade B for short-term endocrine findings; grade D for extrapolation to faster injury recovery.	PMID 16352683 studied CJC-1295 30 mcg/kg subcutaneously as a single administration within ascending-dose research. This is a reported healthy-volunteer exposure, not an injury-treatment recommendation. PMID 16352683 reports two short randomized placebo-controlled trials in healthy adults. Outcomes concerned pharmacokinetics and endocrine responses, not tendon strength, return to sport, or fracture union.	Subcutaneous in PMID 16352683. The study concerns long-acting CJC-1295 with albumin-binding activity, commonly described as the DAC form. · The stated exposure is a single dose in PMID 16352683. Separate study arms investigated repeated weekly or every-other-week administration.	No injury-recovery benefit from pretraining, fasting, or bedtime administration was established. Long persistence does not support a narrow daily dosing window.	Trials in PMID 16352683 lasted 28 and 49 days. Those study durations do not establish six weeks of treatment for an injury.	Research dose escalation does not establish individual titration. No injury-specific target or escalation rule exists. Preparations described as CJC-1295 without DAC cannot inherit this study's pharmacokinetics.

Compound	Role	Reported Dose	Route · Frequency	Timing	Weeks	Titration
Ipamorelin	Ghrelin-receptor agonist and GH secretagogue. Grade B for limited short-term human clinical evidence, not demonstrated benefit. Grade D for musculoskeletal recovery claims. The cited postoperative trial assessed bowel function.	PMID 25331030 administered ipamorelin 0.03 mg/kg by intravenous infusion twice daily from postoperative day 1 through day 7 or hospital discharge.	Intravenous infusion in hospitalized surgical patients in PMID 25331030. This does not validate outpatient subcutaneous administration. · Twice daily in PMID 25331030.	Treatment followed bowel surgery in PMID 25331030. No validated timing relative to exercise, meals, or sleep exists for musculoskeletal recovery.	The exposure in PMID 25331030 lasted up to one week. It cannot substantiate a six-week course.	The cited regimen was fixed by the study protocol. No validated injury-specific escalation, bedtime schedule, or titration alongside CJC-1295 exists.
		PMID 25331030, a phase 2 randomized trial, found no statistically significant differences in key or secondary efficacy analyses. This does not prove equivalence. It did not test tissue healing or a CJC-1295 combination.				

WEEK BY WEEK

Week	Actions	Watch
1	Confirm diagnosis, healing stage, restrictions, and rehabilitation goals. Record baseline function using one reproducible task approved by the treating clinician. Review compound evidence and uncertainties.	Worsening swelling, wound changes, fever, neurological symptoms, and inability to perform previously tolerated daily activities.
2	Review food intake, weight trend, sleep opportunity, and rehabilitation adherence. Repeat the functional assessment under similar conditions. Address persistent pain or sleep disruption with the treating team.	Unintended weight loss, fatigue, disturbed sleep, and symptoms that remain elevated the morning after rehabilitation.
3	Reassess motion and task tolerance. Progress rehabilitation according to the injury-specific plan. If GH-axis exposure has occurred, clinical review includes glucose concerns and adverse symptoms.	Edema, tingling, headaches, rising glucose, and apparent weight gain that may reflect fluid retention.
4	Compare current function with baseline and planned milestones. Persistent stagnation prompts diagnostic and rehabilitation review. Review IGF-1 when clinically indicated after GH-axis exposure.	Pain relief without improved load tolerance, new night pain, and function that deteriorates despite reduced activity.
5	Practice clinician-approved movements relevant to work or sport. Document the response during activity and the following morning. Maintain restrictions where structural healing remains incomplete.	Compensatory movement, recurrent swelling, instability, and an increasing need for analgesics to complete sessions.
6	Repeat baseline assessments and review the next rehabilitation phase. Document any exposure end dates and unresolved adverse effects with the clinician. Set follow-up according to findings.	Persistent functional deficits, abnormal glucose or IGF-1 where measured, and pressure to resume unrestricted training before clearance.

PRE-CHECKS

- Record diagnosis, injury date, affected structure, surgery details, imaging findings when available, and explicit loading restrictions.
- Collect seated blood pressure and resting heart rate on several mornings, body weight, waist circumference, sleep duration, and sleep quality.
- Record resting and activity pain on a 0 to 10 scale, swelling, range of motion, analgesic use, and one repeatable functional task.
- Review medications, supplements, allergies, previous peptide exposure, pregnancy or breastfeeding, diabetes, cancer history, pituitary disease, sleep apnea, and cardiovascular, kidney or liver disease.
- Discuss fasting glucose or HbA1c when metabolic risk or GH-axis exposure makes assessment relevant. Baseline age-adjusted IGF-1 may inform endocrine evaluation.
- CBC, kidney and liver tests, inflammatory markers, or further imaging should follow clinical indications. Normal laboratory results do not establish experimental-drug safety.

STOP RULES

- Stop activity and seek emergency care for chest pain, sudden breathlessness, fainting, or one-sided calf swelling with breathing symptoms.
- Seek urgent same-day assessment for new one-sided calf swelling, even without breathing symptoms.
- Seek urgent assessment for fever with a hot swollen joint, wound drainage, spreading redness, or rapidly increasing pain.
- Stop activity and obtain urgent evaluation for a new pop with loss of function, progressive weakness, numbness, or a cold or pale limb.
- Stop suspected experimental exposure and seek emergency care for facial or tongue swelling, breathing difficulty, or widespread hives with dizziness.
- Pause experimental exposure pending clinical review for persistent edema or sustained palpitations. Severe headache or new visual changes warrant urgent assessment.
- Repeated fasting glucose at or above 126 mg/dL warrants prompt clinical review and appropriate laboratory confirmation. A home meter alone does not establish diabetes.
- Glucose at or above 200 mg/dL with thirst or frequent urination warrants same-day assessment. Vomiting, confusion, or deep rapid breathing warrants emergency care.

EXPECTED TIMELINE

Pain and daily function may improve during the first weeks of appropriate rehabilitation, but the trajectory depends on diagnosis and severity. Tendon remodeling, fracture healing, and postoperative recovery often extend beyond six weeks. Hormone elevation, transient energy changes, or reduced pain cannot demonstrate stronger repaired tissue. The verified evidence does not support a percentage reduction in recovery time from this four-compound combination. Improvement during exposure cannot establish causation when rehabilitation and natural recovery occur simultaneously.

COMMON MISTAKES

- Treating animal doses as human equivalents or changing routes while retaining the same number.
- Equating TB-500 with full-length thymosin beta-4 or long-acting CJC-1295 with preparations described as without DAC.
- Interpreting increased IGF-1, reduced pain, or fluid-related weight gain as proof of tissue healing.
- Changing several exposures and rehabilitation variables simultaneously, making benefits and adverse effects difficult to attribute.

MONITORING

- Summarize weekly pain, swelling, motion, rehabilitation completion, and functional-task performance. Compare equivalent testing conditions.
- Track average morning weight, blood pressure, resting pulse, sleep duration, and adverse symptoms. Measure waist consistently.
- Record session load and next-morning response. Separate symptom improvement from increased tissue capacity.
- Following GH-axis exposure, the clinician sets glucose and IGF-1 reassessment timing. HbA1c is not a useful weekly response marker.
- Record the actual compound identity, formulation, route, exposure dates, and other medication changes when known. Missing information limits interpretation of effects.

EXIT PLAN

Week six ends this assessment block, not necessarily rehabilitation. No evidence-based taper or universal follow-up interval exists for the combination. CJC-1295 had an estimated half-life of 5.8 to 8.1 days in PMID 16352683. Repeated administration produced prolonged IGF-1 elevation, so endocrine effects can persist after the last exposure. A clinician determines follow-up from actual exposure, symptoms, and laboratory findings. A calendar interval cannot establish biological recovery. Reassessment covers function, swelling, sleep, glucose and IGF-1 where indicated, and remaining rehabilitation milestones. Incomplete recovery does not establish a rationale for automatically repeating experimental exposure.

- Using six weeks as a return-to-sport deadline regardless of examination findings.
- Treating a short human trial, a normal laboratory panel, or a nonsignificant efficacy result as proof of long-term safety or effectiveness.

TRACKER FIELDS

Injury site and diagnosis · Days since injury or surgery · Current loading restrictions · Rest pain 0 to 10 · Activity pain 0 to 10 · Next morning pain 0 to 10 · Swelling measurement and method · Range of motion degrees · Functional test name and result · Rehabilitation sessions completed · Exercise load sets and repetitions · Mean morning body weight kg · Waist cm · Mean seated bp mmHg · Mean resting hr bpm · Mean sleep hours · Sleep quality 0 to 10 · Analgesics and other medication changes · Actual exposures dose route frequency and dates if any · Compound identity and formulation if known · Adverse symptoms and onset · Glucose result units and date if measured · Igf1 result age adjusted range and date if measured · Clinician decision and next review

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1. Krivic A et al. Achilles detachment in rat and stable gastric pentadecapeptide BPC 157: Promoted tendon-to-bone healing and opposed corticosteroid aggravation.. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*, 2006. PMID 16583442 DOI 10.1002/jor.20096 (Rat tendon-to-bone healing findings and reported intraperitoneal exposure, timing, and assessment period. Grade C; does not establish human treatment.)

2. Vasireddi N et al. Emerging Use of BPC-157 in Orthopaedic Sports Medicine: A Systematic Review.. *HSS journal : the musculoskeletal journal of Hospital for Special Surgery*, 2025. PMID 40756949 DOI 10.1177/15563316251355551 (Review of 35 preclinical studies and one retrospective clinical study, with searches through June 2024. Supports grade C for musculoskeletal recovery and substantial clinical safety uncertainty.)

3. Esposito S et al. Synthesis and characterization of the N-terminal acetylated 17-23 fragment of thymosin beta 4 identified in TB-500, a product suspected to possess doping potential.. *Drug testing and analysis*, 2012. PMID 22962027 DOI 10.1002/dta.1402 (Analytical identification of the acetylated fragment in examined TB-500 material. Does not support therapeutic dosing, consistent identity across preparations, or human recovery efficacy.)

4. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Reported subcutaneous CJC-1295 exposure, sustained endocrine responses, and prolonged pharmacokinetics in two short randomized trials. Grade B for endocrine findings; no musculoskeletal healing outcomes.)

5. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Reported intravenous ipamorelin regimen in hospitalized surgical patients. No statistically significant key or secondary efficacy differences; does not validate musculoskeletal recovery or long-term safety.)

6. Mendias CL et al. Safety and Efficacy of Approved and Unapproved Peptide Therapies for Musculoskeletal Injuries and Athletic Performance.. *Sports medicine (Auckland, N.Z.)*, 2026. PMID 41966639 DOI 10.1007/s40279-026-02437-0 (Narrative sports-medicine review covering all four compounds. Supports the distinction between preclinical findings and clinical benefit, and the scarcity of rigorous human safety evidence.)

Gut Repair: Evidence and Symptom Review

BEGINNER · 8 WEEKS · CORE: BPC-157, KPV · SUPPORT: LL-37

An eight-week educational framework for evaluating experimental gut peptides, documenting symptoms and identifying concerns that warrant clinical evaluation. BPC-157 and KPV are core research topics; LL-37 is optional research context. The verified studies do not establish a human regimen that repairs the gut, validates this combination or delivers results within eight weeks. Reported exposures below describe animal experiments, not reader recommendations.

WHO IT IS FOR

Adults who train and want to evaluate gut-related peptide claims with a structured symptom record. Beginner describes the educational level, not established safety for self-administration. Appropriate goals include identifying reproducible symptom patterns, understanding evidence quality and preparing a useful discussion with a clinician.

WHO SHOULD NOT RUN IT

Anyone seeking self-treatment for suspected inflammatory bowel disease, gastrointestinal bleeding, infection or unexplained weight loss. Pregnancy, breastfeeding, immunosuppression, active cancer, major kidney or liver disease and recent gastrointestinal surgery require individualized medical assessment. These studies do not establish safety in those populations or provide a complete contraindication profile. This framework cannot replace prescribed treatment or postoperative follow-up.

THE LOGIC

Assessment begins with symptom severity, warning signs and plausible causes. Inflammation, infection, medication effects and noninflammatory disorders require different approaches. Bloating alone does not establish inflammation, increased intestinal permeability or a need for immune modulation. The schedule provides review checkpoints, not a validated sequence of biological priorities or peptide administration.

KPV fits an inflammatory-signaling hypothesis through cell and mouse findings. BPC-157 fits a mucosal injury and repair hypothesis through rat findings. Both receive grade C for proposed human gut-treatment benefits. Their mechanistic overlap does not establish additive benefit. None of the three verified studies supports starting one compound and adding another in a particular week.

LL-37 provides research context for innate immunity. Antimicrobial activity does not establish treatment of a diagnosed intestinal infection. Its administered gut-treatment evidence here is grade C, with grade D cell mechanisms. Human observational associations do not demonstrate that administering LL-37 improves disease. These evidence grades describe support for gut-treatment claims, not established safety.

Adequate energy intake, hydration, sleep, stress management and appropriate training adjustments belong throughout the review. Metabolic concerns and nutritional deficiencies merit assessment whenever clinically relevant. They need not wait until a scheduled week. No cited evidence validates a universal inflammation-first, metabolism-second, tissue-recovery-last treatment hierarchy. Additional metabolic or anabolic peptides would introduce further uncertainty. The eight weeks organize symptom documentation and follow-up, not an experimental drug cycle.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
BPC-157	Core research topic for mucosal injury and tissue repair. Grade C for proposed human gut efficacy; animal healing findings do not establish clinical remission.	PMID 24304574 reports BPC-157 at 10 mcg/kg or 0.01 mcg/kg, administered intraperitoneally once daily in rats. The lower value is a unit conversion from the study's reported nanogram dose. These experimental animal doses are not human dose equivalents. Primary rat study, PMID 24304574. Species, route and injury model limit translation. [Original study] (https://www.jpp.krakow.pl/journal/archive/10_13/pdf/597_10_13_article.pdf).	Intraperitoneal in the cited dose arms. Separate drinking-water arms do not validate human oral formulations or subcutaneous administration. · Once daily in the cited rat experiments, PMID 24304574. No human gut-treatment frequency is established by this study.	In PMID 24304574, postoperative administration began immediately after surgery, with the last dose 24 hours before sacrifice. Human meal or training timing was not studied.	No human exposure weeks assigned. The cited surgical model assessed outcomes through day 14, not an eight-week human course.	No validated human titration steps. Separate experimental dose arms were not an escalation sequence.
KPV	Core research topic for intestinal inflammatory signaling. Grade C for proposed gut-treatment benefits; supporting cultured-cell mechanisms are grade D.	PMID 18061177 reports KPV at 100 micromol/L in drinking water, administered orally with unrestricted access in mice during an eight-day DSS-colitis experiment. This concentration does not specify a fixed daily mass dose because water consumption determines exposure. Primary cell and mouse study, PMID 18061177. PepT1-mediated uptake and inflammatory signaling were studied in cultured cells. Molar units preserve the reported concentration without inventing a daily mass dose. [Original study] (https://pmc.ncbi.nlm.nih.gov/articles/PMC2431115/).	Oral drinking water in mice. This formulation does not establish equivalence to human oral formulations or injected KPV. · Ongoing drinking-water access in PMID 18061177, not a once-daily bolus.	KPV accompanied DSS exposure in this experiment. No human relationship to meals, exercise or bedtime was established.	No human exposure weeks assigned. Eight experimental days do not establish an eight-week human course.	No validated human starting dose, escalation interval or maintenance dose. The experimental concentration was not a titration protocol.
LL-37	Optional research topic for innate immunity. Grade C for proposed administered gut treatment. Human observational findings do not establish treatment efficacy.	PMID 31955203 reports LL-37 at 5 mg/kg, administered intrarectally once daily in mice for 14 days. Exposure covered seven days before and seven days during DSS administration. This is not a human regimen. PMID 31955203 included human observational data, cell experiments and mouse treatment. Reduced mouse colitis did not establish restoration of microbial composition. [Original study] (https://pmc.ncbi.nlm.nih.gov/articles/PMC7216768/).	Intrarectal in the mouse experiment. Systemic administration cannot be assumed equivalent. · Once daily in PMID 31955203. Human gut-treatment frequency remains unestablished by this study.	Administration began before chemically induced colitis and continued during induction. This design does not establish treatment of existing human disease.	No human exposure weeks assigned. Optional research context does not mean introducing LL-37 if symptoms persist.	No validated human titration. Persistent symptoms warrant diagnostic reassessment, not an assumed antimicrobial-peptide escalation.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1	Record seven baseline days when symptoms permit observation. Define the main symptom and its effect on eating, sleep and training. Review medicines, supplements and recent illness.	Blood, fever, nighttime diarrhea, dehydration or unintentional weight loss warrant assessment without waiting to complete the observation period.
2	Review the baseline with a clinician if symptoms persist or recur. Identify indicated testing and one manageable dietary or behavioral change.	Distinguish urgency, loose stools, constipation, reflux and pain. These patterns have different causes and should not share an assumed diagnosis.
3	Maintain adequate food intake and hydration. Keep prescribed treatment consistent. Document the chosen change and avoid introducing several new supplements.	Track whether improvement coincides with medication changes, reduced alcohol, altered fiber intake or lower training stress.
4	Compare weekly averages with baseline. Review available laboratory or stool results. Arrange reassessment if symptoms remain disruptive or worsen.	Less bloating does not prove mucosal healing. Persistent bleeding or abnormal inflammatory testing takes priority over subjective improvement.
5	Review energy intake, sleep regularity and stress alongside bowel symptoms. Reassess training demands against hydration, intake and recovery capacity.	Fatigue, dizziness, poor intake and elevated resting heart rate may reflect illness or inadequate recovery. Earlier assessment remains appropriate whenever these occur.
6	Follow up previously abnormal results and any relevant metabolic concerns. Consider gradual restoration of usual training when symptoms, intake and clinical advice permit.	Look for recurrence associated with training intensity, meal size or specific exposures. Avoid interpreting one good day as durable recovery.
7	Hold useful habits steady. Summarize symptom frequency, functional improvement and unresolved problems. Prepare questions for the endpoint review.	Check whether improvement persists without increasingly restrictive eating or growing reliance on symptom-relief medicines.
8	Complete the endpoint review against week one. Discuss further investigation, treatment adjustment or routine follow-up with the clinician when indicated.	Persistent symptoms, nutritional compromise or abnormal testing warrant continued clinical care. The endpoint does not establish eligibility for a peptide cycle.

PRE-CHECKS

- Document symptom onset, stool frequency and Bristol stool type, pain location, urgency, visible blood, nighttime symptoms, food tolerance and recent travel or antibiotics.
- Record resting heart rate, body weight, sleep duration and training load. Blood pressure may be relevant to dizziness or dehydration. Waist circumference is optional context, not a measure of intestinal healing.
- Review inflammatory bowel disease, celiac disease, ulcers, previous surgery, family gastrointestinal history and medicines affecting bowel function. Include NSAIDs, antibiotics and laxatives.
- For persistent symptoms, discuss whether a CBC and metabolic panel are indicated. Relevant measures may include electrolytes, kidney function, liver tests and albumin. Fatigue, bleeding or suspected deficiency may warrant ferritin or iron studies.
- Fecal calprotectin, CRP, stool pathogen testing and celiac serology depend on the clinical presentation. Celiac testing generally requires continued gluten exposure. Commercial permeability or microbiome panels do not establish eligibility for these peptides.
- Fasting glucose or HbA1c may be relevant with metabolic risk, diabetes symptoms or existing diabetes. Normal results do not establish experimental-peptide safety. These checks evaluate symptoms, not clearance for experimental exposure.
- BPC-157 is prohibited at all times under WADA S0. S0 also covers pharmacological substances without governmental approval for human therapeutic use when no subsequent List section addresses them. Absence of a substance's name does not establish permission. [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

STOP RULES

- Stop any experimental product and obtain urgent care for substantial rectal bleeding, black tarry stools, vomiting blood, fainting or severe abdominal pain. Marked distension with pain, vomiting or inability to pass stool or gas also requires urgent assessment.
- Seek urgent assessment for repeated vomiting, inability to retain fluids, very low urine output, or fever with worsening abdominal symptoms.
- Breathing difficulty, facial or tongue swelling, or widespread hives with dizziness require emergency care.
- Arrange prompt clinical review for persistent nighttime diarrhea, unexplained weight loss, new anemia, progressive symptoms or worsening inflammatory results. Do not independently stop essential prescribed medicines.

EXPECTED TIMELINE

The first two weeks organize symptom patterns and clinical questions. Weeks three through six review changes associated with diagnosis-specific care and stable habits. Weeks seven and eight assess durability and remaining impairment. These are organizational checkpoints, not expected response times. The verified studies provide no reliable human gut-repair timeline for BPC-157, KPV or LL-37. Symptom improvement alone does not confirm healed intestinal tissue.

COMMON MISTAKES

- Treating gut repair as a diagnosis, assuming all bloating indicates inflammation, or interpreting the name as a promised treatment outcome.
- Converting animal doses into personal doses or treating oral, intrarectal and injected exposure as interchangeable.
- Calling human-cell experiments human trials, interpreting endogenous LL-37 measurements as evidence for administering it, or confusing preventive mouse exposure with treatment of established disease.
- Adding several compounds together, masking symptoms with restrictive eating, or using subjective improvement to dismiss bleeding or abnormal tests. Scheduled review weeks never justify postponing needed care.

MONITORING

- Summarize daily stool counts, Bristol types, urgency episodes, nighttime bowel movements and any blood each week.
- Compare average and worst pain and bloating on consistent 0 to 10 scales. Record missed meals, interrupted sleep and missed training.
- Track weekly weight, resting heart rate, sleep and dietary changes under comparable conditions. Include blood pressure when clinically indicated.
- Record medication changes and adverse symptoms. Repeat laboratory or stool testing when clinically indicated, not automatically every week. Monitoring cannot establish safety for these experimental compounds.

EXIT PLAN

End the structured eight-week review by comparing symptoms, function, weight and clinically relevant tests. The cited evidence establishes no taper or washout interval for this combination. It also provides no validated method for calculating human clearance after combined exposure. If exposure occurred, document the compound, route, amount, frequency and last exposure date for the clinician. A further two to four weeks of observation can serve as a practical follow-up window when clinically appropriate. This is not a proven pharmacological washout and does not justify delaying assessment. Continue prescribed disease treatment and reassess relapse rather than automatically restarting experimental compounds.

