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 | Reported doses with provenance

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Educational and informational reference for adults. Not medical advice, not a prescription, and not a recommendation to 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.

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.

+ 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.

– 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.

– 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/867/867fc8166acadfb577dc956d855999a3.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.

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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.
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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.

REFERENCES

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doses, with route and within-day frequency unresolved in the abstract.)

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14. Gusev EI et al. [Semax in prevention of disease progress and development of exacerbations in patients with cerebrovascular insufficiency].. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova*, 2005. PMID 15792140 (Cerebrovascular clinical study reporting tolerability without sufficiently detailed adverse-event frequencies in the abstract.)
15. Alekseeva GV et al. [Use of semax at a follow-up of patients with posthypoxic encephalopathy].. *Anesteziologiia i reanimatologiia*, 1999. PMID 10199046 (Posthypoxic encephalopathy series reporting paroxysmal EEG activity in some patients after Semax exposure.)
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Selank

Tuftsin analog

Synthetic tuftsin analog | Module 4 · Mind & Longevity | Goals: Nootropics, Sleep | Route: Intranasal

A synthetic tuftsin 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 tuftsin 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.

EVIDENCE · GRADE A

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).

RESEARCH USE · REPORTED, NOT RECOMMENDED

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

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.

+ 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.

– 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.

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.

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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.
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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.

EVIDENCE · GRADE C

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.

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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.
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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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month treatment period, experimental vehicle, and PI3K inhibitor experiments. Full-text review identified conflicting route descriptions and incomplete dihexa frequency reporting.)

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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.

EVIDENCE · GRADE C

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.

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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.
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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.

REGULATORY STATUS AND SPORT

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 parabulbar 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 parabulbar administration on each of 10 consecutive days, reported in the secondary review PMID 40141333 for PMID 12195242.**	Parabulbar 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.

+ Thymalin

A proposed relationship between pineal and thymic aging creates a research hypothesis. Historical extract-combination findings do not validate synthetic Epitalon with Thymalin.

– 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.

– 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.

BUYING NOTES

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.

+ 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.

– 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.

– 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.

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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.
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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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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.

+ 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.

– 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.

– 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.

REGULATORY STATUS AND SPORT

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.

+ 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.

– 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.

– 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.

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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.

+ 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.

– 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).

– 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.

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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
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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

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.

+ 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.

– 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.

– 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.

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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.
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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.

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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.

REGULATORY STATUS AND SPORT

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.

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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
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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 YNWNSFGLRF-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.

+ 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.

– 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.

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.

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.

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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.
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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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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

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.

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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
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conversion, so no solution concentration is inferred. Insulin syringe unit markings describe a device volume scale, not oxytocin biological activity, and are not the dosing scale for this nasal preparation.

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.

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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.
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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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numerical regimen.)

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153. Sarkisova KIu et al. [Effects of heptapeptide selank on genetically-based and situation-provoked symptoms of depression in behavior in WAG/Rij and Wistar rats, and in BALB/c mice].. *Zhurnal vysshei nervnoi deiatelnosti imeni I P Pavlova*, 2008. PMID 18661785 (Antidepressant-like animal behavior varied with strain, exposure, and repetition; does not validate human dose escalation.)

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163. Serdiuk AV et al. [The study of chronic partial denervation and quality of life in patients with motor neuron disease treated with semax].. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova*, 2007. PMID 18379501 (Open-label motor neuron disease study with a documented nasal regimen, no disease-course benefit and reported emotional quality-of-life improvement.)

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165. Shandra AA et al. [The delta sleep-inducing peptide and its role in modulating epileptic activity].. *Fiziologicheskii zhurnal imeni I.M. Sechenova*, 1993. PMID 8330074 (Metadata confirms a review concerning epileptic activity. No abstract was available for verification of detailed experimental claims.)

166. Shandra AA et al. [The role of the delta sleep-inducing peptide in the formation of neuropathological syndromes].. *Fiziologicheskii zhurnal imeni I.M. Sechenova*, 1995. PMID 8581045 (Review discussing experimental neurological syndromes after central administration, without quantifying clinical risk.)

167. Shevchenko KV et al. [Kinetics of Semax penetration into the brain and blood of rats after its intranasal administration].. *Bioorganicheskaia khimiia*, 2006. PMID 16523722 DOI 10.1134/s1068162006010055 (Rat radiotracer brain entry and rapid metabolism. Does not establish a numerical human elimination half-life.)

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