2.0

MODULE 2 OF 5 · UU LIFE PEPTIDES 2.0

RECOMPOSITION

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

Module 2 | UU LIFE PEPTIDES 2.0 | Verified references | Reported doses with provenance

A UU LIFE PRODUCT · UU.LIFE

Cards in this module

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

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

Tirzepatide

Mounjaro, Zepbound

Dual GIP/GLP-1 receptor agonist | Module 2 · Recomposition | Goals: Fat loss | Route: SC weekly

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

WHAT IT IS

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

MECHANISM

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

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

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

EVIDENCE · GRADE A

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

As of September 2026, the US Mounjaro label covers type 2 diabetes from age 10 and cardiovascular-event risk reduction in high-risk adults with type 2 diabetes. Zepbound is approved for adult weight reduction and long-term maintenance, and moderate to severe obstructive sleep apnea in adults with obesity. Weight-management eligibility includes obesity, or overweight with a weight-related condition. The EMA Mounjaro authorization includes type 2 diabetes and adult weight management. Sources: current US prescribing information and EMA Mounjaro EPAR. These authorizations do not establish an indication for athletic enhancement.

WADA

Not prohibited under the 2026 WADA Prohibited List. Markers of tirzepatide are included in section 6 of the 2026 WADA Monitoring Program, both in and out of competition. Monitoring does not itself constitute prohibition. The 2026 narrative review supports the non-prohibited classification, but does not justify excluding tirzepatide from monitoring (PMID 42511463). Status is specific to the current annual documents.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Approved route: subcutaneous administration in the abdomen, thigh or upper arm, with site rotation, according to the US prescribing information. The trials summarized here used SC administration. Neither oral nor intramuscular administration is an approved route in these labels.

HALF-LIFE

Approximately 5 days in phase 1 and a population model pooling 19 studies (PMIDs 30473097 and 38356317). The current Zepbound label reports approximately 5 to 6 days in obesity populations. Its median time to peak concentration is 24 hours, with an 8 to 72 hour range. Steady state occurs after approximately 4 weeks of weekly administration.

TIMING

US labels describe weekly administration at any time, independent of meals. They specify at least 72 hours between doses when changing the administration day. Missed-dose guidance uses a 96-hour window, followed by omission if that window has passed. Labels also specify non-oral contraception or additional barrier contraception for 4 weeks after initiation and each escalation.

CYCLE LENGTH

Continuous treatment has been studied through 176 weeks in adults with obesity and prediabetes (PMID 39536238). The labels do not define short treatment cycles. SURMOUNT-4 documented

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

TITRATION

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

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

STACKING

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

– Semaglutide	The Zepbound label does not recommend coadministration with another GLP-1 receptor agonist. Additional clinical benefit and a tolerable combined regimen have not been established.
– Liraglutide	Another GLP-1 receptor agonist, covered by the same Zepbound label limitation. Overlapping activity does not establish additive benefit.
– Retatrutide	Overlapping incretin-receptor activity. The verified studies do not establish combination efficacy, tolerability or dosing.
– Cagrilintide	A separate satiety pathway is insufficient evidence of clinical synergy. The reviewed tirzepatide studies do not establish this combination's benefit or gastrointestinal tolerability.
– Tesamorelin	The cited studies do not establish that adding this agent preserves skeletal muscle during tirzepatide treatment. Combination benefits and risks remain unquantified.
– Ipamorelin	The proposed lean-mass rationale lacks supporting human combination results in the verified evidence. A mechanistic hypothesis is not evidence of muscle preservation.

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

BUYING NOTES

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

COMMON MISTAKES

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

REFERENCES

1. Jastreboff AM et al. Tirzepatide Once Weekly for the Treatment of Obesity.. *The New England journal of medicine*, 2022. PMID 35658024 DOI 10.1056/NEJMoa2206038 (SURMOUNT-1 population, SC weekly doses, weight changes and adverse-event discontinuation.)