TRACKER FIELDS

Week number; week start date; primary symptom; clinician working diagnosis · Mean stools per day; predominant bristol type; urgency episodes; nighttime bowel movements; visible blood days · Mean pain 0 to 10; worst pain 0 to 10; mean bloating 0 to 10; symptom interference 0 to 10 · Body weight kg; optional waist cm; resting heart rate bpm; blood pressure mmHg if indicated; mean sleep hours; training sessions · Food tolerance notes; diet changes; medication changes; missed meals; missed training · Experimental exposure if any; exposure amount and units; route; frequency; last exposure date; adverse events · Test name date result units; clinician review date; stop signal; action taken; next review date

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2. Dalmaso G et al. PepT1-mediated tripeptide KPV uptake reduces intestinal inflammation.. *Gastroenterology*, 2008. PMID 18061177 DOI 10.1053/j.gastro.2007.10.026 (Grade C: oral KPV in mouse colitis. Grade D: PepT1-mediated uptake and inflammatory signaling in cultured cells. Does not establish a human regimen.)

3. Gubatan J et al. Cathelicidin Mediates a Protective Role of Vitamin D in Ulcerative Colitis and Human Colonic Epithelial Cells.. *Inflammatory bowel diseases*, 2020. PMID 31955203 DOI 10.1093/ibd/izz330 (Grade C for gut-treatment extrapolation: intrarectal LL-37 before and during mouse colitis induction. Includes human observational associations and grade D cell mechanisms, not human LL-37 treatment.)

Clean Bulk (GH Axis)

BEGINNER · 12 WEEKS · CORE: CJC-1295, IPAMORELIN · SUPPORT: BPC-157

A 12-week educational framework for evaluating GH-axis claims, organizing hypertrophy fundamentals, and tracking meaningful outcomes. Human studies establish hormone responses to individual compounds. They do not establish that this combination produces additional muscle growth or has an acceptable safety profile over 12 weeks. Beginner describes the educational level, not suitability for self-treatment. The calendar organizes assessment, not peptide administration.

WHO IT IS FOR

Adults with established resistance-training habits who want to distinguish documented pharmacology from bodybuilding claims and prepare an informed clinical discussion. The useful outcome is a reproducible training, nutrition, recovery, and monitoring record.

WHO SHOULD NOT RUN IT

This is unsuitable as a self-directed drug regimen. Pregnancy, breastfeeding, active cancer, unexplained masses, pituitary disease, uncontrolled diabetes, untreated sleep apnea, and significant cardiovascular disease require particular caution and clinical assessment. These are precautionary exclusions, not a validated contraindication list for this untested combination. Under the 2026 WADA Prohibited List, all three compounds are prohibited at all times. CJC-1295 and ipamorelin fall under S2; BPC-157 falls under S0.

THE LOGIC

The hierarchy describes assessment priorities, not a validated sequence of peptide administration. First, investigate persistent inflammation, recurrent illness, and injuries that restrict training. Normal exercise soreness does not establish an inflammatory disorder. BPC-157 appears only as optional evidence to examine. Animal repair findings do not establish immune protection or human tendon healing. Second, assess energy availability and unexplained fatigue. Third, stabilize sleep, stress, and recovery, including evaluation for sleep apnea when indicated. Fourth, review glucose regulation and cardiovascular risk because GH-axis stimulation raises metabolic concerns. These concerns do not quantify adverse-event rates for this exact combination. Then evaluate tissue loading and anabolic claims. CJC-1295 illustrates sustained GHRH activity and increased GH and IGF-1 exposure. Ipamorelin illustrates ghrelin-receptor-mediated GH release. Complementary mechanisms do not demonstrate additional hypertrophy or establish combination safety. The cited CJC-1295 studies used the long-acting, albumin-binding compound commonly described as containing DAC. Their pharmacokinetics cannot be transferred to substances called CJC-1295 without DAC. Evidence B applies to the individual compounds' short-term human endocrine findings. BPC-157 has evidence C for musculoskeletal benefit because human evidence is too weak to establish efficacy. Claims that this exact combination improves hypertrophy have evidence D, reflecting mechanistic speculation rather than a demonstrated treatment effect.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
CJC-1295	Evidence review of sustained GHRH stimulation. Short human studies support increased GH and IGF-1, not established hypertrophy outcomes.	PMID 17018654 reports 60 or 90 mcg/kg CJC-1295 as a single subcutaneous administration, with hormone assessment one week later. These are experimental study exposures, not recommended starting doses. PMIDs 16352683 and 17018654 support short-term human endocrine findings, graded B because the trials were brief. PMID 16352683 reports a half-life of 5.8 to 8.1 days and evidence of accumulation. Neither paper establishes additional hypertrophy from this combination.	Subcutaneous in the cited human research; the findings concern long-acting, albumin-binding CJC-1295. · Single administration in PMID 17018654. PMID 16352683 investigated repeated subcutaneous administration at weekly or biweekly intervals, not a validated 12-week hypertrophy schedule.	No demonstrated hypertrophy advantage from administration before training, after training, while fasting, or before sleep. Prolonged exposure does not establish a useful workout-timing strategy.	Reviewed during weeks 1 to 12; no drug-active weeks are assigned. The placebo-controlled studies in PMID 16352683 lasted 28 and 49 days.	No validated beginner titration exists. Study dose groups are not instructions for individual escalation. Symptoms or a slow scale response do not justify increasing exposure.
Ipamorelin	Evidence review of ghrelin-receptor-mediated GH release. Human pharmacology supports an acute hormone response; combination-related muscle gain remains unestablished.	PMID 25331030 reports 0.03 mg/kg ipamorelin by intravenous infusion twice daily, from postoperative day 1 through day 7 or hospital discharge. This hospital regimen studied postoperative ileus, not hypertrophy. PMID 10496658 documents human pharmacokinetics, an approximately two-hour terminal half-life, and acute GH release. PMID 25331030 supplies the reported clinical dose. It found no significant difference from placebo in key or secondary efficacy analyses. Evidence B describes limited human studies, not demonstrated hypertrophy efficacy.	Intravenous in the cited clinical regimen. It does not validate a subcutaneous bodybuilding equivalent. · Twice-daily intravenous infusion describes the short inpatient regimen in PMID 25331030. No validated frequency exists for this proposed hypertrophy combination.	No established relationship to resistance training, fasting windows, or bedtime for muscle growth. Hospital feeding endpoints do not establish sports-nutrition timing.	Reviewed throughout the framework; no drug-active weeks are assigned. The inpatient exposure in PMID 25331030 was at most seven days.	No evidence-based escalation sequence exists for healthy lifters. Different research dose groups do not establish a personal titration ladder.
BPC-157	Optional evidence review when an injury limits training. It is not established protection against injury, inflammation, or GH-axis adverse effects.	250 to 500 mcg subcutaneously once daily is commonly cited in non-clinical use; not validated in trials. This describes circulating practice, not an established effective dose or a characterized safety profile. PMID 40756949 included 35 preclinical studies and one retrospective clinical study. PMID 41898733 discusses additional small human pilot studies. Evidence C applies to musculoskeletal benefit because human evidence remains too weak to establish efficacy. Neither review validates the reported subcutaneous practice.	Subcutaneous describes the non-clinical practice above. Human pilot studies involving other routes cannot validate it. · Once-daily subcutaneous administration describes non-clinical practice only; an effective human musculoskeletal frequency is unestablished.	No validated timing relative to meals, training, or sleep. Symptoms still require diagnosis and appropriate rehabilitation.	No automatic inclusion and no assigned active weeks. An unresolved injury warrants reassessment of the training plan.	No validated initiation, escalation, maintenance, or tapering sequence exists. Persistent pain calls for reassessment rather than increased experimental exposure.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1 to 2	Establish the baseline before changing the program. Record morning weight, waist, blood pressure, resting pulse, sleep, food intake, and repeatable performance measures. Review medical history and investigate persistent injury or illness.	Large daily fluctuations, unresolved pain, recurrent illness, snoring with daytime sleepiness, or abnormal baseline glucose.
3 to 4	Stabilize meal patterns, adequate energy intake, sleep opportunity, and training attendance. Review the distinction between hormone endpoints and muscle outcomes. Any exposure within a clinical study follows that study's protocol, not this calendar.	Rapid weight increases accompanied by swelling, rising waist circumference, poor recovery, or declining exercise tolerance.
5 to 6	Compare two-week averages rather than isolated weigh-ins. Review training progression and nutrition adherence. If GH-axis exposure has occurred, clinical review may include glucose and age-adjusted IGF-1 reassessment.	New tingling, hand tightness, persistent headache, worsening snoring, rising blood pressure, or increasing fasting glucose.
7 to 8	Assess whether performance changes persist across comparable sessions. Adjust training workload for recovery and joint tolerance. Investigate a stalled bulk through intake and program adherence before attributing it to inadequate hormone stimulation.	Repeated performance decline, pain that changes technique, escalating fatigue, or apparent lean-mass gains accompanied by fluid retention.
9 to 10	Keep measurement conditions consistent and limit unnecessary program changes. Review all adverse symptoms and actual exposures. Decide which outcomes will be reassessed at completion.	Accumulating adverse symptoms, progressively poorer sleep, or reliance on pain relief to maintain excessive loading.
11 to 12	Complete the planned training block and compare baseline with final averages. Review glucose, HbA1c when appropriate, and clinically indicated IGF-1. Document any supervised treatment endpoint and arrange follow-up.	Persistent edema, metabolic deterioration, unresolved neurological symptoms, or pressure to extend exposure because results are disappointing.

PRE-CHECKS

- Collect a baseline week of morning body weight, resting heart rate, and seated blood pressure using a correctly sized cuff. Measure waist at the same anatomical location.
- Record sleep duration, awakenings, snoring, daytime sleepiness, food intake, training frequency, exercise loads, and injury limitations.
- A clinician can assess fasting glucose, HbA1c, lipids, and age-adjusted IGF-1 when GH-axis exposure is being considered or has occurred. Normal results do not establish safety.
- Review kidney and liver function when clinically relevant. CBC, thyroid testing, or additional endocrine investigations should follow symptoms and history rather than an automatic extensive panel.
- Document diabetes, hypertension, edema, neuropathy, sleep apnea, malignancy, pituitary disease, pregnancy possibility, medications, supplements, and prior hormone use. A random GH measurement cannot reliably characterize pulsatile secretion.

STOP RULES

- Stop experimental exposure and obtain emergency care for chest pain, severe breathlessness, fainting, facial or tongue swelling, or sudden neurological symptoms.
- Severe headache with visual changes requires urgent assessment, especially during GH-axis exposure.
- Repeated systolic blood pressure at or above 180 mmHg, or diastolic pressure at or above 120 mmHg, warrants urgent clinical contact. Associated chest pain, breathlessness, visual changes, or neurological symptoms require emergency care. Symptoms warrant emergency care even below these thresholds.
- New persistent edema, rapid unexplained weight gain, palpitations, hand numbness, or worsening sleep-apnea symptoms require stopping exposure and prompt clinical review.
- Repeated fasting glucose at or above 126 mg/dL warrants prompt assessment. Random glucose at or above 200 mg/dL with excessive thirst or urination also warrants prompt assessment. Home readings need clinical confirmation; these are evaluation triggers, not a complete diagnostic algorithm.
- Fever, spreading redness, severe localized pain, or a hot swollen joint after any administered product requires urgent evaluation.

EXPECTED TIMELINE

Training and nutrition trends become easier to interpret over several weeks. CJC-1295 can change endocrine markers within days, as documented in PMID 16352683, but that does not predict muscle gain. No defensible number of kilograms, response deadline, or guaranteed recomposition outcome exists for this combination.

COMMON MISTAKES

- Treating a higher GH or IGF-1 result as proof of additional muscle growth.
- Applying long-acting CJC-1295 evidence to a different compound described as without DAC.
- Converting an inpatient intravenous study into a home subcutaneous schedule.
- Calling fluid-related weight gain a successful clean bulk.
- Using BPC-157 to postpone diagnosis or override rehabilitation limits.

TRACKER FIELDS

Average morning weight kg · Waist cm · Average systolic bp mmHg · Average diastolic bp mmHg · Average resting heart rate bpm · Average sleep hours · Sleep quality 0 to 10 · Average daily energy kcal · Average daily protein g · Training sessions completed · Benchmark exercise load repetitions and effort · Pain location and score 0 to 10 · Edema headache tingling or other symptoms · Actual compound form dose unit route frequency and dates if applicable · Laboratory date results and reference ranges · Clinician review and action

REFERENCES

- Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Short human trials, subcutaneous administration, prolonged GH and IGF-1 responses, accumulation, and pharmacokinetics. These findings do not establish hypertrophy efficacy for the combination.)

MONITORING

- Each week compare average body weight, waist, standardized performance, training attendance, and recovery. Strength improvements alone do not prove hypertrophy.
- Summarize several resting blood pressure and pulse readings, sleep quality, edema, headaches, tingling, appetite, thirst, and urinary frequency.
- If exposure occurs under supervision, the clinician determines glucose and IGF-1 testing intervals. Record laboratory dates and time since exposure. A supraphysiological IGF-1 value is not a validated hypertrophy target.
- Keep dietary carbohydrate, hydration, and measurement conditions reasonably consistent when comparing body-composition results. Water shifts can distort estimated lean mass.

EXIT PLAN

At week 12, close the training block and review performance, symptoms, and laboratory changes. No validated taper or post-cycle regimen exists for this combination. If exposure occurred, the supervising clinician determines discontinuation and follow-up. PMID 16352683 reports prolonged endocrine effects, including IGF-1 remaining above baseline for up to 28 days after repeated administration. Immediate post-discontinuation testing therefore may not represent a recovered baseline. The reported half-life does not establish an individual recovery deadline. Follow-up depends on symptoms, glucose, IGF-1, actual exposure, and clinical findings. Persistent abnormalities require assessment rather than automatic repetition of the training or exposure calendar.

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3. Gobburu JV et al. Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers.. *Pharmaceutical research*, 1999. PMID 10496658 DOI 10.1023/a:1018955126402 (Human ipamorelin pharmacokinetics, approximately two-hour terminal half-life, and acute GH response. It does not validate the proposed hypertrophy combination.)
4. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Reported intravenous hospital regimen, short exposure duration, and no significant difference from placebo in key or secondary efficacy analyses. The study concerned postoperative ileus.)
5. Vasireddi N et al. Emerging Use of BPC-157 in Orthopaedic Sports Medicine: A Systematic Review.. *HSS journal : the musculoskeletal journal of Hospital for Special Surgery*, 2025. PMID 40756949 DOI 10.1177/15563316251355551 (Review of 35 preclinical studies and one retrospective clinical study. Human musculoskeletal efficacy and safety remain inadequately characterized.)
6. Yuan C et al. From Regeneration to Analgesia: The Role of BPC-157 in Tissue Repair and Pain Management.. *International journal of molecular sciences*, 2026. PMID 41898733 DOI 10.3390/ijms27062876 (Updated discussion of preclinical repair mechanisms and limited human pilot studies. It does not establish efficacy for the cited subcutaneous practice.)

Advanced Hypertrophy

ADVANCED · 10 WEEKS · CORE: CJC-1295, IPAMORELIN, IGF-1 LR3 · SUPPORT: PEG-MGF

A 10-week framework for evaluating anabolic peptide claims, documenting training outcomes, and recognizing adverse effects. Published exposures are described where available. This combination has no validated human hypertrophy protocol. Active dosing weeks, escalation steps, and expected muscle gains cannot be established from the cited evidence.

WHO IT IS FOR

Experienced adult trainees seeking to understand GH and IGF-1 pathways, distinguish laboratory findings from clinical outcomes, and discuss exposure with a clinician. Advanced describes the complexity of the evidence and risks. It does not establish eligibility for self-administration.

WHO SHOULD NOT RUN IT

This framework does not establish medical suitability for exposure. Pregnancy, breastfeeding, active cancer, unexplained masses, uncontrolled diabetes, recurrent hypoglycemia, untreated sleep apnea, and significant cardiovascular disease require particular clinical attention. These investigational compounds lack validated hypertrophy prescribing criteria. All four are prohibited at all times under the WADA 2026 Prohibited List, section S2. CJC-1295 and ipamorelin are named; IGF-1 analogues and mechano growth factors are covered classes.

THE LOGIC

The assessment begins with persistent illness, unresolved injury, and inflammatory symptoms that could affect training. Identifying these problems does not imply suppressing normal exercise inflammation or adding an immune peptide. Next assess energy availability, food intake, and recovery demands. Then review sleep, stress, stimulant use, and possible sleep apnea. Evaluate metabolic context through glucose status, blood pressure, and waist trends. Tissue loading and anabolic claims come last, once recovery capacity is understood. This is an organizational framework, not a biological hierarchy validated in peptide trials. CJC-1295 appears first because it stimulates the GHRH receptor and has short-term human endocrine-response data. Ipamorelin follows because it stimulates the ghrelin receptor, another pathway involved in GH release. Complementary mechanisms do not establish superior hypertrophy or acceptable combined risk. IGF-1 LR3 acts farther downstream at the IGF-1 receptor, with altered binding-protein interactions. Its inclusion increases uncertainty rather than completing a proven pathway. PEG-MGF appears only as an educational comparison. Evidence about endogenous MGF or synthetic fragments does not validate a pegylated human treatment. The combined hypertrophy hypothesis is grade D, reflecting mechanistic reasoning without demonstrated clinical benefit. Component grades apply to the stated endpoint and cannot be transferred to the combination.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
CJC-1295	Long-acting GHRH analogue. Grade B for short-term human endocrine pharmacology. Grade C for hypertrophy claims because the human measurements do not establish muscle growth or strength benefits.	PMID 16352683 reports 30 or 60 mcg/kg subcutaneously among studied exposures. Its research schedules included single administration and separate repeated-administration arms using weekly or every-other-week intervals. The abstract does not map each amount to every schedule. These exposures do not establish a 10-week prescription. PMID 16352683 supports endocrine responses and prolonged exposure. These findings cannot be transferred to short-acting modified GRF described as CJC-1295 without DAC.	Subcutaneous in PMID 16352683. The studied long-acting compound contains the albumin-binding modification commonly called DAC. · Single administration or weekly/every-other-week research schedules in PMID 16352683. No validated frequency exists for the proposed combination.	The cited trials do not establish a hypertrophy advantage from administration before training, after training, while fasting, or before sleep.	No active weeks assigned. PMID 16352683 describes studies lasting 28 and 49 days, without establishing a 10-week hypertrophy course.	No validated individual escalation steps. Ascending study cohorts do not establish a self-titration algorithm.
Ipamorelin	Ghrelin-receptor agonist that can stimulate GH release. Grade B for short-term human pharmacology and postoperative clinical exposure. Grade C for hypertrophy claims unsupported by those human endpoints.	PMID 25331030 used 0.03 mg/kg by intravenous infusion twice daily from postoperative day 1 through day 7 or hospital discharge. This inpatient research exposure does not establish a subcutaneous bodybuilding dose. PMIDs 25331030 and 10496658. The postoperative trial found no significant differences in its key or secondary efficacy analyses. Neither study establishes muscle gain.	Intravenous in the cited human studies. A subcutaneous equivalent cannot be assumed. · Twice daily by intravenous infusion in PMID 25331030, for a postoperative indication. No established hypertrophy frequency.	No validated timing relative to resistance exercise, food, or sleep for hypertrophy. Postoperative meal-tolerance testing does not establish a fasting administration rule.	No active weeks assigned. The repeated exposure in PMID 25331030 lasted up to seven days.	No validated hypertrophy escalation steps. The human pharmacokinetic study compared dose cohorts without establishing a long-term personal titration schedule.
IGF-1 LR3	Modified IGF-1 analogue with reduced affinity for IGF-binding proteins. Grade D for the cited myogenic-cell evidence. Human hypertrophy efficacy is not established.	No validated human dose, route, or frequency was identified in the cited evidence. PMID 15817840 examines cell cultures; PMID 42395176 reviews the clinical evidence gap. Neither establishes a numeric human hypertrophy regimen. PMIDs 15817840 and 42395176. Prescription recombinant IGF-1 dosing cannot be transferred to LR3. Class-based risk concerns are not compound-specific incidence estimates.	No established human therapeutic route for hypertrophy. Cell-culture exposure cannot be converted into a human administration route. · Not established in human hypertrophy trials identified by the cited review.	Claims about post-workout targeting, local muscle growth, protection from hypoglycemia through meals, or bedtime use are not validated by the cited evidence.	No active weeks assigned. No evidence-based introductory, loading, or finishing phase was identified.	No validated starting dose or escalation steps. Hypoglycemia is a concern from IGF-related pharmacology; its incidence with LR3 is not established.
PEG-MGF	Educational comparison of a pegylated MGF-related peptide. Grade D for human hypertrophy claims. Related MGF research does not establish equivalence to PEG-MGF.	No validated human dose, route, or frequency was identified. PMID 37171185 reviews related MGF biology; PMID 42395176 discusses PEG-MGF evidence limitations. Neither supplies a validated human hypertrophy regimen. PMIDs 37171185 and 42395176. Endogenous MGF, synthetic E-domain fragments, and PEG-MGF are distinct evidence categories. The cartilage review does not establish a human muscle-growth treatment.	No established human therapeutic route for this goal. · Not established. Weekly schedules cannot be inferred from pegylation alone.	No verified advantage from rest-day, post-training, fed, fasted, or bedtime administration.	No active weeks assigned. Inclusion in this comparison does not imply evidence supporting addition to the other compounds.	No validated titration steps or evidence-based method for adding it to the other compounds.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1	Complete baseline measurements and medical-history review. Document any existing exposure accurately. Identify unresolved illness, injury, or unexplained symptoms before progressing training.	Fever, persistent pain, swelling, unusual fatigue, and uncertainty about actual compound identity.
2	Review food intake, meal consistency, sleep opportunity, alcohol, and stimulant use. Investigate snoring or witnessed breathing pauses.	Under-fueling, daytime sleepiness, disrupted sleep, and excessive resting heart rate.
3	Review glucose, blood pressure, and relevant laboratory results with a clinician. Establish repeatable training benchmarks using consistent technique and effort.	Abnormal glucose, elevated blood pressure, or performance limited by recovery.
4	Audit CJC-1295 and ipamorelin evidence against the documented formulation and exposure history. Continue training records; this review supplies no escalation schedule.	Edema, hand tingling, joint discomfort, headaches, and appetite changes. These findings are not specific to peptide exposure.
5	Compare weight and waist trends with repetitions, loads, and recovery. Review symptoms and any clinician-directed glucose or IGF-1 measurements.	Rapid weight gain without functional improvement, particularly with swelling.
6	Review LR3 and PEG-MGF evidence gaps. Adjust training fatigue when needed. A plateau does not establish a pharmacological indication.	Persistent soreness, declining performance, hypoglycemic symptoms, or pressure to add compounds.
7 to 8	Repeat standardized performance assessments. Discuss any existing exposure and laboratory abnormalities with the clinician assessing the exposure.	Worsening sleep, neurological symptoms, sustained glucose deterioration, and increasing waist circumference.
9 to 10	Prepare the exit review. Repeat baseline measurements under similar conditions. Document unresolved symptoms, laboratory follow-up, and any last exposure date.	Persistent abnormalities requiring follow-up beyond the assessment window. Acute symptoms require action when they occur, regardless of the scheduled review.