2. Frías JP et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes.. *The New England journal of medicine*, 2021. PMID 34170647 DOI 10.1056/NEJMoa2107519 (SURPASS-2 comparative glycemic and weight outcomes, study doses and gastrointestinal adverse events.)
3. Aronne LJ et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity.. *The New England journal of medicine*, 2025. PMID 40353578 DOI 10.1056/NEJMoa2416394 (SURMOUNT-5 maximum-tolerated-dose comparison, administration schedule and weight outcomes.)
4. Aronne LJ et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial.. *JAMA*, 2024. PMID 38078870 DOI 10.1001/jama.2023.24945 (Randomized continuation versus withdrawal and weight change measured from week 36.)
5. Look M et al. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight.. *Diabetes, obesity & metabolism*, 2025. PMID 39996356 DOI 10.1111/dom.16275 (DXA substudy size, fat and lean-mass changes, and limitations of interpreting lean mass as muscle.)
6. Coskun T et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept.. *Molecular metabolism*, 2018. PMID 30473097 DOI 10.1016/j.molmet.2018.09.009 (Receptor pharmacology, mouse experiments, phase 1 regimens, tolerability, pharmacokinetics and investigational formulation methods.)
7. Schneck K et al. Population pharmacokinetics of the GIP/GLP receptor agonist tirzepatide.. *CPT: pharmacometrics & systems pharmacology*, 2024. PMID 38356317 DOI 10.1002/psp4.13099 (Population pharmacokinetic model pooling 19 studies and approximately five-day half-life.)
8. La Vignera S et al. Incretin-Based Therapies in Sports: Pharmacological Mechanisms, Performance-Enhancing Potential, and Anti-Doping Implications-A Narrative Review.. *International journal of molecular sciences*, 2026. PMID 42511463 DOI 10.3390/ijms27146116 (Narrative review of performance-related evidence and non-prohibited status. Monitoring status was checked separately against WADA documents.)
9. Urva S et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists.. *Diabetes, obesity & metabolism*, 2020. PMID 32519795 DOI 10.1111/dom.14110 (Initial gastric-emptying delay, attenuation with repeated exposure and residual delay during escalation in diabetes.)
10. Samms RJ et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice.. *The Journal of clinical investigation*, 2021. PMID 34003802 DOI 10.1172/JCI146353 (Preclinical GIPR-dependent insulin sensitization and white-adipose glucose disposal.)
11. Safwan M et al. Gastrointestinal safety of semaglutide and tirzepatide vs. placebo in obese individuals without diabetes: a systematic review and meta analysis.. *Annals of Saudi medicine*, 2025. PMID 40189856 DOI 10.5144/0256–4947.2025.129 (Pooled gastrointestinal adverse-event risk and nonsignificant pancreatic and biliary findings for tirzepatide.)
12. Alawadhi AA et al. LEAN mass Preservation with Resistance Exercise and Protein during semaglutide and tirzepatide therapy (LEAN-PREP study): a protocol for a randomised controlled trial.. *BMJ open*, 2026. PMID 42020128 DOI 10.1136/bmjopen–2026–116911 (Planned resistance-exercise and protein trial. This publication reports a protocol, not efficacy results.)
13. Reis-Barbosa PH et al. The dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist tirzepatide effects on body weight evolution, adiponectin, insulin and leptin levels in the combination of obesity, type 2 diabetes and menopause in mice.. *Diabetes, obesity & metabolism*, 2024. PMID 39113264 DOI 10.1111/dom.15820 (Ovariectomized obese-diabetic mouse model, daily SC research exposure and weight findings.)
14. Jastreboff AM et al. Tirzepatide for Obesity Treatment and Diabetes Prevention.. *The New England journal of medicine*, 2025. PMID 39536238 DOI 10.1056/NEJMoa2410819 (SURMOUNT-1 extension through 176 treatment weeks in participants with obesity and prediabetes.)

Semaglutide

Ozempic, Wegovy, Rybelsus

GLP-1 receptor agonist | Module 2 · Recomposition | Goals: Fat loss | Route: SC weekly or oral daily