PRE-CHECKS

- Record several days of seated blood pressure and resting heart rate using consistent conditions.
- Collect morning body weight, waist circumference at a fixed landmark, and reproducible performance benchmarks.
- Document sleep duration, quality, snoring, breathing pauses, injury history, and current training volume.
- Discuss fasting glucose and HbA1c with a clinician. Baseline age-adjusted IGF-1 may assist clinical assessment of GH-axis exposure.
- Review diabetes, hypoglycemia, pituitary disease, cancer history, retinopathy, edema, heart disease, pregnancy, breastfeeding, and all medicines or supplements.
- Consider renal function, electrolytes, and liver tests according to history and clinical assessment. Normal results or broad hormone panels do not establish suitability.

MONITORING

- Weekly: compare average morning weight, waist, blood pressure, and resting heart rate with baseline.
- Weekly: log exercises, loads, repetitions, effort, completed sessions, soreness, and joint symptoms.
- Weekly: summarize sleep, appetite, energy, edema, hand numbness, headaches, and visual symptoms.
- If exposure already exists, document each administration and discuss clinician-directed glucose monitoring. Weekly summaries cannot detect every acute hypoglycemic episode.
- Repeat glucose and IGF-1 testing when clinically indicated, particularly after symptoms or exposure changes. Higher IGF-1 is not an established hypertrophy treatment target.

STOP RULES

- Further exposure should stop pending urgent assessment for suspected hypoglycemia. Confusion, fainting, seizure, or inability to self-treat requires emergency care. Glucose below 70 mg/dL requires immediate attention; below 54 mg/dL is clinically significant. Monitoring must not delay treatment.
- Chest pain, severe breathlessness, new focal weakness, throat swelling, or severe headache with visual disturbance requires emergency care.
- Systolic blood pressure at or above 180 mmHg or diastolic pressure at or above 120 mmHg warrants prompt reassessment and urgent medical advice. Associated chest pain, breathlessness, neurological symptoms, or visual changes requires emergency care without waiting for another reading.
- Progressive edema, new persistent numbness, severe joint pain, or worsening sleep apnea symptoms warrants stopping further exposure and obtaining prompt clinical review.
- Repeated fasting glucose at or above 126 mg/dL or IGF-1 above the laboratory's age-adjusted range warrants withholding further exposure pending clinician review. Home glucose readings require clinical confirmation; neither finding supplies an automatic dose-adjustment rule.

EXPECTED TIMELINE

Training-related performance changes may appear before measurable hypertrophy. Early weight changes can reflect glycogen, food mass, or fluid. PMID 16352683 documents prolonged hormonal changes without demonstrating corresponding muscle growth. Ten weeks permits trend assessment but cannot establish whether an uncontrolled combination caused any improvement. Changes in training, food intake, sleep, and measurement conditions also affect interpretation.

EXIT PLAN

At week 10, compare baseline and final performance, waist, weight, sleep, symptoms, and relevant laboratory results. No validated taper, post-cycle therapy, or universal washout exists for this combination in the cited evidence. If exposure occurred, cessation and follow-up require clinical assessment. PMID 16352683 reports a CJC-1295 half-life of 5.8 to 8.1 days and prolonged IGF-1 elevation after repeated exposure. Effects may therefore outlast the final administration. Calendar completion does not establish physiological recovery. Follow-up continues until abnormalities are evaluated and appropriately managed. Human clearance times for LR3 or PEG-MGF cannot be inferred from these CJC-1295 findings.

COMMON MISTAKES

- Treating increased GH or IGF-1 as proof of hypertrophy or assigning the same evidence grade to endocrine and muscle outcomes.
- Confusing long-acting CJC-1295 with modified GRF without DAC.
- Converting intravenous research exposure into a subcutaneous regimen or combining separately studied schedules.
- Treating cell-culture findings, endogenous MGF biology, or a narrative review as proof of human treatment efficacy.
- Calling fluid retention muscle gain or interpreting normal laboratory results as evidence that exposure is harmless.

TRACKER FIELDS

Mean morning weight kg · Waist cm · Mean seated systolic bp mmHg · Mean seated diastolic bp mmHg · Mean resting heart rate bpm · Mean sleep hours and quality · Training sessions exercises loads repetitions effort · Food intake and appetite changes · Pain edema numbness headache visual symptoms · Glucose values mg dL with dates and context · Laboratory results with dates units reference ranges · Existing exposure compound formulation dose unit route frequency dates provenance · Adverse events and clinician actions

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2. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Short intravenous ipamorelin exposure in postoperative patients. Key and secondary efficacy analyses found no significant differences. Does not support a hypertrophy regimen.)
3. Gobburu JV et al. Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers.. *Pharmaceutical research*, 1999. PMID 10496658 DOI 10.1023/a:1018955126402 (Human ipamorelin pharmacokinetics and acute GH release after intravenous research exposure. Does not establish long-term muscle or combination outcomes.)
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Fat Loss with a Muscle-Preservation Objective (Incretin Class)

INTERMEDIATE · 16 WEEKS · CORE: SEMAGLUTIDE, TIRZEPATIDE · SUPPORT: CJC-1295, IPAMORELIN

A 16-week educational framework for understanding clinician-managed incretin treatment while tracking nutrition, strength and recovery. Human trials support weight reduction, including fat loss. Complete muscle preservation is not established, and this combined framework has not been tested as a protocol.

WHO IT IS FOR

Adults with obesity, or overweight with a weight-related complication, whose clinician considers prescription weight management appropriate. STEP 1 and SURMOUNT-1 enrolled adults with BMI at least 30 kg/m2, or at least 27 kg/m2 with a qualifying complication. Both pivotal trials excluded diabetes. Training experience does not replace medical eligibility.

WHO SHOULD NOT RUN IT

This framework is unsuitable for cosmetic cutting in already lean athletes or weight loss during pregnancy. Label contraindications include personal or family history of medullary thyroid carcinoma, MEN2, or serious hypersensitivity to the selected medicine or its excipients. Both labels advise against use with severe gastroparesis. Active eating disorders, malnutrition and unexplained weight loss require assessment. Anyone with an active or recent malignancy, or a strong family history of hormone-sensitive cancer, should not run the growth hormone axis components (GHRH analogs, GHRPs, IGF-1 variants): these pathways stimulate cell growth, and the trials that exist excluded such participants.

THE LOGIC

Readiness assessment covers medical eligibility, concurrent illness, nutritional adequacy, hydration, sleep and psychological health. These are clinical considerations, without an established immune, recovery or metabolic treatment sequence. There is no evidence that an immune peptide or growth-hormone secretagogue must precede incretin treatment. Semaglutide activates GLP-1 receptors; tirzepatide activates GIP and GLP-1 receptors. They are alternative core treatments. Their labels advise against coadministration with another GLP-1 receptor agonist or another product containing the same active ingredient. Both have grade A evidence for weight reduction. Muscle preservation remains a separate objective. In the SURMOUNT-1 DXA substudy, approximately 75% of lost weight was fat and 25% lean mass in both treatment groups, PMID 39996356. These group averages do not predict an individual's losses. DXA lean mass includes water and nonmuscle tissue. CJC-1295 and ipamorelin have no established role in preventing incretin-associated lean-mass loss.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
Semaglutide	Alternative core treatment. Grade A for weight reduction; complete muscle preservation is not established.	Wegovy injection label: 0.25 mg subcutaneously once weekly during weeks 1 to 4 and 0.5 mg subcutaneously once weekly during weeks 5 to 8. Wegovy injection label: 1 mg subcutaneously once weekly during weeks 9 to 12 and 1.7 mg subcutaneously once weekly during weeks 13 to 16. These describe initial label escalation, without constituting individualized instructions. Wegovy US prescribing information, revised June 2026, sections 2.1 and 2.2: injection timing and initial escalation. PMID 33567185: STEP 1 exposure and weight-reduction efficacy.	Subcutaneous, injectable formulation. · Once weekly.	Wegovy injection label: the same day each week, at any time, with or without meals. No established training or bedtime advantage.	Weeks 1 to 16 describe initial escalation if this treatment is prescribed. Subsequent maintenance requires clinical reassessment.	The Wegovy injection label permits delaying escalation for four weeks when a step is not tolerated. STEP 1 studied a maintenance exposure of 2.4 mg subcutaneously once weekly after escalation, PMID 33567185. That trial exposure does not summarize every current maintenance option.
Tirzepatide	Alternative core treatment. Grade A for weight reduction; lean mass also declines during treatment.	Zepbound label: 2.5 mg subcutaneously once weekly for four weeks, followed by 5 mg subcutaneously once weekly. Zepbound label maintenance options for weight management are 5 mg, 10 mg or 15 mg subcutaneously once weekly, selected clinically. The initial phase is not a maintenance regimen. Zepbound US prescribing information, sections 2.1, 2.2 and 2.4: escalation, maintenance and administration timing. PMID 35658024: weight-reduction efficacy. PMID 39996356: body composition.	Subcutaneous. · Once weekly.	Zepbound label: any time, with or without meals. No established relationship to training or sleep.	Weeks 1 to 16 form an observation window if this treatment is prescribed. Escalation need not continue throughout.	Zepbound label: subsequent increases are 2.5 mg per subcutaneous once-weekly dose after at least four weeks at the current dose. Response and tolerability determine further escalation. Zepbound label: the maximum dose is 15 mg subcutaneously once weekly. No later-week dose target is assigned by this framework.
CJC-1295	Experimental context only, excluded from active scheduling. Grade B for short-term human GH and IGF-1 responses. The proposed muscle-preservation benefit is grade D, mechanistic speculation without direct clinical evidence.	PMID 16352683 studied long-acting CJC-1295 with DAC, including 30 mcg/kg or 60 mcg/kg subcutaneously as single administrations. These research exposures do not establish a fat-loss or muscle-preservation dose. PMID 16352683 evaluated endocrine responses in healthy adults. It did not evaluate muscle preservation during incretin treatment or establish long-term safety.	Subcutaneous in the cited study. · Single administration for the exposures described here.	No validated training, meal or bedtime timing for this objective.	None scheduled.	No validated titration for this objective. Findings for the long-acting DAC compound cannot establish a schedule for material described as CJC-1295 without DAC.
Ipamorelin	Experimental context only, excluded from active scheduling. Grade B describes limited human investigation in another indication. The proposed muscle-preservation benefit is grade D, mechanistic speculation without direct clinical evidence.	PMID 25331030 reported 0.03 mg/kg by intravenous infusion twice daily, from postoperative day 1 through day 7 or hospital discharge. This inpatient research exposure does not establish a subcutaneous physique-use dose. PMID 25331030 studied postoperative ileus. It did not assess fat loss, strength, incretin-associated lean-mass changes or long-term use.	Intravenous infusion in the cited trial. · Twice daily in postoperative inpatients.	No validated timing relative to training, food or sleep for muscle preservation.	None scheduled.	No validated titration for this objective. The cited trial found no statistically significant differences from placebo in its key or secondary efficacy analyses.

WEEK	ACTIONS	WATCH
1 to 4	Document the clinician-selected treatment and initial label phase. Establish repeatable meals, an individualized protein target and two or three resistance sessions weekly according to capacity and recovery. Record baseline performance on repeatable exercises. This exercise frequency is a practical framework choice, not a tested incretin protocol.	Early satiety, nausea, bowel changes, hydration and missed meals. Reduced appetite does not confirm adequate nutrition.
5 to 8	Review tolerability before any prescribed escalation. Compare weekly weight averages and waist measurements. Assess protein distribution across meals and whether training volume matches recovery.	Persistent fatigue, dizziness, food aversion or declining repetitions at familiar loads. Investigate inadequate intake before attributing fatigue to medication alone.
9 to 12	Review strength trends, dietary adequacy and daily activity with the care team. Recheck glycemia near week 12 when clinically relevant. Record whether the prescribed dose remains stable or changes.	A smaller waist with maintained performance provides useful context but does not prove muscle preservation. Falling strength across several sessions warrants review.
13 to 16	Complete an outcome review covering weight, waist, strength, symptoms and relevant laboratory changes. Repeat body composition only under comparable conditions. Discuss maintenance or discontinuation before the observation period ends.	Persistent under-eating, treatment burden and unrealistic expectations. Week 16 may mark completion of initial escalation, rather than maximal treatment response.

PRE-CHECKS

- Record height, BMI, seven-day average morning weight, waist circumference, seated blood pressure and resting heart rate. Document strength benchmarks, habitual activity and optional baseline DXA.
- Obtain fasting glucose or HbA1c, renal function and electrolytes when clinically appropriate. Lipids and liver enzymes help characterize metabolic risk. Testing reflects history rather than a universal peptide panel.
- Review pancreatitis, gallstones, gastroparesis, kidney disease, retinopathy, medullary thyroid carcinoma, MEN2, pregnancy intentions, breastfeeding, eating-disorder history and previous weight-loss treatment.
- Review insulin, sulfonylureas, antihypertensives and oral medicines. Anesthesia or sedation requires advance disclosure because delayed gastric emptying can increase aspiration risk. No universal medication-holding interval is assigned here.
- For users of oral hormonal contraception, Zepbound labeling specifies nonoral contraception or an additional barrier method for four weeks after initiation and each escalation. This precaution does not apply equally to every contraceptive method.
- Record usual food intake, protein intake, sleep duration, snoring, daytime sleepiness and recovery. Investigate unexplained fatigue before establishing an energy deficit.
- CJC-1295 and ipamorelin are prohibited at all times under section S2 of [WADA's 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Semaglutide and tirzepatide are monitored, not prohibited, under the [2026 Monitoring Program](https://www.wada-ama.org/sites/default/files/2025-09/2026_list_monitoring_program_en_final_clean_september_2025.pdf).
- Personal and family history of cancer, including hormone-sensitive and thyroid cancers, reviewed with a clinician before any growth hormone axis component.

STOP RULES

- Severe persistent abdominal pain, especially radiating to the back, requires urgent assessment. Both labels specify discontinuation when pancreatitis is suspected. Right-upper-abdominal pain with fever or jaundice also requires urgent evaluation.
- Inability to retain fluids, markedly reduced urination, fainting, or abdominal distension with vomiting and inability to pass stool or gas requires urgent care. Further dosing requires clinical review.
- Tongue or throat swelling, breathing difficulty or collapse requires emergency care. Both labels specify discontinuation for suspected serious hypersensitivity.
- Glucose below 54 mg/dL requires immediate hypoglycemia treatment under the established care plan and prompt clinical review. Seizure, unconsciousness, severe confusion or inability to swallow requires emergency assistance, regardless of the measured glucose.
- Both labels specify discontinuation of weight-loss treatment when pregnancy is recognized, with prompt prescriber contact. New or sudden visual loss requires urgent assessment.
- Persistent nutritional inadequacy, progressive weakness or sustained resting palpitations requires clinician assessment before further escalation. Wegovy labeling specifies discontinuation for a sustained increase in resting heart rate.

EXPECTED TIMELINE

Appetite and gastrointestinal effects may appear early. Weight, waist and performance trends become more interpretable over several weeks. STEP 1 and SURMOUNT-1 evaluated major outcomes at 68 and 72 weeks, respectively, PMIDs 33567185 and 35658024. Their average results are not 16-week forecasts. Neither weight reduction nor increased GH establishes preserved skeletal muscle.

COMMON MISTAKES

- Treating both incretins as a stack or assuming every escalation step is obligatory.
- Allowing appetite suppression to replace adequate meals and resistance training.
- Equating DXA lean mass with skeletal muscle or short-term water changes with tissue loss.
- Using endocrine-marker studies to justify experimental muscle-preservation add-ons.

MONITORING

- Weekly: compare seven-day mean body weight, waist, blood pressure, resting heart rate, appetite, bowel function, nausea and hydration.
- Track average protein and energy intake against individualized targets, completed resistance sessions, exercise loads, repetitions and perceived recovery.
- Record sleep hours, sleep quality, daily steps and fatigue. Persistent deterioration requires review even when weight is falling.
- Sustained loss exceeding roughly 1% of body weight weekly after early fluid shifts warrants review, especially with weakness. This is a practical review trigger, not a validated drug-stopping threshold.
- Substantial vomiting, diarrhea or dehydration warrants prompt assessment of renal function and electrolytes. Glucose monitoring depends on diabetes and concomitant medication; routine weekly laboratory panels are unnecessary.

EXIT PLAN

Week 16 is a decision point, not a mandatory drug holiday. Reassessment covers metabolic benefit, nutrition, strength, tolerability and eligibility for ongoing treatment. No validated taper reliably prevents regain. In the STEP 1 extension, participants regained about two-thirds of prior weight loss during the year after semaglutide and structured lifestyle intervention stopped, PMID 35441470. Nutrition, resistance training and weight tracking remain relevant after discontinuation. Wegovy and Zepbound labeling report approximate elimination half-lives of one week and five to six days, respectively. Substantial clearance takes several weeks. These estimates do not establish switching or pregnancy-planning intervals. For weight management, Wegovy labeling specifies discontinuation at least two months before planned pregnancy. Follow-up within four to eight weeks after stopping is a practical planning interval, individualized by the clinician.

- Planning an abrupt end without discussing maintenance and weight-regain risk.
- Confusing mg with mcg, or converting a dose to mL without the exact prescribed concentration.
- Treating preserved exercise performance as proof that no skeletal muscle was lost.

TRACKER FIELDS

Prescribed compound · Prescribed dose mg · Dose provenance · Route · Frequency · Administration dates · Missed doses · Dose change and reason · Mean morning weight kg · Weekly weight change percent · Waist cm · Mean blood pressure mmHg · Mean resting heart rate bpm · Mean daily energy kcal · Mean daily protein g · Resistance sessions completed · Benchmark exercise loads and repetitions · Mean daily steps · Mean sleep hours · Sleep quality 0 to 10 · Fatigue 0 to 10 · Appetite 0 to 10 · Gastrointestinal symptoms · Hydration concerns · Glucose if indicated mg dL · Laboratory results and dates · Adverse events · Clinician review and next action

REFERENCES

1. Wilding JPH et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2021. PMID 33567185 DOI 10.1056/NEJMoa2032183 (Grade A for semaglutide weight reduction. STEP 1 evaluated 68 weeks of treatment with lifestyle intervention in adults without diabetes. It does not establish complete muscle preservation.)
2. Jastreboff AM et al. Tirzepatide Once Weekly for the Treatment of Obesity.. *The New England journal of medicine*, 2022. PMID 35658024 DOI 10.1056/NEJMoa2206038 (Grade A for tirzepatide weight reduction. SURMOUNT-1 evaluated 72 weeks of treatment in adults without diabetes and documented gastrointestinal adverse events during escalation.)
3. Look M et al. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight.. *Diabetes, obesity & metabolism*, 2025. PMID 39996356 DOI 10.1111/dom.16275 (Grade B for this small DXA substudy, with 160 participants providing baseline and follow-up data. Fat and lean mass decreased; approximately 75% of lost weight was fat and 25% lean mass in both groups.)
4. Wilding JPH et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension.. *Diabetes, obesity & metabolism*, 2022. PMID 35441470 DOI 10.1111/dom.14725 (Grade B for exploratory withdrawal follow-up. Substantial regain and movement of cardiometabolic measures toward baseline followed cessation of semaglutide and structured lifestyle intervention.)
5. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Grade B for short human studies of endocrine responses to long-acting CJC-1295. These studies do not establish muscle preservation during weight loss or incretin treatment.)
6. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Grade B for limited inpatient investigation documenting intravenous exposure. Key and secondary efficacy analyses showed no statistically significant benefit; physique dosing and muscle preservation were not studied.)

Non-Incretin Recomposition

INTERMEDIATE · 12 WEEKS · CORE: AOD-9604, HGH FRAGMENT 176-191 · SUPPORT: CJC-1295, IPAMORELIN

A 12-week framework for evaluating non-incretin peptide claims, tracking fat loss and preserving training performance. The reviewed evidence does not establish this combination as an effective recomposition protocol. Reported research exposures below are evidence records, not personal dosing instructions.

WHO IT IS FOR

Adults who already resistance train and want to assess these compounds against measurable outcomes. Appropriate for understanding research limitations and preparing a clinician discussion. The calendar structures assessment, nutrition, recovery and follow-up. It does not establish a 12-week peptide treatment course.

WHO SHOULD NOT RUN IT

Not a self-directed treatment framework, especially during pregnancy or breastfeeding, or with active cancer, unexplained masses, pituitary disease or uncontrolled diabetes. Untreated sleep apnea, significant cardiovascular disease and previous hypersensitivity also require individualized assessment. These are clinical risk flags, not a validated contraindication list for this experimental combination. AOD-9604, hGH 176-191, CJC-1295 and ipamorelin are prohibited at all times under WADA S2. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

THE LOGIC

The sequence below organizes assessment and evidence review. It does not establish a biological hierarchy or proven peptide sequence. Active infection, inflammatory illness and unresolved injury require appropriate assessment. None of these four compounds has established immune-protection benefits in the reviewed studies. Energy availability, fatigue, neurological symptoms and sleep also affect interpretation of recovery and training performance.

Metabolic assessment centers on consistent intake, activity and waist measurements. AOD-9604 appears first in the evidence review because its development targeted obesity, not because it merits treatment priority. Its positive animal findings did not translate into established human efficacy. FDA's review describes a large randomized obesity study that found no significant weight-loss difference from placebo. The review also notes limited published methodological detail. [FDA December 2024 clinical evidence review, slides 103 to 105](https://www.fda.gov/media/183891/download).