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

WHAT IT IS

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

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

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

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

MECHANISM

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

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

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

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

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

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

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

EVIDENCE · GRADE A

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

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

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

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

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

STACKING

+ Cagrilintide	Controlled human combination evidence exists. A phase 2 trial escalated both components to 2.4 mg each, subcutaneously once weekly, over a 32-week treatment period. Mean weight loss was 15.6 percent with the combination versus 5.1 percent with semaglutide alone (Frias 2023, PMID 37364590). REDEFINE 1 studied the same target amounts, each 2.4 mg subcutaneously once weekly, for 68 weeks. Mean weight loss was 20.4 percent versus 3.0 percent with placebo, using the treatment-policy estimand. Gastrointestinal events occurred in 79.6 percent versus 39.9 percent (Garvey 2025, PMID 40544433). Trial evidence does not establish compatibility, stability or equivalent exposure for independently sourced materials mixed together.	**– Tirzepatide**	Both agents activate GLP-1 receptors. Their concurrent use has no established efficacy or safety advantage in the cited trials. SURMOUNT-5 evaluated separate treatment groups, not combination treatment (PMID 40353578). Overlapping gastrointestinal effects and medication complexity are concerns.
		– Liraglutide	Both are GLP-1 receptor agonists. STEP 8 evaluated separate treatment groups and provides no evidence for using them together (PMID 35015037). Concurrent GLP-1 agonist use is not recommended in the weight-management prescribing information.
		– Retatrutide	GLP-1 receptor activity overlaps. Additional receptor activity does not establish a rationale for combining treatments. No controlled combination evidence was identified in this review, and additive adverse effects remain a concern.
		– Tesamorelin	No controlled evidence identified here establishes additive benefit or muscle preservation with semaglutide. Independent activity on another hormonal pathway is insufficient to classify this pair as a demonstrated synergy.
		– Ipamorelin	No controlled evidence identified here establishes prevention of semaglutide-associated lean tissue loss. Adding a secretagogue introduces another exposure without demonstrated benefit for this purpose.

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

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

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

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

BUYING NOTES

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

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

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

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

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

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

COMMON MISTAKES

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

REFERENCES

1. Wilding JPH et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2021. PMID 33567185 DOI 10.1056/NEJMoa2032183 (STEP 1 population, subcutaneous once-weekly regimen, weight outcomes, escalation and gastrointestinal discontinuations.)
2. Lincoff AM et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes.. *The New England journal of medicine*, 2023. PMID 37952131 DOI 10.1056/NEJMoa2307563 (SELECT eligibility, cardiovascular event reduction, follow-up and permanent discontinuation because of adverse events.)
3. Marso SP et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.. *The New England journal of medicine*, 2016. PMID 27633186 DOI 10.1056/NEJMoa1607141 (SUSTAIN-6 subcutaneous once-weekly exposures, cardiovascular outcomes and diabetic retinopathy complication signal.)
4. Knudsen LB et al. The Discovery and Development of Liraglutide and Semaglutide.. *Frontiers in endocrinology*, 2019. PMID 31031702 DOI 10.3389/fendo.2019.00155 (Molecular modifications, albumin binding, DPP-4 resistance, receptor biology and development rationale.)
5. Gabery S et al. Semaglutide lowers body weight in rodents via distributed neural pathways.. *JCI insight*, 2020. PMID 32213703 DOI 10.1172/jci.insight.133429 (Rodent neural access and activation, reduced food intake and experimental energy-expenditure findings.)
6. Blundell J et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity.. *Diabetes, obesity & metabolism*, 2017. PMID 28266779 DOI 10.1111/dom.12932 (Small human crossover study of appetite, measured meal intake, body weight and resting metabolic rate adjusted for lean mass.)
7. Wilding JPH et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension.. *Diabetes, obesity & metabolism*, 2022. PMID 35441470 DOI 10.1111/dom.14725 (Exploratory withdrawal follow-up, extension sample size, cessation of lifestyle intervention and approximately two-thirds average weight regain.)
8. Neeland IJ et al. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies.. *Diabetes, obesity & metabolism*, 2024. PMID 38937282 DOI 10.1111/dom.15728 (Heterogeneous lean mass changes across GLP-1-based therapies and distinctions between lean tissue, muscle mass and function.)

9. Rubino DM et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial.. *JAMA*, 2022. PMID 35015037 DOI 10.1001/jama.2021.23619 (STEP 8 semaglutide outcomes, permitted lower maintenance exposure for intolerance and gastrointestinal event frequency.)
10. Aronne LJ et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity.. *The New England journal of medicine*, 2025. PMID 40353578 DOI 10.1056/NEJMoa2416394 (SURMOUNT-5 semaglutide comparator doses, 72-week treatment duration and semaglutide-arm weight outcome; separate treatment groups.)
11. Aroda VR et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes.. *Diabetes care*, 2019. PMID 31186300 DOI 10.2337/dc19-0749 (Original oral trial doses, glycemic outcomes and identification of reported weight differences as placebo-adjusted estimates.)
12. Knop FK et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial.. *Lancet (London, England)*, 2023. PMID 37385278 DOI 10.1016/S0140-6736(23)01185-6 (OASIS 1 investigational daily oral regimen, trial population, 68-week outcomes and placebo-controlled design.)
13. Sun X et al. Identification and utility exploration of a highly potent and long-acting bullfrog GLP-1 analogue in GLP-1 and amylin combination therapy.. *Peptides*, 2024. PMID 38582303 DOI 10.1016/j.peptides.2024.171203 (Mouse semaglutide comparator and combination weight outcomes. Does not establish a complete semaglutide dosing schedule from the abstract.)
14. Bjerre Knudsen L et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation.. *Endocrinology*, 2010. PMID 20203154 DOI 10.1210/en.2009-1272 (Class-level thyroid C-cell pharmacology and species differences, with explicit limits on semaglutide-specific and human-risk inference.)
15. Overgaard RV et al. Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials.. *Clinical pharmacokinetics*, 2021. PMID 33969456 DOI 10.1007/s40262-021-01025-x (Oral exposure variability, formulation-dependent bioavailability and effects of administration conditions.)
16. Ikushima I et al. A Randomized Trial Investigating the Pharmacokinetics, Pharmacodynamics, and Safety of Subcutaneous Semaglutide Once-Weekly in Healthy Male Japanese and Caucasian Subjects.. *Advances in therapy*, 2018. PMID 29536338 DOI 10.1007/s12325-018-0677-1 (Dedicated human subcutaneous pharmacokinetics and prolonged elimination half-life.)
17. Granhall C et al. Safety and Pharmacokinetics of Single and Multiple Ascending Doses of the Novel Oral Human GLP-1 Analogue, Oral Semaglutide, in Healthy Subjects and Subjects with Type 2 Diabetes.. *Clinical pharmacokinetics*, 2019. PMID 30565096 DOI 10.1007/s40262-018-0728-4 (Oral clinical pharmacokinetics and prolonged systemic exposure.)
18. Jensen L et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species.. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 2017. PMID 28323117 DOI 10.1016/j.ejps.2017.03.020 (Proteolysis, fatty-acid side-chain metabolism and urinary and fecal elimination of drug-related material.)
19. Frias JP et al. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial.. *Lancet (London, England)*, 2023. PMID 37364590 DOI 10.1016/S0140-6736(23)01163-7 (Controlled phase 2 combination exposures, 32-week weight outcomes and limits of extrapolation to independently prepared combinations.)
20. Garvey WT et al. Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2025. PMID 40544433 DOI 10.1056/NEJMoa2502081 (REDEFINE 1 combination regimen, treatment-policy weight outcome and gastrointestinal event frequency.)
21. Perkovic V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes.. *The New England journal of medicine*, 2024. PMID 38785209 DOI 10.1056/NEJMoa2403347 (FLOW regimen, population, follow-up and reduction in the primary kidney-related composite.)
22. Sanyal AJ et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis.. *The New England journal of medicine*, 2025. PMID 40305708 DOI 10.1056/NEJMoa2413258 (ESSENCE interim histological outcomes, studied subcutaneous regimen and limits of inference about long-term clinical liver outcomes.)

Retatrutide (LY3437943)

LY3437943

Triple GIP/GLP-1/glucagon receptor agonist | Module 2 · Recomposition | Goals: Fat loss | Route: SC weekly

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

WHAT IT IS

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

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

MECHANISM

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

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

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

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

EVIDENCE · GRADE A

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

STACKING

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

– Tirzepatide

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

– Semaglutide

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

– Liraglutide	Additional GLP-1 receptor agonism has no established retatrutide combination benefit. Different dosing intervals do not eliminate overlapping exposure or adverse-effect concerns.
– Cagrilintide	A separate satiety pathway is a hypothesis, not demonstrated synergy with retatrutide. No pairing trial was identified. Added gastrointestinal intolerance is plausible; efficacy and interaction risks remain unquantified.
– Tesamorelin	No retatrutide combination trial was identified. Evidence from a separate disease population does not establish protection against retatrutide-associated lean mass loss. The proposed muscle-preservation rationale remains unsupported.