HGH Fragment 176-191 is a related comparison topic. AOD-9604 is a modified C-terminal analogue; findings cannot automatically transfer to the native fragment. The reviewed evidence does not establish additive benefit from their combination. Early native-fragment experiments also challenge blanket claims of glucose neutrality.

CJC-1295 and ipamorelin enter the review as GH-axis compounds. Their documented hormonal effects do not establish fat loss, muscle preservation or improved sleep. Optional review does not mean automatic addition after a plateau. Resistance training and adequate recovery remain relevant throughout. No reviewed study validates the four-compound combination, its order or a 12-week escalation schedule.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
AOD-9604	Core evidence topic. Grade C for positive fat-loss rationale from animals; the human development record does not establish effective obesity treatment. Lipolysis is a mechanism, not proof of sustained fat loss.	PMID 11146367 reported 500 mcg/kg orally once daily for 19 days in obese Zucker rats. This animal exposure is not a human dose and must not be scaled directly by body weight. PMID 11146367 supplies the animal dose and metabolic findings. Reduced weight gain in rats must not be presented as an equivalent percentage of human weight loss.	Oral in the cited rat experiment. This does not validate subcutaneous administration. · Once daily in PMID 11146367; no validated human recomposition frequency is established by that animal study.	The cited study does not establish superior outcomes from timing exposure before training, during fasting or before sleep. It does not support meal restriction around exposure.	Evidence review during weeks 1 to 12; no active human treatment weeks assigned. The cited animal exposure lasted 19 days.	No validated human recomposition titration steps. Neither absent weight loss nor apparent tolerance establishes a reason to escalate.
HGH Fragment 176-191	Core comparison topic. Grade C for animal metabolic observations, with no verified human recomposition efficacy in the reviewed records. Native hGH 176-191 and modified AOD-9604 are distinct evidence categories.	No verified human dose with route and frequency was identified in the reviewed records. PMID 645904 reports single experimental rat exposures in molar units. Its abstract does not specify the peptide administration route sufficiently to document a complete regimen here. PMID 645904 examined native C-terminal fragments in rats, including hGH 176-191. It reported glucose elevation and reduced insulin sensitivity. It does not support human dosing or claims of glucose neutrality.	No clinically validated route for human fat loss was established by the reviewed evidence. · No validated repeated human schedule. A single animal exposure cannot establish daily human use.	The reviewed evidence does not establish a human fasting, pretraining, post-training or bedtime advantage.	Comparison and risk review during weeks 1 to 12; no active treatment weeks assigned.	No validated starting dose, increments or ceiling for human recomposition. A numerical schedule would exceed the verified evidence.
CJC-1295	Optional GH-axis evidence review. Grade B for small, short human pharmacodynamic trials; insufficient evidence for recomposition. The studied long-acting compound contains the albumin-binding modification commonly called DAC.	PMID 16352683 included 30 or 60 mcg/kg subcutaneously as a single administration in separate dose-ranging cohorts. These are examples of studied exposures, not a proposed weekly prescription. The publication also reports separate repeated-dose cohorts. PMID 16352683 documents GH and IGF-I increases, a 5.8 to 8.1 day estimated half-life and cumulative effects. Biochemical activity does not establish clinical recomposition benefit or long-term tolerability.	Subcutaneous in the cited human trials. Results cannot be transferred to formulations described as CJC-1295 without DAC. · PMID 16352683 included one-time administration and separate cohorts receiving two or three doses at weekly or every-two-week intervals.	The reviewed trials do not establish an advantage relative to meals, training or bedtime. Sustained exposure limits conclusions based on a brief administration window.	No active weeks assigned. The published studies lasted 28 and 49 days, not a validated 12-week fat-loss course.	Investigators used ascending-dose study designs. These do not establish an individual escalation algorithm based on sleep, soreness or scale weight.

Compound	Role	Reported Dose	Route - Frequency	Timing	Weeks	Titration
Ipamorelin	Optional secretagogue evidence review. Grade B for limited human pharmacology and a short surgical trial; insufficient evidence for fat loss, muscle retention or improved sleep.	PMID 25331030 reported 0.03 mg/kg by intravenous infusion twice daily from postoperative day 1 through day 7 or hospital discharge. This inpatient regimen does not validate outpatient subcutaneous use. PMID 25331030 supplies the dose and found no significant difference in its key or secondary efficacy analyses. PMID 10496658 documents acute GH stimulation in healthy volunteers, not long-term fat loss.	Intravenous infusion in the cited surgical trial. · Twice daily during short postoperative treatment in PMID 25331030, not a validated 12-week schedule.	The study schedule related to postoperative care. The reviewed evidence does not establish a timing advantage relative to resistance training, food restriction or sleep.	No active weeks assigned. The cited treatment lasted up to seven postoperative days.	The cited regimen does not establish a recomposition titration strategy. No evidence-based escalation follows from a plateau or subjective recovery change.

WEEK BY WEEK

Week	Actions	Watch
1 to 2	Establish baseline measurements and review illness, injury, medicines and prior peptide exposure. Keep training and food intake consistent enough to interpret trends.	Unexplained fatigue, fever, worsening pain, abnormal blood pressure or glucose, and large day-to-day weight changes.
3 to 4	Review sleep regularity and inadequate recovery. Assess whether a sustainable dietary energy deficit, adequate protein and resistance training fit the individual's health and recovery.	Excessive hunger, deteriorating performance, persistent sleepiness, dizziness and menstrual disruption.
5 to 6	Compare weekly mean weight and standardized waist readings. Review AOD-9604 and fragment evidence with a clinician if considering research participation.	A plateau accompanied by inconsistent intake, reduced activity or fluid retention. It does not establish peptide failure or justify escalation.
7 to 8	Review training recovery and cardiometabolic measurements. Any discussion of GH-axis research should account for unresolved sleep or endocrine concerns.	Edema, tingling, headaches, rising glucose, worsening snoring or breathlessness.
9 to 10	Maintain consistent measurement conditions. Adjust one nutrition or activity variable at a time if progress and recovery justify it.	Rapid weight loss with falling strength, persistent exhaustion or increasing preoccupation with food.
11 to 12	Repeat baseline comparisons, document adverse events and prepare maintenance intake. Any actual research exposure follows the study's approved discontinuation and follow-up plan.	Persistent symptoms, unresolved laboratory abnormalities and water shifts that could distort the final body-composition estimate.

PRE-CHECKS

- Collect seven mornings of body weight, waist at a consistent anatomical landmark, seated blood pressure and resting heart rate. Record measurement conditions.
- Document habitual intake, training frequency, representative lift performance, daily steps, sleep duration and snoring or witnessed breathing pauses.
- Discuss fasting glucose or HbA1c and a lipid profile. Renal function, electrolytes and liver enzymes depend on history, medicines and clinical assessment.
- If GH-axis research participation is under consideration, discuss baseline age-adjusted IGF-I and pituitary history. A random GH measurement is generally uninformative because secretion is pulsatile.
- Review diabetes, edema, cardiovascular disease, cancer history, headaches, visual symptoms, pregnancy potential, eating disorders, medications and previous adverse reactions.

STOP RULES

- If exposure occurs, stop it and seek emergency care for breathing difficulty, facial or tongue swelling, chest pain, fainting or new focal neurological symptoms.
- Stop and obtain urgent assessment for severe headache with visual changes, rapidly increasing edema or new breathlessness.
- Repeated fasting glucose at or above 126 mg/dL, or random glucose at or above 200 mg/dL with thirst or frequent urination, requires prompt clinical assessment. Home readings warrant evaluation but do not independently confirm a diagnosis.
- Systolic pressure above 180 mmHg or diastolic pressure above 120 mmHg warrants repeat measurement after at least one minute and immediate medical contact if persistent. Accompanying chest pain, breathlessness or neurological symptoms require emergency care without waiting for reassessment. These adult thresholds do not cover pregnancy-specific emergencies. [American Heart Association blood-pressure emergency guidance](https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings/when-to-call-911-for-high-blood-pressure).
- Stop and contact a clinician for spreading redness, warmth, drainage or fever following any administered product. Persistent tingling, worsening apnea symptoms or unexplained masses also warrant assessment.

EXPECTED TIMELINE

Early weight movement commonly reflects water, glycogen and digestive contents. Several weeks of consistent measurements are more informative than isolated readings. By week 12, assess waist, weight trend, strength and adverse events together. The reviewed evidence supplies no credible timeline for visible peptide-specific fat loss from this combination.

COMMON MISTAKES

- Treating AOD-9604 and native hGH 176-191 as identical or assuming their combination adds benefit.
- Converting an animal dose directly into a human dose.
- Using increased GH or IGF-I as proof of fat loss or muscle gain.
- Confusing long-acting CJC-1295 with formulations described as without DAC.
- Interpreting fluid-related lean-mass changes as new muscle.
- Assigning an evidence grade to a compound without specifying the outcome being graded.

MONITORING

- Weekly: compare seven-day mean weight, standardized waist, average steps, dietary adherence and resistance-training performance.
- Weekly: summarize blood pressure, resting heart rate, sleep duration, sleep quality, hunger, fatigue, swelling and sensory symptoms.
- Document every actual exposure and concurrent medication change. Record events as associations unless causation has been assessed.
- Repeat glucose and other indicated laboratory tests according to baseline risk and clinician judgment; HbA1c is not a weekly response marker.

EXIT PLAN

At week 12, consolidate sustainable nutrition and training habits and reassess the original goals. The reviewed evidence establishes no taper, cycling schedule or universal washout for this combination. PMID 16352683 documents CJC-1295-related hormonal effects persisting for weeks, so clinical follow-up may extend beyond the final exposure. Any actual study participation follows its specified discontinuation and follow-up plan. Persistent symptoms or abnormal tests take priority over an arbitrary restart date.

TRACKER FIELDS

Mean morning weight kg · Waist cm · Mean seated systolic bp mmHg · Mean seated diastolic bp mmHg · Mean resting heart rate bpm · Mean daily steps · Mean daily energy intake kcal · Mean daily protein g · Resistance sessions completed · Reference lift load and repetitions · Mean sleep hours · Sleep quality 0 to 10 · Hunger 0 to 10 · Fatigue 0 to 10 · Edema headache tingling or other symptoms · Actual compound formulation dose route frequency and dates if applicable · Medication changes · Laboratory test name date value units and reference range · Clinician review and next action

REFERENCES

1. Ng FM et al. Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone.. *Hormone research*, 2000. PMID 11146367 DOI 10.1159/000053183 (Grade C. Oral AOD9604 exposure and reduced weight gain in obese rats; no human treatment schedule or established human fat-loss efficacy.)

2. Ng FM et al. Hyperglycemic action of synthetic C-terminal fragments of human growth hormone.. *The American journal of physiology*, 1978. PMID 645904 DOI 10.1152/ajpendo.1978.234.5.E521 (Grade C. Native fragments including hGH 176-191 affected glucose and insulin sensitivity in rats; the abstract does not specify peptide administration route.)

3. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Grade B for small, short human pharmacodynamic trials. Documents subcutaneous exposure, persistent GH and IGF-I effects and accumulation; no recomposition efficacy endpoint.)

4. Gobburu JV et al. Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers.. *Pharmaceutical research*, 1999. PMID 10496658 DOI 10.1023/a:1018955126402 (Grade B for acute human pharmacology. Documents GH stimulation, not sustained fat loss, muscle retention or improved sleep.)

5. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Grade B for a short clinical trial. Documents intravenous dosing in surgical patients and no significant key or secondary efficacy differences; no recomposition evidence.)

Metabolic and Mitochondrial Reset

INTERMEDIATE · 8 WEEKS · CORE: MOTS-C, SS-31 · SUPPORT: NAD+

An eight-week framework for evaluating mitochondrial and metabolic claims, establishing a reproducible baseline, and reviewing measurable outcomes. Reset is an organizational title, not a demonstrated biological effect. No cited study validates this combination, sequence, or duration for extending human lifespan.

WHO IT IS FOR

Adults who train consistently and want to understand MOTS-c, SS-31, and optional NAD+ evidence before discussing eligibility with a clinician. The schedule organizes assessment and follow-up. Reported experimental and prescription doses describe source material and do not establish a personal administration plan.

WHO SHOULD NOT RUN IT

People seeking a proven anti-aging drug cycle, treatment for unexplained fatigue without evaluation, or a substitute for diabetes care. Pregnancy, breastfeeding, active infection, unstable cardiovascular disease, and significant kidney or liver disease require separate medical assessment. Serious hypersensitivity to elamipretide or its excipients is a labeled contraindication. MOTS-c is prohibited at all times under section S4.4.1 of the WADA 2026 Prohibited List. WADA section M2.2 also restricts intravenous infusions and injections independently of the substance. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Anyone with an active or recent malignancy, or a strong family history of hormone-sensitive cancer, should not run the growth hormone axis components (GHRH analogs, GHRPs, IGF-1 variants): these pathways stimulate cell growth, and the trials that exist excluded such participants.

THE LOGIC

The assessment starts with potential illness, inadequate recovery, sleep disruption, and medication effects before interpreting metabolic or functional measurements. This is an editorial assessment sequence, not a validated biological hierarchy or order for administering compounds. Infection, inflammatory disease, insufficient food intake, or medication effects can explain fatigue and distort an apparent response. Persistent symptoms warrant diagnosis before attribution to mitochondrial dysfunction.

SS-31, also called elamipretide, comes first in the evidence review because it targets cardiolipin-associated mitochondrial membrane function and has human intervention data. Its FDA accelerated approval concerns muscle strength in Barth syndrome in patients weighing at least 30 kg. Approval rests on an intermediate endpoint and may require confirmatory evidence of clinical benefit. It does not establish general longevity efficacy. Source: FORZINITY prescribing information, September 2025.

In MMPOWER-3, treatment did not improve the primary walking-distance or fatigue outcomes in primary mitochondrial myopathy, PMID 37268435. Disease-specific approval therefore cannot establish benefit in healthy trainees. A regular sleep window, adequate food intake, and stable training reduce major confounders. None of the cited studies establishes this sequence as treatment for insomnia or impaired recovery.

MOTS-c is reviewed next because its experimental actions involve metabolic signaling, including AMPK activation. Mouse treatment findings and human exercise-associated changes in endogenous MOTS-c represent different evidence categories. Neither establishes that administering MOTS-c improves human healthspan.

NAD+ is optional because it is a metabolic cofactor, not a peptide. Its small intravenous pilot measured circulating and urinary metabolites over a short observation period. It did not establish durable mitochondrial restoration. No cited evidence shows that adding NAD+ improves either other compound. Additional tissue-repair or anabolic exposures would further weaken attribution.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
SS-31	Core energy-related evidence review. Grade A reflects approved-drug status for a specific disease under this product's scale. Accelerated approval does not establish longevity efficacy. MMPOWER-3 supplies human randomized evidence with negative primary efficacy results. Healthy-adult longevity benefit remains unestablished.	MMPOWER-3 reported elamipretide 40 mg subcutaneously once daily for 24 weeks in adults with primary mitochondrial myopathy, PMID 37268435. This trial exposure does not establish an eight-week longevity dose. PMID 37268435 supplies the trial dose, route, frequency, duration, and outcomes. The FORZINITY label supplies indication-specific administration and contraindication information. Neither source tests this combination.	Subcutaneous in PMID 37268435 and the approved formulation. · Once daily in PMID 37268435.	The FDA label specifies the same time each day. Neither cited source establishes optimal timing relative to training, meals, or sleep. Source: [FORZINITY prescribing information, September 2025] (https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215244s000lbl.pdf).	Evidence review during weeks 2 and 3. No automatic treatment weeks are assigned. Any prescribed exposure follows its clinical indication and prescriber.	No validated longevity titration exists. The trial used a fixed regimen. The FDA label requires dose reduction in adults with severe renal impairment. Dialysis dosing is not established.

Compound	Role	Reported Dose	Route · Frequency	Timing	Weeks	Titration
MOTS-c	Core metabolic-signaling evidence review. Grade C for treatment claims based on mouse experiments. Human exercise-associated endogenous changes do not establish efficacy or safety of administered MOTS-c.	Lee and colleagues reported MOTS-c 0.5 mg/kg intraperitoneally once daily for eight weeks in a mouse high-fat-diet experiment, PMID 25738459. This animal exposure does not establish a human dose. PMID 25738459 supports the mouse exposure and metabolic findings. PMID 33473109 separates mouse treatment outcomes from human endogenous exercise responses. Neither study supplies a validated human administration regimen.	Intraperitoneal in the cited mouse experiment. It does not validate a human subcutaneous regimen. · Once daily in the cited eight-week mouse experiment, PMID 25738459.	No validated human timing relative to training, food, or sleep is established by these references. Exercise-induced endogenous changes do not establish a preworkout administration window.	Evidence review during weeks 4 and 5. No human active-treatment weeks are established by these sources.	No supported human starting dose, escalation steps, or maintenance schedule can be derived from the cited animal studies.

NAD+	Optional cofactor-related evidence review. Grade B for a small randomized human infusion and metabolite pilot. Grade C for longevity claims because the available human observations cannot support that outcome.	Grant and colleagues reported 750 mg NAD+ intravenously over six hours as a single study infusion, PMID 31572171. This metabolite experiment did not validate a recurring longevity regimen. PMID 31572171 randomized eight participants to NAD+ and three to saline control, with short observation of metabolites. It did not test this combination, exercise adaptation, or lifespan.	Intravenous in PMID 31572171. These findings do not establish equivalent oral, intramuscular, or subcutaneous effects. · One study infusion in PMID 31572171, without an established weekly maintenance frequency.	The study collected baseline samples after an overnight fast, PMID 31572171. That experimental control does not establish a fasting requirement for benefit. Optimal timing relative to training and sleep remains unknown.	Optional evidence review in week 6. No routine infusion weeks are assigned.	No validated eight-week escalation, loading phase, or maintenance schedule was established. Infusion tolerability and clinical decisions require the supervising clinician.

WEEK BY WEEK

Week	Actions	Watch
1	Collect baseline measurements across several ordinary days. Record training, meals, caffeine, alcohol, and sleep. Identify one primary outcome, such as fatigue during a repeatable activity.	Acute illness, persistent unexplained fatigue, snoring with daytime sleepiness, or declining exercise tolerance.
2	Review medical history, baseline results, and reversible causes with a clinician where indicated. Examine SS-31 evidence and distinguish its accelerated approval from longevity claims.	Abnormal glucose, kidney results, blood pressure, or symptoms requiring diagnostic follow-up.
3	Repeat the same submaximal walking or cycling task under similar conditions. Maintain a consistent sleep window and training load. Document any independently prescribed treatment.	Changes in exertion, heart rate, recovery, sleep, and any treatment-associated symptoms.
4	Review MOTS-c animal findings alongside human endogenous exercise data. Compare weekly averages with baseline. Record dietary or training changes that could explain differences.	Overinterpretation of a single workout, glucose reading, or wearable recovery score.
5	Repeat waist, weight averages, and the standardized activity. Check whether perceived improvement appears across multiple observations and whether function improves without increased fatigue.	Persistent resting-heart-rate elevation, insomnia, reduced exercise tolerance, or symptomatic glucose changes.
6	Review optional NAD+ evidence and its limited outcomes. Record the decision and rationale. The schedule assigns an evidence review without establishing an infusion indication.	Confusing altered plasma metabolites or a transient sensation with durable clinical benefit.
7	Keep measurement conditions stable. Prepare a record of symptoms, functional outcomes, exposures, adverse events, and unresolved questions for the final review.	Escalating training, changing several supplements, or restricting calories enough to obscure interpretation.
8	Repeat baseline measurements and clinically indicated laboratory tests. Review the primary outcome, adverse events, and next steps. End the assessment without automatic cycling.	Unresolved abnormalities, worsening function, or pressure to continue despite no measurable benefit.

PRE-CHECKS

- Measure seated blood pressure and resting heart rate on several days after quiet rest, using consistent equipment and conditions.
- Record morning body-weight averages, waist circumference, usual training volume, and a reproducible submaximal functional task.
- Log sleep duration, awakenings, sleep quality, daytime sleepiness, fatigue, and exercise recovery for one week.

MONITORING

- Compare weekly blood-pressure and resting-heart-rate averages with baseline, noting illness, caffeine, heat, and hydration.
- Track average weight, waist, sleep duration, fatigue, and recovery using the same methods each week.
- Repeat the same submaximal task and record duration or distance, heart rate, and perceived exertion.

- Discuss fasting glucose or HbA1c and a lipid panel according to metabolic risk and routine screening needs.
- If pharmacologic exposure is being considered clinically, review creatinine/eGFR, electrolytes, and liver chemistry. CBC, thyroid testing, or iron studies depend on symptoms and history.
- Review diabetes treatment, hypoglycemia, kidney disease, cardiovascular symptoms, allergies, pregnancy status, medications, and supplements. Document previous serious hypersensitivity to elamipretide or formulation ingredients. Baseline testing does not establish safety.
- Personal and family history of cancer, including hormone-sensitive and thyroid cancers, reviewed with a clinician before any growth hormone axis component.
- Monitor glucose at a clinician-agreed frequency when diabetes, glucose-lowering medication, or symptoms make it relevant.
- Record all exposures and adverse events, including administration-site reactions and possible hypersensitivity. Repeat laboratory tests for clinical indications rather than assuming weekly testing is necessary.

STOP RULES

- Stop an ongoing administration and seek emergency care for breathing difficulty, facial or throat swelling, widespread hives with dizziness, collapse, or severe chest pain.
- New fainting, persistent palpitations, or disproportionate breathlessness requires prompt clinical assessment before further exposure or strenuous exercise.
- Glucose below 70 mg/dL requires prompt attention under the person's hypoglycemia plan, even without symptoms. Confusion, seizure, or inability to swallow is an emergency.
- Systolic pressure at or above 180 mmHg or diastolic pressure at or above 120 mmHg warrants urgent assessment. Associated chest pain, neurological symptoms, or severe breathlessness requires emergency care. Without symptoms, a repeated reading after quiet rest helps confirm persistence. Source: [American Heart Association blood-pressure guidance](https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings).
- Fever with expanding administration-site redness, persistent vomiting, jaundice, dark urine, or markedly reduced urine output requires prompt assessment before further exposure.