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

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

SOLVENT

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

STORAGE

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

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

BUYING NOTES

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

COMMON MISTAKES

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

REFERENCES

1. Coskun T et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept.. *Cell metabolism*, 2022. PMID 35985340 DOI 10.1016/j.cmet.2022.07.013 (Receptor activity, mouse intake and energy-expenditure mechanisms, and single-dose human observations through day 43.)
2. Urva S et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial.. *Lancet (London, England)*, 2022. PMID

36354040 DOI 10.1016/S0140-6736(22)02033-5 (Approximately six-day half-life, dose-proportional exposure, fixed and escalating research regimens, and 12-week study duration.)

3. Jastreboff AM et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial.. *The New England journal of medicine*, 2023. PMID 37366315 DOI 10.1056/NEJMoa2301972 (Obesity trial population, weekly subcutaneous doses, starting-dose groups, weight outcomes, gastrointestinal tolerability and heart rate changes.)
4. Rosenstock J et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA.. *Lancet (London, England)*, 2023. PMID 37385280 DOI 10.1016/S0140-6736(23)01053-X (Diabetes regimens, active comparator design, HbA1c and weight changes, gastrointestinal event rates and absence of reported severe hypoglycaemia.)
5. Sanyal AJ et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial.. *Nature medicine*, 2024. PMID 38858523 DOI 10.1038/s41591-024-03018-2 (Liver substudy population, weekly subcutaneous doses, relative liver-fat changes and normalization rates at week 24.)
6. Bajaj HS et al. Efficacy and safety of retatrutide, a GIP, GLP-1, and glucagon receptor agonist, in people with type 2 diabetes and inadequate glycaemic control with diet and exercise (TRANSCEND-T2D-1): a double-blind, randomised, phase 3 trial.. *Lancet (London, England)*, 2026. PMID 42250575 DOI 10.1016/S0140-6736(26)00967-0 (Phase 3 diabetes population, maintenance targets, 40-week treatment-regimen estimand results and adverse-event discontinuations.)
7. Ma J et al. Comparison of the effects of Liraglutide, Tirzepatide, and Retatrutide on diabetic kidney disease in db/db mice.. *Endocrine*, 2025. PMID 39212900 DOI 10.1007/s12020-024-03998-8 (Ten-week mouse kidney study and preclinical metabolic findings. The retrieved abstract does not state the dosing interval.)
8. Urva S et al. The novel GIP, GLP-1 and glucagon receptor agonist retatrutide delays gastric emptying.. *Diabetes, obesity & metabolism*, 2023. PMID 37311727 DOI 10.1111/dom.15167 (Retatrutide-associated delayed gastric emptying.)
9. Coskun T et al. Effects of retatrutide on body composition in people with type 2 diabetes: a substudy of a phase 2, double-blind, parallel-group, placebo-controlled, randomised trial.. *The lancet. Diabetes & endocrinology*, 2025. PMID 40609566 DOI 10.1016/S2213-8587(25)00092-0 (DXA fat-mass reductions and the proportion of lean-mass loss relative to total weight loss. Does not establish strength preservation.)
10. Brown C et al. Retatrutide: Obesity drug opens to "compassionate use" in US after speculation Trump took it.. *BMJ (Clinical research ed.)*, 2026. PMID 42567543 DOI 10.1136/bmj-2026-100530 (News report concerning US compassionate access. Not an efficacy trial or marketing authorization.)
11. Branine N et al. Online-Sourced Retatrutide Complicating Impending Diabetic Ketoacidosis in a Patient With Type 1 Diabetes and Concurrent Shigella Gastroenteritis.. *Cureus*, 2026. PMID 42669023 DOI 10.7759/cureus.115260 (Confounded case involving an online-labelled product, gastrointestinal illness, ketonaemia, dehydration and acute kidney injury. Causation was not established.)
12. Drucker DJ et al. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity.. *Diabetes care*, 2024. PMID 38843460 DOI 10.2337/dci24-0003 (Class-level discussion of gastrointestinal motility, anaesthesia, pancreatic and biliary concerns, and interpretation of muscle-related outcomes.)

Cagrilintide

CagriSema (with semaglutide)

Long-acting amylin analog | Module 2 · Recomposition | Goals: Fat loss | Route: SC weekly

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

WHAT IT IS

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

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

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

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

MECHANISM

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

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

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

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

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

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

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

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

EVIDENCE · GRADE A

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

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

STACKING

+ Semaglutide

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

– Liraglutide

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

– Tirzepatide

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

– Retatrutide

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

SAFETY

COMMON EFFECTS

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

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

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

BUYING NOTES

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

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

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

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

COMMON MISTAKES

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

REFERENCES

1. Lau DCW et al. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial.. *Lancet (London, England)*, 2021. PMID 34798060 DOI 10.1016/S0140-6736(21)01751-7 (Randomized monotherapy evidence, 706 participants across all groups, 26-week weight outcomes, gastrointestinal events and escalation. Reported cagrilintide targets were 0.3 to 4.5 mg subcutaneously once weekly, PMID 34798060.)

2. Enebo LB et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial.. *Lancet (London, England)*, 2021. PMID 33894838 DOI 10.1016/S0140-6736(21)00845-X (Phase 1b combination study, half-life of 159 to 195 hours, peak concentration timing, dose-dependent exposure and semaglutide pharmacokinetics. Cagrilintide targets were 0.16 to 4.5 mg subcutaneously once weekly, PMID 33894838.)

3. Garvey WT et al. Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2025. PMID 40544433 DOI 10.1056/NEJMoa2502081 (REDEFINE 1, 3417 participants, component arms, 68-week treatment-policy weight outcomes and gastrointestinal adverse events. Combination targets were 2.4 mg of each component subcutaneously once weekly, PMID 40544433.)

4. Frias JP et al. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial.. *Lancet (London, England)*, 2023. PMID 37364590 DOI 10.1016/S0140-6736(23)01163-7 (Phase 2 component comparisons in 92 adults, 32-week weight and HbA1c outcomes, background medication and hypoglycemia observations. Each component's target was 2.4 mg subcutaneously once weekly, PMID 37364590.)

5. Kruse T et al. Development of Cagrilintide, a Long-Acting Amylin Analogue.. *Journal of medicinal chemistry*, 2021. PMID 34288673 DOI 10.1021/acs.jmedchem.1c00565 (Molecular development, stabilization and lipidation of a long-acting amylin analogue. Does not establish preparation or storage instructions for independently sourced material.)

6. Carvas AO et al. Cagrilintide lowers bodyweight through brain amylin receptors 1 and 3.. *EBioMedicine*, 2025. PMID 40609154 DOI 10.1016/j.ebiom.2025.105836 (RAMP1/3 knockout experiments and brainstem activation findings. The reported mouse experiment used cagrilintide 3 nmol/kg subcutaneously once daily for three weeks, PMID 40609154.)

7. Ludwig MQ et al. A cross-species atlas of the dorsal vagal complex reveals neural mediators of the effects of cagrilintide on energy balance.. *Nature metabolism*, 2026. PMID 42260119 DOI 10.1038/s42255-026-01539-3 (Cross-species brainstem cell mapping, acute and longer-term neuronal responses, and functional evidence involving Prlh in rats. Does not establish human dosing or fully independent neural circuits.)

8. Ahmed M et al. Efficacy and Safety of Cagrilintide and Cagrisema Versus Semaglutide as Anti-Obesity Medications: A Systematic Review, Meta-Analysis and Meta-Regression.. *Diabetes, obesity & metabolism*, 2026. PMID 41834765 DOI 10.1111/dom.70667 (Pooled weight comparisons, nausea and administration-site events, a serious-adverse-event association for monotherapy, and LDL cholesterol differences. The abstract does not establish causation for the serious-event imbalance.)

9. Cao J et al. Structural and dynamic features of cagrilintide binding to calcitonin and amylin receptors.. *Nature communications*, 2025. PMID 40204768 DOI 10.1038/s41467-025-58680-y (Structural characterization of cagrilintide at AMY1R, AMY2R, AMY3R and calcitonin receptors, including receptor-complex dynamics.)

10. Gu YM et al. Structural and mechanistic insights into dual activation of cagrilintide in amylin and calcitonin receptors.. *Acta pharmacologica Sinica*, 2026. PMID 40847076 DOI 10.1038/s41401-025-01635-2 (AMY1R and calcitonin receptor structures, Gs signaling and specific binding features. The PubMed issue publication year is 2026, following online publication in 2025.)