EXPECTED TIMELINE

Weeks 1 and 2 establish measurement consistency and identify confounders. Weeks 3 through 6 may reveal changes associated with sleep, training, diet, illness, or clinical treatment. These observations cannot establish causality. Week 8 supports reassessment of function and tolerability. It cannot demonstrate lifespan extension, biological-age reversal, or a mitochondrial reset.

EXIT PLAN

End the assessment at week 8 and review changes against the original primary outcome. No validated combined washout interval exists for these compounds. A pharmacokinetic half-life does not establish complete biological recovery. If exposure occurred, the treating clinician or study protocol determines discontinuation and follow-up. Prescribed disease treatment should not stop merely because this educational calendar ends. Continue ordinary measurements for another two to four weeks as an observation period, not a proven washout. When clinically indicated, HbA1c reassessment around three months may better capture sustained glucose change.

COMMON MISTAKES

- Treating an eight-week mouse experiment as a human treatment schedule.
- Equating endogenous MOTS-c responses to exercise with benefits from administered peptide.
- Interpreting accelerated disease-specific approval as proof of healthy-adult longevity benefit.
- Assuming mechanistic overlap proves synergy or determines sequencing.
- Changing multiple exposures while claiming to identify a single cause.
- Calling transient energy, weight fluctuation, or an isolated laboratory change proof of rejuvenation.

TRACKER FIELDS

Blood pressure average mmHg · Resting heart rate average bpm · Morning weight average kg · Waist cm · Sleep average hours · Sleep quality 0 to 10 · Fatigue 0 to 10 · Recovery 0 to 10 · Training minutes and session count · Standardized task duration or distance · Standardized task heart rate and exertion · Glucose value unit and fasting status if indicated · Compound dose route frequency and provenance if exposed · Exposure dates and timing · Adverse event onset severity and resolution · Medication diet caffeine alcohol or illness changes · Laboratory results and dates · Clinician review and next action

REFERENCES

1. Lee C et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance.. *Cell metabolism*, 2015. PMID 25738459 DOI 10.1016/j.cmet.2015.02.009 (Grade C for mouse treatment findings; grade D for cellular mechanisms. Supports the reported animal exposure, without establishing human dosing. Source: [Primary study] (https://doi.org/10.1016/j.cmet.2015.02.009).)
2. Reynolds JC et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis.. *Nature communications*, 2021. PMID 33473109 DOI 10.1038/s41467-020-20790-0 (Grade C for administered MOTS-c performance and healthspan claims: treatment experiments involved mice. Human findings concern endogenous responses to exercise. Neither establishes human treatment efficacy.)
3. Karaa A et al. Efficacy and Safety of Elamipretide in Individuals With Primary Mitochondrial Myopathy: The MMPOWER-3 Randomized Clinical Trial.. *Neurology*, 2023. PMID 37268435 DOI 10.1212/WNL.000000000000207402 (Human randomized trial supporting the reported regimen and negative primary walking-distance and fatigue outcomes in primary mitochondrial myopathy. Does not establish healthy-adult longevity efficacy.)
4. Grant R et al. A Pilot Study Investigating Changes in the Human Plasma and Urine NAD+ Metabolome During a 6 Hour Intravenous Infusion of NAD.. *Frontiers in aging neuroscience*, 2019. PMID 31572171 DOI 10.3389/fnagi.2019.00257 (Grade B for short-term human infusion and metabolite observations in a small randomized pilot. Supports the reported single exposure, without demonstrating longevity or combined-treatment benefit.)

Deep Sleep and Nightly Recovery

BEGINNER · 6 WEEKS · CORE: DSIP, EPITALON · SUPPORT: CJC-1295, IPAMORELIN

A six-week framework for measuring sleep, addressing recovery barriers, and evaluating evidence for DSIP, Epitalon, CJC-1295, and ipamorelin. The cited studies do not establish this combination as an effective sleep protocol. Reported doses describe research exposures, not a personal treatment schedule. The six-week duration belongs to the assessment framework, not a validated peptide regimen.

WHO IT IS FOR

Adults who train regularly, experience inconsistent sleep or morning recovery, and want to distinguish documented findings from speculative peptide claims. Beginner describes the educational level. The practical foundation is a sleep diary, consistent routines, and assessment of persistent symptoms.

WHO SHOULD NOT RUN IT

Not suitable as a self-directed peptide cycle, treatment for suspected sleep apnea, or substitute for evaluating persistent insomnia. Pregnancy, breastfeeding, active cancer, pituitary disease, uncontrolled diabetes, and unexplained daytime sleepiness are reasons for medical assessment rather than experimental exposure. These studies do not establish comprehensive contraindications or safety in those populations.

THE LOGIC

The assessment begins with sleep opportunity, symptoms, and potentially reversible disruptions. Pain, illness, breathing problems, under-fueling, excessive training, stimulant exposure, and metabolic disorders can be evaluated together. There is no validated hierarchy requiring inflammation or immunity treatment before sleep assessment. Breathing pauses, dangerous sleepiness, and other concerning symptoms warrant assessment immediately, regardless of the week shown below.

DSIP comes first in the evidence discussion because it has direct human insomnia studies. Their small samples and inconsistent findings do not establish dependable benefit. PMID 3622582 reported improvements in sleep and daytime function, whereas PMID 1299794 found weak effects and little expected therapeutic benefit. Epitalon follows as a circadian hypothesis: altered melatonin secretion in older monkeys does not establish better human sleep. Epitalon and the pineal extract epithalamin are different preparations, and their evidence cannot be exchanged.

CJC-1295 and ipamorelin appear last as background on growth hormone stimulation, which is not an established insomnia treatment. Higher GH or IGF-1 does not demonstrate deeper sleep or improved recovery. The cited studies establish neither a therapeutic combination nor a sequence or six-week escalation for these compounds. Accordingly, the weekly schedule covers assessment, evidence review, and access to established sleep care. It assigns no experimental drug exposure.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
DSIP	Direct sleep evidence review. Grade B describes the small human studies; Grade C applies to a dependable therapeutic sleep claim because findings are weak and inconsistent.	PMID 1299794 reports DSIP 25 nmol/kg intravenously once each afternoon on three consecutive days. The original molar dose is retained without an independently sourced mass conversion. This research exposure does not establish an effective personal sleep dose. Bes F, 1992, PMID 1299794: 16 patients, weak objective improvements, unchanged subjective sleep quality, and limited expected therapeutic benefit. Schneider-Helmert D, 1987, PMID 3622582: positive findings in 14 patients. These small studies do not establish consistent clinical benefit.	Intravenous in PMID 1299794. These findings do not validate subcutaneous or intranasal substitution. · Once daily for three consecutive study days, PMID 1299794.	Afternoon before the assessed nights, PMID 1299794. The study does not establish a training interval, fasting requirement, or optimal bedtime interval.	No active weeks assigned. The cited exposure lasted three days, not six weeks.	No validated sleep titration is established by the cited studies. The fixed-dose trial does not support escalation for persistent symptoms.
Epitalon	Circadian evidence review. Grade C: animal findings support a biological hypothesis, not established human insomnia treatment. The cited study contains no human sleep outcomes.	PMID 14743609 reports Epitalon 10 mcg per animal intramuscularly once daily for 7 to 10 consecutive days in monkeys. This animal research exposure does not establish a human sleep dose. Goncharova ND, 2003, PMID 14743609: nighttime melatonin increased in older monkeys. Melatonin levels did not change in young monkeys. Neither finding demonstrates improved human sleep.	Intramuscular in the monkey study, PMID 14743609. · Once daily for 7 to 10 consecutive days, PMID 14743609.	The abstract does not establish administration timing relative to food, activity, or sleep. Nighttime hormone sampling is not evidence for bedtime administration.	No active human weeks assigned. The cited animal study does not establish a six-week human sleep regimen.	No validated human sleep titration is established by this study. Animal exposure does not establish a starting dose or escalation sequence.
CJC-1295	Background evidence review only. Grade B for short human endocrine trials; Grade D for proposed sleep benefits based on mechanistic extrapolation.	PMID 16352683 reports CJC-1295 doses including 30 or 60 mcg/kg subcutaneously in single-dose research cohorts. These are endocrine research exposures, not established sleep doses. Teichman SL, 2006, PMID 16352683: sustained GH and IGF-I increases and an estimated half-life of 5.8 to 8.1 days. These short endocrine trials did not establish insomnia efficacy or long-term combination safety.	Subcutaneous long-acting CJC-1295 in PMID 16352683, the preparation associated with the drug affinity complex, or DAC. · Single administration in the cited single-dose cohorts. Separate cohorts received repeated weekly or biweekly administrations, PMID 16352683.	No validated sleep, meal, or training interval is established. Findings cannot be transferred to preparations described as CJC-1295 without DAC.	No active weeks assigned. Inclusion in the evidence review does not establish a reason for exposure when sleep remains poor.	No sleep titration was established. Ascending research cohorts are not an individual escalation plan.

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
Ipamorelin	Background evidence review only. Grade B for short human clinical investigation; Grade D for proposed sleep benefits. The cited trial assessed postoperative gastrointestinal recovery.	PMID 25331030 reports ipamorelin 0.03 mg/kg by intravenous infusion twice daily after bowel surgery, from postoperative day 1 through day 7 or hospital discharge. This was not a sleep trial. Beck DE, 2014, PMID 25331030: randomized proof-of-concept study with no significant difference in the key or secondary efficacy analyses. It cannot establish sleep efficacy or outpatient combination safety.	Intravenous infusion in hospitalized surgical patients, PMID 25331030. · Twice daily for up to seven postoperative days or hospital discharge, PMID 25331030.	Administration followed postoperative care. The study does not validate bedtime use, fasting intervals, or timing around resistance training.	No active weeks assigned. The postoperative study does not support a six-week sleep course.	No validated sleep titration or escalation with CJC-1295 was established by this study.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1	Record seven nights before changing multiple variables. Establish usual sleep opportunity, work schedule, training load, caffeine timing, alcohol exposure, and pain patterns. Complete baseline measurements. Concerning symptoms warrant assessment without waiting for the diary to finish.	Snoring, witnessed breathing pauses, morning headaches, restless legs, and unintended daytime sleep episodes.
2	Address identified pain or illness with appropriate care. Establish consistent wake timing and review daylight exposure relative to the work schedule. Assess food intake and excessive training fatigue.	Whether sleep improves as underlying disruptions resolve. Record changes rather than attributing improvement to a peptide hypothesis.
3	Review the diary and DSIP evidence. Adjust one modifiable factor, such as late caffeine or disruptive training timing. Discuss cognitive behavioral therapy for insomnia when symptoms persist.	Sleep latency, time awake during the night, daytime function, and anxiety caused by monitoring sleep.
4	Review Epitalon's animal evidence and maintain consistent light and sleep timing appropriate to the work schedule. Persistent breathing or circadian symptoms warrant clinical evaluation.	Schedule drift, increasing time in bed without additional sleep, and misleading wearable sleep-stage changes.
5	Review metabolic history and any clinically indicated results. Assess CJC-1295 and ipamorelin as unproven sleep interventions. No addition or combination is assigned.	If exposure already exists, report swelling, tingling, glucose changes, headaches, and worsening snoring to the treating clinician.
6	Compare weekly averages with baseline. Document sustainable changes and arrange follow-up for unresolved insomnia. Close the assessment without an automatic peptide cycle extension.	Meaningful daytime improvement, persistent impairment, and adverse symptoms requiring continued evaluation.

PRE-CHECKS

- Record available blood-pressure measurements, morning resting heart rate, body weight, and recent weight change when relevant to the clinical assessment. These measurements do not validate experimental exposure.
- Collect a seven-day sleep diary and baseline Insomnia Severity Index. Record sleep opportunity, shift work, naps, snoring, witnessed apnea, and daytime sleepiness.
- Review medications, supplements, caffeine, alcohol, nicotine, sedatives, psychiatric history, restless legs, pain, endocrine disease, and previous peptide exposure.
- Fasting glucose or HbA1c may be relevant with metabolic risk or existing GH-axis exposure. Clinician-directed IGF-1 belongs to endocrine assessment, not routine insomnia screening. CBC, ferritin, TSH, kidney or liver tests should follow symptoms and history.
- CJC-1295 and ipamorelin are prohibited at all times under WADA 2026 section S2.2.4. S0 covers pharmacological substances without governmental approval for human therapeutic use that are not addressed by subsequent sections. Absence of a compound's name is not clearance. Source: [WADA 2026 Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).
- Personal and family history of cancer, including hormone-sensitive and thyroid cancers, reviewed with a clinician before any growth hormone axis component.

STOP RULES

- If experimental exposure is occurring, stop further exposure and seek emergency care for breathing difficulty, facial swelling, chest pain, fainting, or severe headache with visual changes.
- Pause exposure and contact a clinician promptly for new edema, persistent numbness, palpitations, marked blood-pressure change, excessive thirst or urination, or reproducible glucose deterioration.
- Seek prompt assessment for new witnessed apnea, worsening daytime sleepiness, or dangerous drowsiness while driving. Do not drive while sleepy.
- Spreading redness, heat, severe local pain, or fever after parenteral exposure requires urgent assessment.
- Persistent or worsening insomnia should trigger diagnostic reassessment, not escalation or addition of another compound.

EXPECTED TIMELINE

The first two weeks establish baseline patterns and identify practical changes. Some people notice improvement during this period, but the timing and magnitude vary. Assess sustained daytime function across weeks 3 to 6. The cited evidence provides no reliable timeline for peptide-related deeper sleep, circadian restoration, or faster muscular recovery.

COMMON MISTAKES

- Treating the compound name DSIP as proof of deep-sleep enhancement.

MONITORING

- Calculate weekly average sleep latency, wake time after sleep onset, total sleep time, and sleep efficiency. Sleep efficiency equals estimated sleep time divided by time in bed, multiplied by 100.
- Track daytime sleepiness, perceived recovery, training performance, pain, and adverse symptoms. Repeat the Insomnia Severity Index at midpoint and completion.
- Review clinically relevant blood pressure, resting heart rate, and weight trends. Additional glucose or IGF-1 monitoring depends on actual exposure and clinical findings. Normal results do not establish safety.
- Use wearables for consistent trends, with the same device and settings where possible. Their estimated deep-sleep minutes cannot confirm a peptide effect.

EXIT PLAN

End the six-week assessment by retaining useful routines and reviewing unresolved symptoms. No peptide discontinuation procedure is needed if none was used. For existing exposure, a clinician should direct discontinuation and reassessment. The cited studies do not establish a taper or universal follow-up interval for this combination. Long-acting CJC-1295 can complicate interpretation beyond the final administration because endocrine effects persist, PMID 16352683. Continue the diary during follow-up and reassess abnormal symptoms or tests. A brief symptom-free period does not establish that adverse effects have resolved.

- Substituting epithalamin findings for Epitalon evidence or converting monkey doses into human doses.
- Confusing long-acting CJC-1295 with preparations described as without DAC.
- Changing several compounds, training load, and sleep habits simultaneously.
- Interpreting sedation, vivid dreams, elevated IGF-1, or wearable sleep stages as proof of restorative sleep.
- Using normal laboratory results to dismiss persistent symptoms or treating six weeks of assessment as a validated drug cycle.

TRACKER FIELDS

Nights logged · Mean bedtime · Mean wake time · Mean time in bed minutes · Mean sleep latency minutes · Mean wake after sleep onset minutes · Mean total sleep minutes · Mean sleep efficiency percent · Insomnia severity index when due · Daytime sleepiness 0 to 10 · Morning recovery 0 to 10 · Training sessions and load · Latest training finish time · Last caffeine time · Alcohol days · Pain 0 to 10 · Mean blood pressure mmHg if relevant · Mean resting heart rate bpm if relevant · Body weight kg if relevant · Waist cm if relevant · Glucose and IGF1 results if ordered · Actual exposures with dose unit route frequency and dates · Adverse events and actions · Weekly change and follow up decision

REFERENCES

1. Bes F et al. Effects of delta sleep-inducing peptide on sleep of chronic insomniac patients. A double-blind study.. *Neuropsychobiology*, 1992. PMID 1299794 DOI 10.1159/000118919 (Direct human DSIP exposure, intravenous route, afternoon timing, three-day duration, and weak therapeutic findings in 16 patients. Subjective sleep quality did not improve.)

2. Schneider-Helmert D et al. Effects of delta-sleep-inducing peptide on 24-hour sleep-wake behaviour in severe chronic insomnia.. *European neurology*, 1987. PMID 3622582 DOI 10.1159/000116143 (Small positive placebo-controlled, double-blind study in 14 patients. Comparison with PMID 1299794 illustrates inconsistent findings across the cited human DSIP studies.)

3. Goncharova ND et al. [Peptide correction of age-related pineal disturbances in monkeys].. *Advances in gerontology = Uspekhi gerontologii*, 2003. PMID 14743609 (Animal Epitalon exposure and increased nighttime melatonin in older monkeys, without established human sleep benefit. No DOI was present in the esummary response.)

4. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Human subcutaneous CJC-1295 research exposure, prolonged GH and IGF-I responses, and estimated half-life. The measured endocrine effects do not establish sleep efficacy.)

5. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Human intravenous ipamorelin exposure and frequency after bowel surgery. No significant difference occurred in key or secondary efficacy analyses. Sleep efficacy was not established.)

Cognitive Focus

BEGINNER · 4 WEEKS · CORE: SEMAX, SELANK

A four-week framework for understanding Semax and Selank, measuring concentration, and evaluating whether anxiety, poor sleep, or inadequate recovery explains the problem. The cited human evidence does not establish this pair as an effective four-week cognitive enhancement protocol. The doses below describe research exposures, not recommended treatment.

WHO IT IS FOR

Adults who train consistently and want to evaluate cognitive claims with objective measurements. Beginner describes the educational level, not established suitability for unsupervised peptide use. The framework also supports a clinician discussion when persistent anxiety or attention problems interfere with work, relationships, or training.

WHO SHOULD NOT RUN IT

Not an appropriate self-directed experiment during pregnancy or breastfeeding, in minors, or with unexplained cognitive decline, seizures, unstable cardiovascular disease, mania, psychosis, or severe insomnia. These are precautionary exclusions, not a verified regulatory contraindication list. Previous hypersensitivity to the compound or formulation requires clinical review. Persistent symptoms suggesting ADHD, depression, sleep apnea, thyroid disease, or anemia require assessment. Athletes subject to testing need an authoritative substance-status determination.

THE LOGIC

Begin with symptom history, functional impairment, sleep, medication effects, caffeine, energy availability, and training recovery. Acute neurological or psychiatric warning signs take priority over tracking. Investigation of inflammatory, endocrine, or other medical causes should follow symptoms and clinical findings. The cited studies do not support a mandatory immune, energy, nervous-system, metabolic, and tissue-repair hierarchy for improving focus.

Selank comes first in the evidence discussion because anxiety may compete with attention. PMID 25176261 examined patients with anxiety-related disorders. Its findings do not establish cognitive enhancement in healthy trainees. Semax comes second because the cited healthy-volunteer research primarily concerns brain-network measurements. This order is an editorial framework, not a clinically validated administration sequence.

Evidence grading follows the claim. Selank's limited anxiety-treatment evidence is grade B. Small human imaging experiments provide grade B evidence of acute physiological effects. Evidence supporting meaningful focus improvement in healthy adults remains grade C, meaning insufficient human evidence for that claim. Semax-related neurotrophin findings in rats are grade C. No cited study establishes additive benefits, an optimal sequence, or a four-week combined regimen.

Accordingly, this framework assigns four weeks to assessment and monitoring. That duration is an organizational choice, not a treatment duration validated by these studies. Existing clinician-directed treatment is recorded with its own indication and plan. A personal log can identify patterns, but cannot establish causation, exclude placebo effects, or determine long-term safety.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS
Selank	Anxiety-related attention hypothesis. PMID 25176261 compared treatments in 60 patients and reported anxiety improvement and mild nootropic effects. Grade B for the studied anxiety context. Grade C for extrapolation to meaningful focus improvement in healthy adults.	PMID 32342318 reports Selank 0.2 mg intranasally once during a single imaging session. This is a reported research exposure, not a recommended daily dose or four-week regimen. Bibliographic metadata verified through NCBI esummary for PMID 32342318. The exposure was checked against the English full-text methods. [Primary study text] (https://www.researchgate.net/publication/340081770_Functional_connectomic_approach_to_studying_Selank_and_Semax_effects).	Intranasal in PMID 32342318. Equivalence with subcutaneous administration or chemically modified derivatives is not established by this evidence. · Single administration in PMID 32342318. A repeated daily frequency for this focus framework is not established.	No validated timing relative to training, food, or sleep follows from the cited evidence. For tracking, use consistent assessment times. Record their relationship to meals, exercise, bedtime, and any prescribed exposure.	Weeks 1-4: evidence review and tracking. No evidence-based active-week assignment is available for a four-week focus course.

Compound	Role	Reported Dose	Route · Frequency	Timing	Weeks
Semax	Exploratory attention-related neurophysiology. PMID 30225715 studied 24 healthy volunteers using resting-state imaging. Grade B for the measured physiological effects. Grade C for meaningful cognitive enhancement in healthy adults. The cited neurotrophin mechanism study used rats.	PMID 32342318 reports Semax 1.2 mg intranasally once during a single imaging session. This research exposure is not a recommended starting dose, daily schedule, or titration target. Bibliographic metadata verified through NCBI esummary for PMID 32342318. The exposure was checked against the English full-text methods. [Primary study text] (https://www.researchgate.net/publication/340081770_Functional_connectomic_approach_to_studying_Selank_and_Semax_effects).	Intranasal in PMID 32342318. Findings cannot be assumed to apply to another route or formulation. · Single administration in PMID 32342318. No validated repeated frequency for four-week cognitive enhancement follows from this study.	The cited evidence establishes no training, fasting, meal, or bedtime advantage. Keep cognitive testing separate from immediate post-exercise fatigue. Use the same relationship to meals and sleep throughout tracking.	Weeks 1-4: evidence review and tracking. No trial-supported active-week assignment is provided.