11. D'Ascanio AM et al. Cagrilintide: A Long-Acting Amylin Analog for the Treatment of Obesity.. *Cardiology in review*, 2024. PMID 36883831 DOI 10.1097/CRD.0000000000000513 (Review of amylin-related satiation mechanisms and combination rationale. The PubMed issue publication year is 2024, following online publication in 2023.)

12. Gabery S et al. Characterization of 0839 - A tool compound for pre-clinical mode-of-action studies of amylin analogues such as cagrilintide.. *Life sciences*, 2025. PMID 40628316 DOI 10.1016/j.lfs.2025.123845 (Direct cagrilintide and related-tool-compound comparisons in rodents, species-dependent responses, fat-mass findings and semaglutide combination effects. The two compounds are not identical.)

13. Larsen AT et al. Does receptor balance matter? - Comparing the efficacies of the dual amylin and calcitonin receptor agonists cagrilintide and KBP-336 on metabolic parameters in preclinical models.. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, 2022. PMID 36242844 DOI 10.1016/j.biopha.2022.113842 (Preclinical receptor-balance experiments and weight and glucose outcomes in obese and diabetic rat models. Does not establish clinical benefits from calcitonin receptor activation alone.)

14. Davies MJ et al. Cagrilintide-Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes.. *The New England journal of medicine*, 2025. PMID 40544432 DOI 10.1056/NEJMoa2502082 (REDEFINE 2, 1206 participants, 68-week treatment-policy weight outcomes and gastrointestinal adverse events in adults with type 2 diabetes.)

15. Yamauchi T et al. Efficacy and safety of co-administered cagrilintide and semaglutide versus semaglutide alone in adults with overweight or obesity with or without type 2 diabetes in Japan and Taiwan (REDEFINE 5): a multicentre, randomised, active-controlled, phase 3a trial.. *The lancet. Diabetes & endocrinology*, 2026. PMID 42009015 DOI 10.1016/S2213-8587(25)00402-4 (REDEFINE 5, 331 participants in Japan and Taiwan, 68-week combination-versus-semaglutide outcomes using the primary trial product estimand.)

16. Buse JB et al. Cagrilintide-semaglutide (CagriSema) versus semaglutide or cagrilintide in people with type 2 diabetes (REIMAGINE 2): a double-blind, randomised, controlled, phase 3 study.. *The lancet. Diabetes & endocrinology*, 2026. PMID 42251859 DOI 10.1016/S2213-8587(26)00125-7 (REIMAGINE 2, 2713 participants and a 152-person cagrilintide arm. Combination targets were 2.4 mg each or 1.0 mg each subcutaneously once weekly, PMID 42251859.)

17. Dutta D et al. Efficacy and Safety of Cagrilintide Alone and in Combination with Semaglutide (Cagrisema) as Anti-Obesity Medications: A Systematic Review and Meta-Analysis.. *Indian journal of endocrinology and metabolism*, 2024. PMID 39676787 DOI 10.4103/ijem.ijem_45_24 (Earlier pooled efficacy and tolerability comparisons, including lower vomiting with cagrilintide monotherapy than with GLP-1 comparators. Included trials overlap with other cited evidence.)

18. Gabe MBN et al. Cagrilintide is not associated with clinically relevant QTc prolongation: A thorough QT study in healthy participants.. *Diabetes, obesity & metabolism*, 2024. PMID 39279639 DOI 10.1111/dom.15951 (Randomized QT study in 105 healthy participants. Cagrilintide was escalated to 4.5 mg subcutaneously once weekly, without clinically relevant QTc prolongation, PMID 39279639.)

19. Nielsen MJF et al. Renal or Hepatic Impairment Does Not Affect Pharmacokinetics, Safety, or Tolerability of Subcutaneous Cagrilintide.. *Clinical pharmacokinetics*, 2026. PMID 42228334 DOI 10.1007/s40262-026-01654-0 (Small organ-impairment pharmacokinetic studies. Single subcutaneous administrations were 0.6 mg for the renal study and 0.9 mg for the hepatic study, PMID 42228334.)

20. Rosenstock J et al. Cagrilintide-semaglutide (CagriSema) as an add-on to basal insulin in adults with type 2 diabetes (REIMAGINE 3): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study.. *Lancet (London, England)*, 2026. PMID 42251856 DOI 10.1016/S0140-6736(26)01022-6 (REIMAGINE 3, 274 participants receiving basal insulin, 40-week glycemic and weight outcomes, and absence of reported severe hypoglycemia under trial conditions.)