Week by Week

Week	Actions	Watch
1	Establish a seven-day baseline without introducing new cognitive interventions. Record sleep, caffeine, training load, concentration, and anxiety. Practice one brief attention task before retaining scores. Define a practical outcome, such as correctly completed tasks during a fixed work period.	Large day-to-day variability, short sleep, missed meals, excessive training fatigue, or anxiety that predicts worse concentration.
2	Review anxiety and sleep, using Selank's evidence as context for a clinician discussion if symptoms are significant. Maintain consistent work-test conditions. If treatment already exists, document the actual prescription and changes. The research exposure does not supply a treatment schedule.	Distinguish feeling calmer from completing more accurate work. Record drowsiness, agitation, headaches, nasal symptoms, and sleep changes without assuming the compound caused them.
3	Review persistent attention complaints and Semax's evidence limitations. Repeat the same functional measurements. This week's placement does not establish a switch or addition. Document changes in illness, workload, medication, and training that could explain performance.	Faster responses with more mistakes, increased confidence without better output, worsening anxiety, or reduced sleep duration.
4	Compare weekly averages with baseline and review any adverse events. Close the evaluation and, where treatment exists, follow the prescriber's treatment plan. Retain the same measurements during subsequent observation rather than automatically extending the evaluation.	Whether improvement is consistent across comparable days, whether it costs sleep or accuracy, and whether symptoms persist after any prescribed exposure ends.

Pre-checks

- Record seated blood pressure and resting heart rate under consistent conditions if monitoring is clinically appropriate. Document known hypertension, arrhythmias, fainting, and cardiovascular medication.
- Record recent weight change and energy intake as general context. Unintended weight loss or aggressive calorie restriction may explain fatigue and impaired concentration. Waist circumference is optional, not a validated cognitive-response measure.
- Collect seven nights of sleep duration, bedtime, awakenings, and daytime sleepiness. Review snoring, witnessed breathing pauses, shift work, and persistent insomnia.
- Document anxiety, depression, attention symptoms, headaches, seizures, head injury, psychiatric history, allergies, nasal disease, and all medicines or supplements. Interaction data are limited. A clinician should review existing treatment and relevant risks.
- Consider fasting glucose or HbA1c when diabetes risk, symptoms, or overdue screening makes it relevant. HbA1c is not a useful weekly response marker for this framework.
- CBC, ferritin, vitamin B12, TSH, renal function, or liver testing should follow symptoms and history. Routine cortisol, BDNF, cytokine panels, and brain imaging do not validate peptide suitability or response.
- Set one primary functional outcome and its success criterion before reviewing results. Use the same device, task difficulty, testing time, and environment. These checks are general assessment measures, not a validated peptide-screening package.
- WADA status: neither name appears in the 2026 Prohibited List, but absence by name does not establish permission. S2 prohibits listed substances and substances with similar chemical structure or biological effects. S0 applies when its non-approval criteria are met. This review does not resolve either compound's individual classification. Athletes need an authoritative determination for the exact substance and formulation. [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

Stop Rules

- Stop any suspected exposure and seek emergency care for breathing difficulty, facial or tongue swelling, chest pain, fainting, seizure, or sudden severe headache. New weakness or speech disturbance also requires emergency assessment.
- Stop any suspected exposure and obtain urgent assessment for severe agitation, confusion, hallucinations, or suicidal thoughts. Markedly reduced need for sleep with unusual energy or impulsivity also warrants urgent assessment.

Monitoring

- Weekly: summarize correctly completed work, error rate, and attention-task performance. Retain raw scores so practice effects and unusually easy sessions remain visible.
- Weekly: compare concentration and anxiety ratings with sleep duration, sleep quality, daytime sleepiness, and caffeine exposure.
- Weekly: summarize resting heart rate and blood pressure if measured, using consistent conditions. Record symptoms alongside abnormal readings. These are general observations, not validated markers of peptide response.
- Weekly: review headaches, nasal irritation, nosebleeds, dizziness, agitation, drowsiness, palpitations, and medication changes. This symptom list is precautionary, not an established adverse-reaction frequency profile.
- Weekly: record training volume, perceived exertion, illness, and major changes in food intake or workload. Routine repeat laboratory testing is unnecessary without a clinical indication.

- Stop any suspected exposure and contact a clinician for persistent palpitations, repeated resting tachycardia, substantial blood-pressure changes, worsening insomnia, or impaired daytime functioning.
- Stop any suspected exposure and seek assessment for recurrent nosebleeds, persistent nasal pain, significant rash, or recurrent symptoms. Deliberate re-exposure is inappropriate when an allergic reaction is suspected.
- If work accuracy declines, anxiety worsens, or apparent focus comes at the expense of sleep, pause the evaluation and review the cause. Escalation is not justified by these findings.

EXPECTED TIMELINE

Acute imaging effects were assessed within minutes, without establishing an onset time for useful cognitive improvement. PMID 25176261 reported anxiety benefits lasting one week after treatment in patients, which does not predict a healthy person's response. Four weeks can reveal symptom trends and adverse events. An uncontrolled personal log cannot prove efficacy or establish tolerability beyond the observed period.

EXIT PLAN

End the formal evaluation after week 4. Any prescribed treatment continues or ends according to its own clinical plan. The cited studies establish no taper or washout interval for this combined focus concept. A further one to two weeks of observation can help compare symptoms with baseline if clinically appropriate. This is a tracking interval, not a proven pharmacological washout or reason to interrupt prescribed treatment. Reassess sleep, anxiety, functional accuracy, blood pressure if relevant, and adverse events. Persistent or progressive cognitive symptoms warrant evaluation rather than automatic cycling.

COMMON MISTAKES

- Treating altered brain connectivity or rat neurotrophin expression as proof of better human attention.
- Converting a single research administration into a repeated daily regimen.
- Introducing both compounds and several lifestyle changes together, then assigning improvement to one factor.
- Mistaking stimulation, calmness, or test familiarity for better real-world performance.
- Assuming normal laboratory results establish safety, or that symptom tracking excludes uncommon adverse effects.
- Treating the order of the educational discussion as a validated treatment sequence.

TRACKER FIELDS

Week number, week start date, days logged · Correct tasks per fixed session, task error rate, attention task name, attention task score · Concentration rating 0 to 10, anxiety rating 0 to 10, daytime sleepiness rating 0 to 10 · Average sleep hours, bedtime, awakenings per night, sleep quality rating 0 to 10 · Average seated systolic bp mmHg if measured, average seated diastolic bp mmHg if measured, average resting heart rate bpm if measured · Body weight kg if relevant, recent weight change, training sessions, training load notes · Caffeine amount and time, alcohol use, illness, workload changes · Compound if prescribed, actual dose with prescription provenance, route, frequency, exposure dates and times · Timing relative to meals training and sleep, adverse events, medication changes · Stop rule triggered, clinician contact, weekly interpretation, next review date

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2. Lebedeva IS et al. Effects of Semax on the Default Mode Network of the Brain.. *Bulletin of experimental biology and medicine*, 2018. PMID 30225715 DOI 10.1007/s10517-018-4234-3 (Grade B physiological evidence from 24 healthy volunteers examining acute default-mode-network changes. Does not demonstrate improved everyday focus or validate a four-week regimen.)
3. Medvedev VE et al. [A comparison of the anxiolytic effect and tolerability of selank and phenazepam in the treatment of anxiety disorders].. *Zhurnal nevrologii i psikiatrii imeni S.S. Korsakova*, 2014. PMID 25176261 (Grade B comparative clinical evidence from 60 patients with anxiety-related disorders. Reports anxiolytic and mild nootropic effects, with anxiety benefits persisting one week after treatment. Limited generalizability to healthy adults.)
4. Shadrina M et al. Comparison of the temporary dynamics of NGF and BDNF gene expression in rat hippocampus, frontal cortex, and retina under Semax action.. *Journal of molecular neuroscience : MN*, 2010. PMID 19662538 DOI 10.1007/s12031-009-9270-z (Grade C animal evidence showing region-dependent and time-dependent neurotrophin gene-expression changes. Does not validate human cognitive benefit.)

Neuro-Regeneration

ADVANCED · 8 WEEKS · CORE: CEREBROLYSIN, SEMAX · SUPPORT: DIHEXA

An eight-week framework for evaluating neurological symptoms, understanding reported research exposures, and measuring function. *Neuro-Regeneration* is the protocol title, not a demonstrated outcome. No identified human trial establishes this combination, sequence, or duration for nervous-system regeneration or cognitive enhancement in healthy adults.

WHO IT IS FOR

Adults who train and want an evidence-based discussion with a clinician about persistent cognitive concerns. The framework helps distinguish neurological rehabilitation studies from healthy-adult enhancement claims. Advanced describes the complexity of evaluating the evidence, not eligibility for stronger doses. The eight weeks organize observation and review, not drug administration.

WHO SHOULD NOT RUN IT

Self-directed treatment of stroke, concussion, dementia, unexplained cognitive decline, or psychiatric illness. Cerebrolysin prescribing information lists epilepsy, severe renal impairment, and hypersensitivity to its components as contraindications. Pregnancy, breastfeeding, other seizure history, kidney disease, and active cancer require individual clinical assessment. These agents lack established benefit for elective enhancement in these populations. Sudden neurological symptoms require emergency evaluation. [Cerebrolysin prescribing information] (https://cerebrolysin.com/wp-content/uploads/2022/06/CEREBROLYSIN_ProductMonograph_2021_SCREEN.pdf)

THE LOGIC

Assessment begins with possible causes of cognitive symptoms, including infection, inflammatory illness, medication effects, and mood disorders. This does not justify adding immune-modulating peptides. Energy availability, hydration, training fatigue, and possible anemia are relevant next considerations. Sleep assessment includes insomnia and possible sleep apnea. Glucose abnormalities and other metabolic contributors warrant evaluation when indicated. These domains overlap and may require simultaneous clinical care. Their order is an organizing principle, not a validated biological sequence or prerequisite for peptide treatment.

Cerebrolysin comes first in the evidence discussion because it has substantially more clinical investigation in neurological disease. Under this product's scale, multiple human randomized trials qualify as A for the studied disease settings. This classification is not a GRADE certainty rating or evidence of healthy-adult cognitive enhancement. CARS reported improved upper-limb motor recovery alongside rehabilitation. The Cochrane review found no established mortality benefit and a potential increase in nonfatal serious adverse events. These studies address different treatment settings and endpoints.

Semax comes next because its human evidence is more limited. Grade B describes small human studies and short-term physiological findings. The imaging study enrolled 24 volunteers, with 14 receiving Semax and 10 receiving placebo. A separate post-stroke study assessed rehabilitation, circulating BDNF, and function. Neither imaging changes nor higher circulating BDNF demonstrate regenerated neurons, improved intelligence, or durable enhancement. Evidence for healthy-adult enhancement remains C, too weak to support the claim.

Dihexa remains outside the active schedule. Its historical animal work is C at best, with an expression of concern affecting a prominent study. A central HGF/c-Met mechanism paper was subsequently retracted. No human treatment trial was identified in the targeted PubMed search. Human-cell experiments do not establish human therapeutic efficacy or dosing. No identified controlled evidence supports synergy among these compounds, and simultaneous exposure would complicate attribution of benefits and adverse effects.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
Cerebrolysin	Core evidence-review compound. A porcine brain-derived mixture of peptides and amino acids studied in neurological disease. Post-stroke recovery findings cannot be transferred directly to healthy trainees.	CARS, PMID 26564102, reported 30 mL by intravenous infusion once daily for 21 days, beginning 24 to 72 hours after stroke onset. Participants also received rehabilitation. This is a disease-specific research exposure, not a recommended nootropic dose. Dose, route, frequency, and duration were checked in the full CARS report, PMID 26564102. PMID 37818733 informs the broader acute-stroke benefit and harm assessment. [CARS trial](https://pmc.ncbi.nlm.nih.gov/articles/PMC4689177/)	Intravenous infusion in CARS, PMID 26564102. This research involved clinical administration. · Once daily by intravenous infusion in CARS, PMID 26564102. No validated healthy-adult maintenance frequency.	CARS anchored treatment to stroke onset. It did not establish workout, meal, bedtime, or fasted-training timing for cognitive enhancement.	CARS, PMID 26564102, used 21 consecutive treatment days. No active enhancement weeks are assigned here; any prescribed course follows its clinical indication.	CARS used a fixed regimen. No evidence-based escalation, loading phase, or symptom-driven titration exists for this eight-week enhancement framework.
Semax	Core evidence-review compound with limited human neurological and imaging data. Short-term network effects are not equivalent to established cognitive enhancement.	PMID 30225715 studied a single intranasal administration. The FDA Semax review reports that study's exposure as 1.2 mg intranasally once. This is a reported research exposure, not an approved FDA dosing label or a repeated eight-week regimen. PMID 30225715 establishes the study identity and intranasal imaging design. FDA's review supplies the numerical exposure and states that adverse events were not discussed for this study. [FDA Semax review] (https://www.fda.gov/media/193348/download)	Intranasal in the cited imaging study. Findings do not establish equivalence for injectable or chemically modified versions. · One intranasal administration in the imaging experiment, PMID 30225715. A daily enhancement schedule cannot be inferred.	Imaging occurred before and shortly after administration. Training, food, and sleep timing were not validated as determinants of benefit.	No active enhancement weeks assigned. The cited single-exposure experiment cannot support continuous use or a Cerebrolysin-to-Semax transition.	No validated titration steps for this goal. Lack of a noticeable effect is not evidence supporting escalation.
Dihexa	Evidence appraisal only. No established human therapeutic role or demonstrated human regeneration benefit. The retrieved evidence does not justify optional therapeutic support.	No validated human dose, route, frequency, or titration was identified. The retrieved evidence does not support a numerical human regimen. Animal exposures cannot establish a human treatment dose. PMID 23055539 describes preclinical work and has a linked expression of concern in its PubMed record. PMID 40312093 documents retraction of a separate central HGF/c-Met mechanism paper. These records support publication-status limitations, not human treatment.	No established human route. Oral activity reported in animals does not validate oral, topical, or injectable human administration. · Not established in human treatment trials identified by the targeted search.	Human relationships to training, meals, and sleep are unknown.	None. Excluded throughout weeks 1 to 8.	None established. The evidence does not support a trial-and-escalate sequence.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1	Record seven days of baseline sleep, symptoms, blood pressure, resting pulse, and training. Define one functional target, such as completing a normal work block with fewer attention lapses.	Abrupt onset, progressive decline, focal symptoms, or impairment affecting driving and everyday safety. These findings override the review schedule.
2	Review history, medications, sleep, and relevant laboratory results with a clinician. Identify reversible contributors. Keep caffeine, training load, and assessment timing consistent.	Sleep apnea features, under-fueling, excessive fatigue, mood symptoms, and medication-related sedation.

WEEK	ACTIONS	WATCH
3	Review Cerebrolysin's disease-specific evidence and whether an actual clinical indication exists. Record the decision and its rationale. There is no automatic compound start.	Confusing post-stroke motor improvement with enhancement of memory in healthy adults. Check contraindications if clinical treatment is being considered.
4	Conduct the midpoint review and repeat the selected functional assessment under baseline conditions. If treatment was independently prescribed, document actual exposure and clinician instructions.	Headache, dizziness, agitation, sleep deterioration, allergic symptoms, or reduced exercise tolerance. Concurrent changes limit interpretation.
5	Review Semax evidence, including the distinction between imaging endpoints and meaningful function. Assess progress from sleep and other foundational changes before attributing benefit to treatment.	Practice effects, expectancy, increased caffeine, and simultaneous lifestyle changes.
6	Arrange an interim clinical review if symptoms persist or treatment is underway. Compare function, adverse effects, and baseline variability. Dihexa remains excluded.	Subjective stimulation without functional benefit, escalating exposure, or accumulating adverse effects.
7	Confirm the endpoint of any prescribed course with its prescriber. Continue stable habits and observation. The framework does not justify extending exposure to fill eight weeks.	Worsening sleep, persistent symptoms, or pressure to add compounds when improvement is absent.
8	Repeat baseline measurements and review the functional target. Record whether further diagnostic work, rehabilitation, or follow-up is needed.	Persistent decline, adverse effects after the last exposure, and apparent benefits that disappear when testing conditions are matched.

PRE-CHECKS

- Record seated home blood pressure and resting heart rate on several days, using consistent conditions. Record body weight and waist circumference for metabolic context.
- Collect a seven-day sleep diary, bedtime and wake time, awakenings, daytime sleepiness, snoring, caffeine, alcohol, training load, and estimated energy intake.
- Document symptom onset, duration, severity, head injuries, migraines, seizures, psychiatric history, kidney disease, allergies, cancer history, and all medications and supplements.
- Review Cerebrolysin contraindications and relevant local prescribing information if clinical treatment is being considered. Specialist assessment does not remove a labeled contraindication.
- Discuss creatinine and eGFR when clinical treatment is being considered. CBC, electrolytes, liver tests, TSH, vitamin B12, fasting glucose, or HbA1c should follow symptoms, history, and metabolic risk.
- Choose one repeatable cognitive task and one everyday functional measure. Persistent or progressive impairment warrants a clinician-led cognitive and neurological assessment.
- For tested athletes, experimental Dihexa is prohibited at all times under WADA's rules for non-approved pharmacological substances. This applies the S0 category rule; Dihexa is not individually named. Cerebrolysin, Semax, and administration methods require status confirmation with the responsible anti-doping authority. Absence of a named listing does not establish permission. [2026 WADA Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf)

STOP RULES

- Stop any experimental exposure and seek emergency care for new facial droop, unilateral weakness, speech difficulty, sudden severe headache, seizure, unconsciousness, or acute confusion.
- Seek emergency care for breathing difficulty, tongue or throat swelling, chest pain, or fainting.
- Pause further exposure and obtain prompt clinical assessment for marked agitation, severe insomnia, unusually elevated mood, or hallucinations. Suicidal intent or inability to remain safe requires emergency care.
- Obtain same-day assessment for persistent vomiting, significantly reduced urine output, severe dizziness, or a substantial sustained change in blood pressure or pulse.
- For clinician-administered treatment, fever or increasing redness, warmth, swelling, or pain at an administration site requires prompt review.
- Stop pursuing enhancement and reassess the diagnosis when everyday function worsens, adverse effects outweigh any benefit, or exposure escalates without measurable improvement.

EXPECTED TIMELINE

No reliable eight-week regeneration timeline exists. The Semax imaging study measured immediate physiological changes, not lasting functional benefit. CARS assessed its primary recovery outcome at 90 days. Improvements after correcting sleep or under-fueling may occur during this framework, but cannot establish a peptide effect. Progressive symptoms warrant earlier assessment, not completion of the schedule.

COMMON MISTAKES

- Treating evidence grade A as proof of benefit for every goal or as a high-certainty GRADE assessment.
- Copying stroke-treatment doses into a healthy-adult enhancement plan.
- Interpreting increased BDNF or altered fMRI activity as regenerated neurons.
- Stacking agents and losing the ability to attribute effects.
- Citing Dihexa research without distinguishing an expression of concern from a retracted publication.
- Mistaking repeated-test improvement or better sleep for drug efficacy.

TRACKER FIELDS

Primary functional target · Cognitive task name · Task score and errors · Everyday function result · Assessment time and conditions · Mean sleep hours · Sleep quality 0 to 10 · Daytime sleepiness 0 to 10 · Mean seated blood pressure · Mean resting heart rate · Body weight kg · Waist cm · Training sessions and tolerance · Caffeine and alcohol · Medication or supplement changes · Compound and actual exposure if prescribed · Exposure route frequency and dates · Prescriber and indication · Adverse event onset duration severity · Laboratory results if obtained · Clinician review and decision · Days since last exposure
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MONITORING

- Summarize weekly blood pressure, resting pulse, sleep duration, sleep quality, body weight, and training tolerance against personal baseline.
- Repeat the functional task at the same time of day with similar sleep, caffeine, and meal conditions. Record errors as well as speed.
- Log headaches, dizziness, agitation, anxiety, mood elevation, nasal symptoms, and other adverse events with onset and duration.
- Review any actual exposure and concurrent medication changes weekly. Repeat laboratory testing according to clinical indication; normal results cannot establish experimental-drug safety.
- Do not use circulating BDNF, consumer brain scores, or subjective stimulation as proof of regeneration. Home tracking cannot establish treatment causality or replace neurological assessment.

EXIT PLAN

End the review at week 8 without an automatic repeat cycle. Any prescribed course ends according to the treating clinician's plan. No validated combined taper or washout interval exists for these agents. Short plasma persistence would not establish the end of biological effects. Arrange follow-up after the last clinical exposure and reassess symptoms, sleep, functional performance, and adverse events. Record time since last exposure without labeling it a proven washout. Persistent impairment calls for diagnostic reassessment rather than another compound.

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Longevity Maintenance

INTERMEDIATE · 10 WEEKS · CORE: EPITALON, THYMALIN · SUPPORT: NAD+, THYMOSIN ALPHA-1

A 10-week framework for evaluating longevity claims, establishing measurable baselines and reviewing documented exposures. The verified references do not validate this four-compound sequence or establish that it extends healthy lifespan in adults who train. The intended practical outcome is better judgment and a usable health record.

WHO IT IS FOR

Adults with established training habits who want to understand the evidence behind Epitalon, Thymalin, NAD+ and Thymosin Alpha-1. This educational framework supports discussion with a clinician. Its calendar organizes assessment and follow-up. Reported drug exposures describe the literature and are not instructions for self-administration.

WHO SHOULD NOT RUN IT

Pregnant or breastfeeding people, minors, or anyone seeking experimental treatment for unexplained fatigue, recurrent infections or suspected endocrine disease without evaluation. Active cancer, transplantation, autoimmune disease, immunosuppressive treatment, serious organ disease or unresolved acute illness require specialist assessment. These exclusions concern experimental exposure, not access to the educational material. A known allergy to a compound or formulation component precludes exposure to that preparation.

THE LOGIC

The assessment begins with illness history, immune concerns and recovery because untreated disease and inadequate recovery can dominate fatigue and performance. Thymalin belongs in this first evidence review. Thymosin Alpha-1 addresses a related immune domain, but overlapping mechanisms do not establish additive benefit or justify combining them.

Energy comes next, represented by a review of NAD+. NAD+ is a coenzyme, not a peptide. Its biochemical importance does not establish that intravenous administration improves healthspan. Persistent fatigue first warrants attention to sleep, nutrition, medications and clinically indicated investigation.

Nervous system function and sleep follow. Epitalon is often placed here through pineal biology and telomerase hypotheses. However, the cited Epitalon experiment involved cultured human cells. The older human longevity report used Epithalamin, a different pineal extract. Its outcomes cannot establish an Epitalon dose, bedtime schedule or clinical benefit.

Metabolism is then assessed through blood pressure, waist, glucose and lipids. Tissue maintenance follows through recoverable training and adequate nutrition. No additional anabolic compound is justified by this framework. This order organizes assessment and does not establish a biological prerequisite or pharmacological sequence. The component evidence does not establish the efficacy or safety of a combined maintenance cycle. Evidence grades below apply to the stated outcome, not every possible use of a compound.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
Thymalin	Primary immune-domain review topic. Historical controlled human research exists. Its reporting limitations and different study populations leave the longevity claim at grade C for adults who train.	PMID 14523363 reports Thymalin 10 mg intramuscularly once daily for 10 days in the St. Petersburg cohort. This historical study exposure is not a maintenance recommendation. PMID 14523363, methods checked in a reproduced full text. The paper describes multiple cohorts with different schedules. Thymalin is a thymic peptide preparation and is not interchangeable with the defined peptide Thymosin Alpha-1.	Intramuscular in the cited cohort. Findings do not establish equivalence with subcutaneous administration or differently characterized preparations. · Once daily during the cited short course. The report also describes repeat courses over subsequent years, not continuous weekly maintenance.	No validated relationship to training, food or bedtime was established. Morning or evening superiority cannot be inferred.	Evidence review in weeks 1 and 2. No administration weeks are assigned because the historical course does not validate this 10-week sequence.	The cited cohort used a fixed exposure. This study does not establish upward titration or symptom-driven adjustment for longevity.
NAD+	Optional energy-domain review topic. Grade B for the small human infusion and metabolite study. Grade D for mechanistic extrapolation to lifespan extension, which the study did not measure.	PMID 31572171 reports NAD+ 750 mg intravenously once, infused over 6 hours on a single study day. This was a metabolic pilot exposure, not a validated longevity regimen. PMID 31572171, publisher full-text methods checked. Eight participants received NAD+ and three received saline. Metabolite changes describe handling of the administered compound, not rejuvenation.	Intravenous infusion under study supervision. The findings do not establish subcutaneous, oral or intranasal equivalence. · One study-day infusion. Weekly or repeated maintenance sessions cannot be derived from this experiment.	The study does not establish optimal timing relative to resistance training, meals or sleep. Infusion-related sensations are not evidence of improved cellular function.	Optional evidence review in weeks 3 and 4. No recurring exposure is scheduled.	No longevity titration was established. The studied infusion duration is a method detail, not a template for self-directed rate adjustment.
Epitalon	Primary review topic for telomerase and pineal hypotheses. Grade B for the cited cultured-cell findings. Those findings do not demonstrate human longevity or sleep benefits.	Epitalon 10 mg subcutaneously once daily for 10 days is commonly cited in non-clinical use; not validated in trials. This describes an unvalidated convention, not a recommended exposure. The non-clinical convention was not verified as a study exposure. PMID 12937682 supports a laboratory mechanism only. Epithalamin exposure in PMID 14523363 must not be relabeled as Epitalon exposure.	Subcutaneous in the non-clinical convention. PMID 12937682 studied cultured cells and establishes no human administration route. · Daily in the non-clinical convention. No clinically validated longevity frequency is established by the cited evidence.	Bedtime use is a mechanistic extrapolation. No verified human study here establishes superiority before sleep, after training or away from meals.	Evidence review in weeks 5 and 6. No active administration weeks are assigned.	No starting dose, escalation sequence or maximum tolerated longevity dose is established by the cited evidence. Telomerase findings cannot supply these parameters.
Thymosin Alpha-1	Optional immune-domain review topic alongside Thymalin. Grade B for the cited small hepatitis B trial. Grade D for mechanistic extrapolation to healthy lifespan extension, which the trial did not measure.	PMID 17075991 reports Thymosin Alpha-1 1.6 mg subcutaneously twice weekly for 6 months in chronic hepatitis B. This disease-specific exposure is not a longevity recommendation. PMID 17075991, publisher full text checked. The trial randomized 62 patients between active treatments and included 30 historical untreated controls. Disease-specific outcomes cannot establish general immune enhancement. Transplantation or deliberate immunosuppression requires specialist review before any immune-modulating treatment.	Subcutaneous in the cited trial. · Twice weekly in the cited trial. Its duration cannot be shortened to this calendar while assuming equivalent outcomes.	No longevity-specific relationship to food, exercise or bedtime was established. Training recovery is not a validated indication from this study.	Optional review in weeks 1 and 2. No routine add-on weeks are assigned. A medical indication requires its own treatment plan.	The study used a fixed regimen, not progressive escalation. It establishes neither longevity titration nor an evidence-based combination schedule with Thymalin.

WEEK	ACTIONS	WATCH
1	Collect seven days of baseline observations. Review illnesses, medications and immune history. Keep training and nutrition broadly consistent.	Fever, unexplained weight loss, persistent fatigue or recurrent infections requiring evaluation.
2	Review Thymalin and Thymosin Alpha-1 evidence with a clinician. Identify whether an actual immune disorder needs diagnosis.	Confusing normal training fatigue with immune deficiency or assuming two immune agents are complementary.
3	Review energy intake, alcohol, caffeine, training load and fatigue patterns before assessing NAD+ claims.	Exertional breathlessness, palpitations, excessive daytime sleepiness or declining exercise tolerance.
4	Compare energy and recovery with baseline. Record whether any medically supervised exposure occurred and its exact documentation.	Attributing ordinary fluctuations or infusion sensations to mitochondrial improvement.
5	Review Epitalon evidence and its distinction from Epithalamin. Establish a consistent sleep opportunity and waking time.	Insomnia, witnessed apneas, loud snoring or persistent daytime impairment.
6	Compare sleep duration, awakenings and daytime function across two weeks. Assess unresolved symptoms clinically.	Overinterpreting wearable sleep stages or treating subjective improvement as proof of telomere change.
7	Review blood pressure, weight and waist trends. Assess available glucose and lipid results in their cardiovascular context.	Persistent hypertension, rising glucose or unintended weight change.
8	Review tissue recovery through a repeatable submaximal exercise measure. Adjust excessive workload without adding compounds.	Persistent tendon pain, falling performance or soreness that fails to resolve.
9	Consolidate the record. Repeat abnormal or clinically indicated tests using comparable collection conditions.	Abnormalities obscured by illness, dehydration or unusually strenuous recent training.
10	Compare outcomes with baseline and document the exit decision. Arrange follow-up for unresolved symptoms or adverse events.	Automatic repeat cycles, escalating exposure after no benefit or calling short-term changes lifespan extension.

PRE-CHECKS

- Record seated blood pressure with an appropriate cuff, resting heart rate, morning body weight, waist circumference and seven days of sleep and fatigue observations.
- Review fasting glucose or HbA1c and a lipid panel when due or clinically relevant. CBC with differential, creatinine/eGFR and liver chemistry depend on symptoms, history or contemplated medical treatment.
- Document cancer, autoimmune disease, transplantation, allergies, kidney or liver disease, pregnancy possibility, prescription medicines and supplements. Persistent fatigue may warrant targeted thyroid, anemia or sleep-apnea assessment.
- Routine cytokine panels, telomere tests and commercial biological-age scores do not establish suitability or prove that this framework works. Normal baseline tests do not resolve experimental-treatment risks.
- WADA S0 prohibits pharmacological substances lacking approval by any governmental health authority for human therapeutic use, unless addressed elsewhere in the List. This prohibition applies at all times. Absence of a named compound is not clearance. Exact substance and preparation status requires verification. Source: 2026 WADA Prohibited List, section S0.
- WADA M2.2 prohibits intravenous infusions or injections totaling more than 100 mL per 12 hours, subject to specified exceptions. Those exceptions concern legitimate hospital treatment, surgery or clinical diagnostic investigations. Other circumstances require applicable therapeutic use exemption review. Ingredient status and administration-method status are separate. Source: 2026 WADA Prohibited List, section M2.2.

STOP RULES

- Stop any ongoing experimental exposure and seek emergency care for breathing difficulty, facial or tongue swelling, fainting, chest pain or new neurological deficits.
- Stop experimental exposure and obtain prompt assessment for fever with spreading redness, warmth, drainage or increasing pain at an administration site.
- Seek prompt assessment for jaundice, dark urine, markedly reduced urination, persistent vomiting or a new widespread rash.
- Pause experimental exposure for persistent palpitations, substantial sleep deterioration, new joint swelling or other possible autoimmune symptoms pending clinical review.
- Repeated systolic pressure of at least 180 mmHg or diastolic pressure of at least 120 mmHg requires urgent clinical contact. Associated chest pain, breathlessness, visual changes or neurological symptoms require emergency care without waiting for repeat measurements.
- Unexplained cytopenias, renal deterioration or significant liver-test abnormalities require clinician-directed review before further experimental exposure.

EXPECTED TIMELINE

Weeks 1 through 3 establish variability and identify treatable problems. Sleep, fatigue and recovery may change over subsequent weeks through ordinary behavioral adjustments. Ten weeks cannot establish lifespan extension, reduced cancer risk or meaningful rejuvenation. Neither a favorable laboratory result nor absence of symptoms validates the compounds. Changes during observation cannot establish which intervention caused them.

COMMON MISTAKES

- Substituting Epitalon for Epithalamin when interpreting human studies.
- Treating historical doses or non-clinical conventions as personalized prescriptions.
- Starting several interventions together and assigning causality afterward.
- Confusing metabolic, telomerase or immune-marker changes with longer healthy life.

MONITORING

- Weekly: compare average resting heart rate, standardized blood pressure readings, average morning weight and waist circumference with baseline.
- Weekly: summarize sleep duration, awakenings, fatigue, infection symptoms, training sessions and a consistent performance measure.
- Record each adverse event, onset, severity, duration and clinician response. If exposure occurred under medical care, record the compound, formulation, dose, route, frequency and provenance.
- Repeat laboratory tests according to baseline findings and clinical judgment. Normal results do not establish long-term safety. Weekly broad laboratory panels are not routinely informative.

EXIT PLAN

At week 10, end the assessment block and document whether any objective change, adverse event or unresolved issue exists. The verified references establish no combined washout interval or longevity taper for these compounds. Any actual medical treatment follows its prescriber's plan. Continue observation for another two to four weeks if useful. This follow-up period does not demonstrate clearance or a biological reset. Reassess abnormal findings and avoid assuming that a completed calendar justifies repetition.

- Using a certificate of analysis as proof of clinical efficacy, sterility or long-term safety.
- Interpreting an evidence-review calendar as a validated administration sequence.

TRACKER FIELDS

Blood pressure average mmHg · Resting heart rate average bpm · Morning weight average kg · Waist cm · Sleep average hours · Night awakenings average · Fatigue 0 to 10 · Infection symptoms and days · Training sessions and load · Standardized performance measure · Medication and supplement changes · Compound id and formulation if exposed · Reported dose route frequency and source if exposed · Exposure dates and times if applicable · Adverse event onset severity duration · Laboratory results units and dates · Clinician review and decision

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Libido and Sexual Response

BEGINNER · 4 WEEKS · CORE: PT-141, KISSPEPTIN-10 · SUPPORT: OXYTOCIN

A four-week framework for distinguishing low desire from impaired arousal, identifying reversible contributors, and understanding documented peptide interventions. This educational assessment framework is not a validated three-compound treatment regimen. Beginner refers to the educational level, not suitability for self-treatment. Success means clearer decisions and measurable symptom assessment, without a promise of improved sexual performance.

WHO IT IS FOR

Adults who train and experience persistent, personally distressing changes in desire or sexual response. The framework supports discussion with a clinician. Bremelanotide evidence is strongest for premenopausal women with acquired, generalized hypoactive sexual desire disorder, abbreviated HSDD. Acquired means developing after previously normal desire; generalized means occurring across situations, stimulation types, or partners. Its labeled indication excludes symptoms caused by medical or psychiatric conditions, relationship problems, or medication or substance effects. This evidence does not establish effectiveness for every adult, men, or postmenopausal women.

THE LOGIC

Assessment begins with symptom definition and potentially reversible contributors. Active illness, pain, medication effects, relationship context, mood, sleep, energy availability, and excessive training load deserve consideration. Diabetes and endocrine disorders warrant investigation when symptoms or risk factors support it. There is no validated sequence requiring inflammation treatment before nervous-system, metabolic, or sexual-health assessment. Routine inflammatory panels are unnecessary without clinical indications. Tissue-repair and anabolic peptides have no established role in this framework. Adequate recovery and treatment of underlying disease may address contributors that pharmacological stimulation leaves unresolved.

Among these compounds, PT-141, or bremelanotide, comes first in evidence review because randomized trials demonstrated clinical benefit in its defined HSDD population. It is a melanocortin receptor agonist; its precise therapeutic mechanism in HSDD remains incompletely understood. Grade A applies to the approved indication, supported by two randomized phase 3 trials, PMID 31599840. Improvements concerned desire and related distress. This does not establish a universal aphrodisiac effect or guarantee an individual response.

Kisspeptin-10 comes second as reproductive-axis research. Small human experiments support LH stimulation consistent with activation of the GnRH pathway, grade B for endocrine effects, PMID 21632807. Libido benefit specifically from kisspeptin-10 remains grade C under this product's scale because supporting human evidence is insufficient. The cited sexual-processing trials used kisspeptin-54, a different molecular form, PMIDs 36735255 and 36287566. These provide grade B evidence for acute laboratory outcomes. They cannot establish durable symptom improvement or a repeated subcutaneous kisspeptin-10 protocol.

Oxytocin is included only as an evidence discussion. A small randomized trial found no statistically significant superiority over placebo, PMID 26151620. This is grade B human evidence with a negative efficacy result, not proof that all possible regimens are ineffective. Neither that study nor the other cited trials validates sequencing or combining all three compounds.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
PT-141	Primary evidence discussion for patients meeting the labeled HSDD criteria. Melanocortin receptor agonist with grade A evidence specific to that indication.	The Vyleesi prescribing information reports bremelanotide 1.75 mg subcutaneously as needed, at least 45 minutes before anticipated sexual activity. The same label permits no more than one administration per 24 hours and does not recommend more than eight administrations monthly. Dose, indication, and restrictions: Vyleesi prescribing information, sections 1, 2, 4, 5, 7, and 8, DailyMed. https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=f1d0c1b5-2f39-4bad-a6a4-0066e3ad5dcf . Randomized efficacy evidence: PMID 31599840.	Subcutaneous in the approved formulation. Other preparations or routes cannot be assumed equivalent. · Event-based under the Vyleesi label. The label does not describe a daily cycle or a weekly exposure target.	The label states that the optimal administration window and duration of efficacy are incompletely characterized. No validated training or bedtime window is established. Recording meals, exercise, and sleep may help interpret symptoms and tolerability.	Weeks 2 to 4 are review and observation windows only when treatment has been independently prescribed after assessment.	The label provides a fixed dose, not a beginner escalation ladder. Intolerance warrants prescriber review.
Kisspeptin-10	Research topic, not an established libido treatment. Hormone release and subjective desire are different outcomes; the molecular form matters.	PMID 21632807 reports kisspeptin-10 at 0.01 to 3.0 mcg/kg intravenously as single bolus research exposures in healthy men. These were endocrine experiments, not libido prescriptions or a validated repeated-treatment schedule. Kisspeptin-10 bolus dosing and endocrine outcomes: PMID 21632807. Acute sexual-response studies used kisspeptin-54, PMIDs 36735255 and 36287566. Their findings do not validate substitution between forms.	Intravenous in the cited experiment. That study does not establish an equivalent subcutaneous libido regimen. · Single bolus research exposures in the reported dose-finding experiment. Separate infusion experiments also assessed endocrine responses. No validated four-week frequency for sexual symptoms follows from these findings.	The verified abstract establishes no useful relationship to training, meals, sexual activity, or sleep. Research scheduling cannot be assumed to improve clinical outcomes.	Weeks 1 to 4: evidence review only. No administration phase is assigned outside an authorized clinical study.	No validated libido titration exists. The cited dose-response experiment found that greater exposure did not consistently produce a greater LH response.
Oxytocin	Optional research discussion. The relevant small trial provides grade B evidence without demonstrated superiority over placebo.	PMID 26151620 reports oxytocin 32 IU intranasally per sexual-intercourse occasion, within 50 minutes beforehand, during eight-week treatment periods. This describes the trial exposure, not a recommended regimen. PMID 26151620: 30 women, randomized crossover design, eight-week treatment periods separated by a two-week washout, without a statistically significant treatment advantage.	Intranasal in the sexual-function trial. Obstetric routes and indications are not interchangeable. · Event-linked in the trial. The abstract does not establish a universal weekly frequency or a validated maximum exposure.	The study linked exposure to intercourse. No established training, food, or sleep timing improves sexual outcomes.	Week 3: evidence review only. No routine addition is assigned during this four-week framework.	No evidence-supported libido escalation sequence follows from this trial. Lack of benefit does not justify increasing exposure.

WEEK BY WEEK

WEEK	ACTIONS	WATCH
1	Collect seven days of baseline observations. Define the main problem as desire, arousal, erection, lubrication, orgasm, pain, or distress. Review medications and recovery with a clinician. Select one primary outcome before evaluating an intervention. Complete the baseline questionnaire using its full specified recall period.	Sleep loss, aggressive dieting, excessive training, relationship pressure, depressive symptoms, and whether the problem occurs across situations.
2	Review baseline findings and any indicated tests. Address reversible contributors with appropriate clinical support. If bremelanotide was independently prescribed, document the existing prescription and each exposure. Otherwise, the framework continues as assessment and tracking.	Tolerability, blood pressure, headache, flushing, nausea, and whether perceived improvement concerns desire, distress, or physical arousal.
3	Compare symptom patterns with baseline while keeping major lifestyle variables consistent where practical. Review the kisspeptin molecular-form distinction and oxytocin's negative trial. Persistent symptoms warrant diagnostic review rather than automatic additions.	Changes in distress, sexual comfort, sleep, and recovery. Separate medication-associated observations from changes in relationship context or opportunity.
4	Repeat the baseline questionnaire using its specified recall period. Review the primary outcome, adverse effects, and treatment burden. Document a clinician-agreed continuation, discontinuation, or referral decision. Close the tracking period without automatic cycling.	Meaningful personal benefit, unresolved symptoms, and adverse effects that persist beyond an exposure. Questionnaire changes alone do not establish causality.

PRE-CHECKS

- Record seated blood pressure and resting heart rate on several rested days. Document sleep duration, training volume, dietary restriction, and recent weight change. Weight and waist measurements are optional when metabolic assessment makes them relevant.
- Document onset, duration, distress, situational versus generalized symptoms, pain, menstrual or menopausal status, erectile symptoms, and relevant medical or surgical history.
- Review antidepressants, antihypertensives, opioids, hormonal medicines, alcohol, and recreational substances. Medication changes belong with the prescriber. The Vyleesi label advises avoiding concomitant oral naltrexone for alcohol or opioid addiction because reduced absorption may undermine treatment.
- Bremelanotide can also alter absorption of other oral medicines through delayed gastric emptying. The prescriber should review drugs requiring reliable threshold concentrations or rapid onset, plus significant kidney or liver impairment.
- Consider fasting glucose or HbA1c when metabolic risk or erectile symptoms justify screening. Consider lipids according to cardiovascular risk. Four weeks is generally too short for HbA1c to evaluate this framework.
- Endocrine testing is selective: morning testosterone in symptomatic men, repeated on another morning if low; LH, FSH, prolactin, or TSH when findings justify them. Menstrual phase and hormone therapy affect interpretation.
- Assess pregnancy possibility and reproductive plans. The Vyleesi label specifies effective contraception during treatment and discontinuation if pregnancy is suspected. Breastfeeding requires individualized review. Screen for depression, sleep apnea, pelvic pain, and low energy availability when symptoms suggest them.
- Sport status: the 2026 WADA Prohibited List prohibits kisspeptin and its agonist analogues at all times in males under S2.2.1. Source: WADA 2026 Prohibited List. https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf.

STOP RULES

- Stop exposure and seek emergency care for chest pain, severe breathlessness, fainting, new neurological symptoms, or facial swelling with breathing difficulty.
- A repeated blood pressure of at least 180 mmHg systolic or 120 mmHg diastolic requires urgent assessment. Associated concerning symptoms require emergency care without waiting for repeat measurements. Persistent lesser elevations also require review before further exposure.
- Stop and contact the prescriber for severe or persistent vomiting, dehydration, new pigmentation changes, or symptomatic slowing of heart rate. Bremelanotide-associated pigmentation may persist after discontinuation.
- An erection lasting four hours requires emergency assessment regardless of the suspected cause.
- Stop exposure and seek clinical review for suspected pregnancy, new pelvic pain, abnormal bleeding, or major mood deterioration.

EXPECTED TIMELINE

Week 1 establishes an observation baseline. Event-related observations may occur during weeks 2 to 4, but four weeks cannot establish durable effectiveness. Bremelanotide's pivotal randomized treatment periods lasted 24 weeks, PMID 31599840. Acute kisspeptin-54 laboratory responses do not predict sustained kisspeptin-10 benefit. Oxytocin's eight-week treatment periods did not demonstrate superiority over placebo, PMID 26151620. Changes during this framework remain vulnerable to expectation, context, and natural symptom variation.

COMMON MISTAKES

- Treating low desire, erectile dysfunction, and orgasm difficulty as the same diagnosis.
- Applying bremelanotide's evidence outside its established indication or overlooking medical, relationship, and medication explanations.
- Citing kisspeptin-54 studies as proof for kisspeptin-10.
- Equating an LH or testosterone increase with improved sexual wellbeing.
- Changing several interventions simultaneously and assigning causality to the peptide.
- Interpreting improvement during both placebo and oxytocin periods as proof of oxytocin efficacy.
- Treating the beginner educational level or four-week calendar as validation of a treatment regimen.

TRACKER FIELDS

MONITORING

- Weekly: average desire and distress scores, each 0 to 10, plus arousal, orgasm satisfaction, pain, sleep, fatigue, and training load. Informal scores track personal patterns and do not establish a diagnosis.
- Use a suitable validated questionnaire at baseline and week 4, such as the FSFI when appropriate. Its four-week recall period differs from the seven-day observation baseline. Weekly informal ratings are not interchangeable with validated scoring.
- Track sexual opportunities and context without setting performance targets. No opportunity to assess response is different from treatment failure.
- If bremelanotide is prescribed, blood-pressure monitoring should follow the clinician's plan. Its label describes peak pressure effects around two to four hours, usually resolving within 12 hours.
- Repeat abnormal or clinically indicated laboratory tests at a clinician-selected interval. Routine weekly hormone panels do not establish libido improvement.

EXIT PLAN

End the assessment at week 4 and review benefit against adverse effects and burden. The Vyleesi label specifies discontinuation after eight weeks without symptom improvement. It does not prescribe tapering. This framework establishes no combination washout or reset interval. Oxytocin's two-week research washout was a crossover-design feature, not proof of a necessary clinical reset. Participants in research follow the study's discontinuation rules. Unresolved pain, endocrine symptoms, mood, sleep, and medication effects warrant reassessment rather than automatic repetition.

Primary symptom · Desire score 0 to 10 · Distress score 0 to 10 · Arousal score 0 to 10 · Orgasm satisfaction 0 to 10 · Sexual pain 0 to 10 · Sexual opportunities and context · Validated questionnaire name date score recall period · Blood pressure readings mmHg · Resting heart rate bpm · Weight kg if relevant · Waist cm if relevant · Average sleep hours · Fatigue score 0 to 10 · Training hours and intensity · Menstrual or menopausal context · Medication and alcohol changes · Prescribed exposure name dose unit route datetime · Exposure timing relative to food training sleep · Adverse event onset severity duration · Laboratory result date units · Clinician review and next decision

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Skin, Hair and Connective Tissue

BEGINNER · 12 WEEKS · CORE: GHK-CU, ARGIRELINE · SUPPORT: EPITALON

A 12-week educational framework for assessing topical peptide evidence, tracking skin tolerance and appearance, and recognizing when hair or connective tissue symptoms need diagnosis. Modest cosmetic improvement is possible. Hair regrowth, tendon repair and systemic rejuvenation are not established outcomes of this framework.

WHO IT IS FOR

Adults who train, have stable general health and intact skin, and want to evaluate cosmetic peptide claims using consistent photographs and symptom records. Beginner refers to the tracking framework and topical scope. The compounds have not been validated together as a clinical protocol, and simultaneous exposure is not required.

WHO SHOULD NOT RUN IT

People seeking treatment for sudden hair loss, infected wounds, scarring alopecia, acute tendon injury or uncontrolled inflammatory skin disease. Known allergy to a formulation or its ingredients excludes that formulation. Pregnancy, breastfeeding, active cancer treatment or recent skin procedures require individualized clinical review. These are assessment precautions, not a validated contraindication list for every cosmetic peptide.

THE LOGIC

Assessment begins with symptoms that can obscure cosmetic interpretation: dermatitis, infection, allergy, scalp inflammation and unexplained shedding. Sleep, stress, energy availability, recent illness and existing treatments provide additional context. Metabolic disease and nutritional deficiencies merit assessment when the history supports it. This is a practical review order, not a biological hierarchy or treatment sequence proven in trials.

GHK-Cu research concerns extracellular matrix turnover, fibroblast activity and tissue remodeling. PMID 29986520 summarizes small human cosmetic studies, including conference reports and a book chapter. Its reporting does not establish a standardized concentration or reproducible amount per application. Cosmetic evidence is provisionally B, with low confidence because much of the evidence is summarized indirectly. Hair regrowth and clinical tendon repair are not established by these sources. Laboratory collagen findings do not demonstrate stronger tendons in exercising adults.

Argireline has narrower human evidence concerning facial wrinkles. A randomized study enrolled 60 participants and evaluated topical exposure over four weeks, supporting grade B, PMID 23417317. Its small size and short follow-up limit generalization. Proposed effects on neurotransmitter release do not establish clinically meaningful muscle paralysis from ordinary topical exposure.

Epitalon remains research context only, with no active treatment phase. Its cell-culture telomere findings are grade D for this skin goal, PMID 40908429. The paper has a published correction replacing incorrect figures, PMID 41240216. Human cells in a dish are not human clinical evidence. The broader review discusses human research on other endpoints, but does not validate skin rejuvenation or this framework, PMID 40141333. Separating observation periods can help characterize irritation, but cannot prove synergy or isolate ingredient effects without adequate controls.

COMPONENTS · DOSES AS REPORTED IN THE SOURCES NAMED

COMPOUND	ROLE	REPORTED DOSE	ROUTE · FREQUENCY	TIMING	WEEKS	TITRATION
GHK-Cu	Topical evidence candidate for skin texture and appearance. Provisionally B, with low confidence, for small cosmetic studies summarized in PMID 29986520. Hair and musculoskeletal benefits remain unestablished.	Topical concentrations around 0.05% to 0.1%, applied once or twice daily: commonly cited in non-clinical use; not validated in trials. This range is not established by PMID 29986520. That review reports topical cream applied twice daily for 12 weeks, without a reproducible concentration or mg per application. PMID 29986520 supports biological rationale and secondary descriptions of cosmetic schedules. Several underlying reports have limited accessible methods. The non-clinical concentration range is not a therapeutic target.	Topical exposure on intact skin. The cited cosmetic observations do not validate injectable administration, open-wound treatment or delivery through microneedling. · Twice-daily topical application is described in PMID 29986520. This reports a study schedule, not an individual recommendation or evidence that formulations are interchangeable.	No demonstrated relationship to meals, training or bedtime. Cleansing, sweating and other topical exposures belong in the record because they can affect interpretation and tolerance.	Weeks 2 to 12 are an observation window if topical use is independently chosen. Eleven weeks of exposure does not reproduce the review's 12-week observations.	No validated concentration escalation exists. Limited-area tolerance assessment may identify irritation but cannot exclude later allergy. Formulation instructions and clinical context remain relevant; no escalation schedule is assigned.
Argireline	Topical evidence candidate for localized facial wrinkle appearance. Grade B: a retrieved randomized study enrolled 60 participants and assessed four weeks, PMID 23417317.	PMID 18498523 reports a topical emulsion described as containing 10% Argireline for 30 days; application frequency is unspecified in its abstract. PMID 23417317 reports topical application twice daily for four weeks; its abstract does not specify concentration or mg per application. These details cannot be merged into one verified regimen. PMIDs 18498523 and 23417317 support formulation-specific cosmetic observations. They do not validate interchangeable preparations, a combined GHK-Cu regimen or the entire 12-week framework.	Topical facial skin exposure. The randomized study evaluated skin around the eyes, not the ocular surface. These studies do not establish scalp or tendon applications. · Twice-daily topical application was studied in PMID 23417317. The amount delivered remains formulation-specific and cannot be calculated from application frequency alone.	No established food, sleep or exercise timing requirement. Consistent photographs and expression improve comparison. Permitted application areas depend on the formulation; skin around the eyes differs from direct eye exposure.	Weeks 4 to 7 provide a four-week assessment window. Observation through week 12 extends beyond the randomized trial's duration and does not establish longer-term efficacy.	No validated step-up concentration schedule exists. A declared percentage may describe an ingredient solution rather than pure peptide. The abstract alone cannot resolve formulation equivalence or justify concentration escalation.

Compound	Role	Reported Dose	Route · Frequency	Timing	Weeks	Titration
Epitalon	Research context only. Grade D for skin rejuvenation: telomere and gene-expression endpoints in cultured cells do not establish clinical cosmetic benefit.	PMID 40908429 reports direct culture-medium exposure to 1 mcg/mL Epitalon daily for three weeks in normal human fibroblast and epithelial cells. Culture medium was refreshed daily. This is an in vitro concentration, not a topical, oral or injectable human dose. No validated human skin regimen is established by these references. PMID 40908429 provides the culture exposure details; PMID 41240216 corrects its figures. PMID 40141333 reviews broader research. Findings concerning the pineal extract Epithalamin cannot automatically be attributed to synthetic Epitalon.	Documented example: direct cell-culture exposure. No human administration route is assigned within this framework. · Daily cell-culture treatment in PMID 40908429. This does not establish a human treatment frequency for skin, hair or connective tissue outcomes.	No validated timing relative to training, food or sleep for this goal. Pineal and melatonin mechanisms do not establish a bedtime skin regimen.	No active treatment weeks. Research review may occur at any point without adding exposure.	None. Laboratory concentrations cannot be converted into personal dosing by body weight, skin area or solution volume. No human escalation or repeat-cycle schedule is assigned.

WEEK BY WEEK

Week	Actions	Watch
1	Establish baseline photographs, skin scores, scalp pattern, sleep and training records. Document cleansing, moisturizer and sun protection. Active dermatitis or unexplained shedding warrants assessment before cosmetic interpretation.	Pre-existing redness, scaling, itching, broken skin and rapidly changing hair density. Baseline symptoms can later be mistaken for formulation effects.
2 to 3	If GHK-Cu topical use is independently chosen, record formulation, declared concentration, exposure area and actual frequency. Document other cosmetic changes and any limited-area tolerance observations.	Immediate burning and delayed eczema. Early softness may reflect the moisturizer base rather than tissue remodeling. Lack of early irritation does not exclude later allergy.
4 to 7	If Argireline is independently evaluated, record its start date and define one wrinkle region for comparison. Weekly photographs use matched lighting and expression. Epitalon remains research context only.	Irritation, eye symptoms and changes in lighting or expression that can mimic improvement. Concurrent GHK-Cu exposure limits attribution; the calendar does not establish a combination regimen.
8 to 10	Review four-week Argireline observations against baseline. Record whether change is visible in matched images and meaningful to the participant. Document training changes and scalp or tendon symptoms separately.	Increasing concentration to chase a plateau, worsening shedding, or pain interpreted as beneficial remodeling. Continued exposure does not establish additional benefit.
11 to 12	Complete matched endpoint photographs and score changes, exposure consistency, irritation and cost. Record the continuation or discontinuation decision. Persistent hair or connective tissue concerns warrant diagnosis.	Changes attributable to sun protection, hydration, recovery or another treatment. These confounders belong in the final assessment, even when appearance improves.

PRE-CHECKS

- Document general health and average sleep duration. Blood pressure, resting heart rate, body weight and waist circumference are optional context, not required topical-peptide screening or efficacy endpoints.
- Photograph the same facial regions and scalp part using fixed lighting, distance, camera settings and hair condition. Define one primary endpoint, such as wrinkle appearance at rest.
- Document eczema, rosacea, contact allergy, scalp disease, hair-loss pattern, recent illness, restrictive dieting, medications, supplements, procedures and existing topical treatments.
- Fasting glucose or HbA1c is relevant when diabetes risk, poor healing or routine screening indicates it. Ordinary cosmetic exposure alone does not establish a need for a metabolic panel.
- For unexplained diffuse shedding or fatigue, a clinician may select CBC, ferritin and TSH based on history. Routine copper, hormone, inflammatory-marker and telomere panels are not established monitoring requirements.
- Sport eligibility requires separate verification. WADA S0 prohibits pharmacological substances without governmental approval for human therapeutic use when no subsequent list section addresses them. The prohibition applies at all times. Absence of a compound's name does not establish permission, and cosmetic availability does not establish therapeutic approval. This framework does not establish compound-specific clearance. Source: WADA 2026 Prohibited List, section S0.

STOP RULES

- Stop the suspected formulation and seek emergency care for breathing difficulty, faintness, or swelling of the lips, tongue or throat. Generalized hives require prompt assessment, especially with systemic symptoms.
- Stop exposure and obtain prompt assessment for blistering, marked facial swelling, severe burning, eye pain or visual disturbance.
- Stop use over an affected area and seek assessment for spreading warmth or redness, pus, fever, or a deteriorating wound.
- Persistent dermatitis after withdrawal, sudden patchy hair loss, scalp scarring or rapidly worsening shedding warrants clinical review.
- An acute tendon pop, new weakness, major swelling or inability to bear weight requires urgent injury assessment.

EXPECTED TIMELINE

Texture changes within days may reflect hydration. Argireline's retrieved randomized evidence concerns four weeks, PMID 23417317. The GHK-Cu review describes cosmetic assessments over eight to twelve weeks, PMID 29986520. Neither timeframe guarantees visible benefit. Twelve weeks may document a hair trend, but cannot establish follicular recovery or tendon repair from these compounds.

MONITORING

- Weekly: score dryness, redness, itching and burning from 0 to 10. Record duration, location and relationship to each formulation.
- Weekly: record actual exposure days, missed applications, declared concentration, other cosmetic changes, sun exposure and consistency of sun protection.
- Weekly: capture matched photographs and record sleep, stress, training load and relevant weight changes. Apparent improvement from memory alone is unreliable.
- Track hair shedding consistently without interpreting daily fluctuations as regrowth evidence. Record tendon pain during loading and next-day function; worsening symptoms require separate assessment.
- Repeat laboratory tests only for a clinical indication or an abnormal baseline result. No validated blood test measures whether these topical peptides improve cosmetic appearance.

EXIT PLAN

At week 12, compare baseline and endpoint images with dates concealed if practical. No taper requirement is established by these sources for ordinary topical cosmetic exposure. A two-to-four-week observation break is an optional tracking choice, not a validated pharmacological washout. Record whether appearance changes or irritation persist, while documenting basic skin care and other exposures. No Epitalon course

COMMON MISTAKES

- Equating an ingredient-solution percentage with pure peptide concentration or a known mg dose.
- Treating smoother facial skin as evidence of stronger tendons or hair regrowth.
- Changing several formulations, procedures and supplements together, then attributing improvement to one peptide.
- Converting laboratory telomere findings into claims of longer life, proven clinical benefit or established long-term safety.
- Escalating exposure despite irritation or judging progress from unmatched photographs.
- Combining a concentration from one paper with a frequency from another and presenting the result as a verified regimen.

TRACKER FIELDS

Formulation name and batch · Ingredient id and declared concentration · Exposure area and actual frequency · Exposure days and missed applications · Dryness redness itching burning scores 0 to 10 · Adverse event onset duration and action · Standardized photo identifiers · Primary skin endpoint score · Scalp photo and shedding trend · Tendon pain and function if relevant · Average sleep hours and stress score · Training load and body weight if relevant · Sun exposure and skin care changes · Clinician review and continue pause stop decision

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33. Medvedev VE et al. [A comparison of the anxiolytic effect and tolerability of selank and phenazepam in the treatment of anxiety disorders].. *Zhurnal neurologii i psikiatrii imeni S.S. Korsakova*, 2014. PMID 25176261 (Grade B comparative clinical evidence from 60 patients with anxiety-related disorders. Reports anxiolytic and mild nootropic effects, with anxiety benefits persisting one week after treatment. Limited generalizability to healthy adults.)
34. Mendias CL et al. Safety and Efficacy of Approved and Unapproved Peptide Therapies for Musculoskeletal Injuries and Athletic Performance.. *Sports medicine (Auckland, N.Z.)*, 2026. PMID 41966639 DOI 10.1007/s40279-026-02437-0 (Narrative sports-medicine review covering all four compounds. Supports the distinction between preclinical findings and clinical benefit, and the scarcity of rigorous human safety evidence.)
35. Mills EG et al. Effects of Kisspeptin on Sexual Brain Processing and Penile Tumescence in Men With Hypoactive Sexual Desire Disorder: A Randomized Clinical Trial.. *JAMA network open*, 2023. PMID 36735255 DOI 10.1001/jamanetworkopen.2022.54313 (Grade B acute human evidence for kisspeptin-54: laboratory sexual-processing, tumescence, and selected behavioral outcomes. It does not establish chronic kisspeptin-10 efficacy.)
36. Muin DA et al. Effect of long-term intranasal oxytocin on sexual dysfunction in premenopausal and postmenopausal women: a randomized trial.. *Fertility and sterility*, 2015. PMID 26151620 DOI 10.1016/j.fertnstert.2015.06.010 (Grade B small human trial: reported intranasal exposure and crossover washout. No statistically significant efficacy advantage over placebo was demonstrated.)
37. Muresanu DF et al. Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial.. *Stroke*, 2016. PMID 26564102 DOI 10.1161/STROKEAHA.115.009416 (Reported Cerebrolysin regimen and upper-limb motor outcomes during post-stroke rehabilitation. Does not establish healthy-adult enhancement or combination efficacy.)
38. Ng FM et al. Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone.. *Hormone research*, 2000. PMID 11146367 DOI 10.1159/000053183 (Grade C. Oral AOD9604 exposure and reduced weight gain in obese rats; no human treatment schedule or established human fat-loss efficacy.)
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40. Pampusch MS et al. Production of recombinant porcine IGF-binding protein-5 and its effect on proliferation of porcine embryonic myoblast cultures in the presence and absence of IGF-I and Long-R3-IGF-I.. *The Journal of endocrinology*, 2005. PMID 15817840 DOI 10.1677/joe.1.06037 (Grade D porcine cell-culture evidence involving Long-R3-IGF-I and binding-protein interactions. Does not establish human dose, route, frequency, or hypertrophy efficacy.)
41. Panikratova YR et al. Functional Connectomic Approach to Studying Selank and Semax Effects.. *Doklady biological sciences : proceedings of the Academy of Sciences of the USSR, Biological sciences sections*, 2020. PMID 32342318 DOI 10.1134/S001249662001007X (Grade B pilot human imaging evidence. Supports the documented single intranasal exposures and acute connectivity findings. Separate treatment groups do not establish combination efficacy.)
42. Pickart L et al. Regenerative and Protective Actions of the GHK-Cu Peptide in the Light of the New Gene Data.. *International journal of molecular sciences*, 2018. PMID 29986520 DOI 10.3390/ijms19071987 (GHK-Cu mechanisms and secondary descriptions of small topical cosmetic studies, including twice-daily topical cream exposure for 12 weeks. Several underlying reports are conference material or a book chapter. Does not establish a standardized concentration, injectable regimen or clinical tendon repair.)
43. Reynolds JC et al. MOTs-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis.. *Nature communications*, 2021. PMID 33473109 DOI 10.1038/s41467-020-20790-0 (Grade C for administered MOTs-c performance and healthspan claims: treatment experiments involved mice. Human findings concern endogenous responses to exercise. Neither establishes human treatment efficacy.)
44. Schneider-Helmert D et al. Effects of delta-sleep-inducing peptide on 24-hour sleep-wake behaviour in severe chronic insomnia.. *European neurology*, 1987. PMID 3622582 DOI 10.1159/000116143 (Small positive placebo-controlled, double-blind study in 14 patients. Comparison with PMID 1299794 illustrates inconsistent findings across the cited human DSIP studies.)
45. Shadrina M et al. Comparison of the temporary dynamics of NGF and BDNF gene expression in rat hippocampus, frontal cortex, and retina under Semax action.. *Journal of molecular neuroscience : MN*, 2010. PMID 19662538 DOI 10.1007/s12031-009-9270-z (Grade C animal evidence showing region-dependent and time-dependent neurotrophin gene-expression changes. Does not validate human cognitive benefit.)
46. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Reported subcutaneous CJC-1295 exposure, sustained endocrine responses, and prolonged pharmacokinetics in two short randomized trials. Grade B for endocrine findings; no musculoskeletal healing outcomes.)
47. Thurston L et al. Effects of Kisspeptin Administration in Women With Hypoactive Sexual Desire Disorder: A Randomized Clinical Trial.. *JAMA network open*, 2022. PMID 36287566 DOI 10.1001/jamanetworkopen.2022.36131 (Grade B acute kisspeptin-54 evidence in premenopausal women with HSDD. Brain-processing findings do not establish durable symptom improvement or chronic kisspeptin-10 efficacy.)
48. Vasireddi N et al. Emerging Use of BPC-157 in Orthopaedic Sports Medicine: A Systematic Review.. *HSS journal : the musculoskeletal journal of Hospital for Special Surgery*, 2025. PMID 40756949 DOI 10.1177/15563316251355551 (Supports grade C for the BPC-157 repair claim: predominantly preclinical findings and weak human orthopedic evidence. Its search ended in June 2024. It does not establish a validated human repair regimen or a complete account of subsequently published evidence.)
49. Wang X et al. A first-in-human, randomized, double-blind, single- and multiple-dose, phase I study of recombinant human thymosin β 4 in healthy Chinese volunteers.. *Journal of cellular and molecular medicine*, 2021. PMID 34346165 DOI 10.1111/jcmm.16693 (Grade B for short-term human tolerability and pharmacokinetics of the specific recombinant thymosin beta-4 preparation. This small phase I trial does not validate TB-500 dosing, long-term safety or tendon repair.)
50. Wang Y et al. The anti-wrinkle efficacy of argireline, a synthetic hexapeptide, in Chinese subjects: a randomized, placebo-controlled study.. *American journal of clinical dermatology*, 2013. PMID 23417317 DOI 10.1007/s40257-013-0009-9 (Randomized trial involving 60 participants and twice-daily topical Argireline for four weeks. Supports limited short-term wrinkle evidence. The abstract does not specify concentration or mg per application.)
51. Wilding JPH et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2021. PMID 33567185 DOI 10.1056/NEJMoa2032183 (Grade A for semaglutide weight reduction. STEP 1 evaluated 68 weeks of treatment with lifestyle intervention in adults without diabetes. It does not establish complete muscle preservation.)
52. Wilding JPH et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension.. *Diabetes, obesity & metabolism*, 2022. PMID 35441470 DOI 10.1111/dom.14725 (Grade B for exploratory withdrawal follow-up. Substantial regain and movement of cardiometabolic measures toward baseline followed cessation of semaglutide and structured lifestyle intervention.)
53. You J et al. Efficacy of thymosin alpha-1 and interferon alpha in treatment of chronic viral hepatitis B: a randomized controlled study.. *World journal of gastroenterology*, 2006. PMID 17075991 DOI 10.3748/wjg.v12.i41.6715 (Disease-specific Thymosin Alpha-1 exposure and outcomes in chronic hepatitis B. Grade B for this small trial with randomized active treatments and historical untreated controls. It does not establish healthy-adult longevity or combination benefit with Thymalin.)
54. Yuan C et al. From Regeneration to Analgesia: The Role of BPC-157 in Tissue Repair and Pain Management.. *International journal of molecular sciences*, 2026. PMID 41898733 DOI 10.3390/ijms27062876 (Updated discussion of preclinical repair mechanisms and limited human pilot studies. It does not establish efficacy for the cited subcutaneous practice.)
55. Ziganshina LE et al. Cerebrolysin for acute ischaemic stroke.. *The Cochrane database of systematic reviews*, 2023. PMID 37818733 DOI 10.1002/14651858.CD007026.pub7 (Systematic assessment of acute-stroke trials. Found no established mortality benefit and a potential increase in nonfatal serious adverse events with Cerebrolysin.)

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