Liraglutide

Victoza, Saxenda

GLP-1 receptor agonist | Module 2 · Recomposition | Goals: Fat loss | Route: SC daily

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

WHAT IT IS

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

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

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

MECHANISM

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

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

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

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

EVIDENCE · GRADE A

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Approved administration is subcutaneous, with the abdomen, thigh, and upper arm listed in US prescribing information. Labels describe site rotation. No approved oral or intranasal liraglutide formulation was identified in the labeling reviewed. Route-specific efficacy and exposure cannot be inferred from an unapproved preparation.

HALF-LIFE

Approximately 13 hours after subcutaneous administration (PMID 21923591; Saxenda and Victoza US prescribing information). Peak concentrations occur around 11 hours in the weight-management label and 8 to 12 hours in the diabetes label. Half-life does not determine an exact time when all effects end. Label restart rules address gastrointestinal tolerability, not a guaranteed clearance deadline.

TIMING

US labels describe daily administration independent of meals. For a missed dose, they specify resuming with the next scheduled dose, without an extra replacement dose. After more than three days since the last administration, the Saxenda label specifies restarting at 0.6 mg subcutaneously once daily, followed by escalation. This is label documentation, not an individualized restart plan.

CYCLE LENGTH

There is no validated bodybuilding cycle in the evidence reviewed. Weight-management studies examined sustained treatment, including 56 weeks in SCALE and one year in the maintenance trial. LEADER's median follow-up was 3.8 years. The adult Saxenda response checkpoint is week 16 after initiation. Continued treatment depends on indication, response, and tolerability. These studies do not establish a tapering schedule or guarantee maintenance after withdrawal.

TITRATION

The Saxenda US label describes 0.6, 1.2, 1.8, 2.4, then 3.0 mg subcutaneously once daily, with weekly increases. It permits approximately one additional week before escalation when an increase is poorly tolerated. For adults, lower doses are escalation steps, and inability to tolerate maintenance treatment is a discontinuation criterion. The Victoza US label describes 0.6 mg subcutaneously once daily for one week, then 1.2 mg once daily. If needed, its maximum is 1.8 mg subcutaneously once daily after at least one week at the preceding dose. These are separate indication-specific label schedules.

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

STACKING

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

– Semaglutide	The Saxenda US label does not recommend coadministration with another GLP-1 receptor agonist. Added efficacy and the size of any added toxicity are not established. STEP 8 compared separate treatments, not concurrent administration.
– Tirzepatide	Its GLP-1 receptor activity overlaps with liraglutide. No controlled evidence supporting this combination was verified. The label's restriction on concurrent GLP-1 receptor agonists applies; gastrointestinal effects are a potential overlapping concern.
– Retatrutide	Its GLP-1 receptor activity overlaps with liraglutide. No combination trial was verified, and efficacy or tolerability cannot be inferred from separate-agent studies.

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

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

BUYING NOTES

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

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

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

COMMON MISTAKES

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

REFERENCES

1. Pi-Sunyer X et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management.. *The New England journal of medicine*, 2015. PMID 26132939 DOI 10.1056/NEJMoa1411892 (SCALE population, subcutaneous daily trial regimen, 56-week efficacy, and adverse-event findings.)
2. Marso SP et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.. *The New England journal of medicine*, 2016. PMID 27295427 DOI 10.1056/NEJMoa1603827 (LEADER regimen, high-risk diabetes population, cardiovascular outcomes, follow-up duration, and pancreatitis findings.)
3. Lundgren JR et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined.. *The New England journal of medicine*, 2021. PMID 33951361 DOI 10.1056/NEJMoa2028198 (Maintenance trial regimen, structured exercise, weight and body-fat outcomes, and limits of between-group comparisons.)
4. Rubino DM et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial.. *JAMA*, 2022. PMID 35015037 DOI 10.1001/jama.2021.23619 (Separate-agent comparison, trial regimens, weight reduction, treatment discontinuation, and study completion.)
5. Secher A et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss.. *The Journal of clinical investigation*, 2014. PMID 25202980 DOI 10.1172/JCI75276 (Rodent brain uptake and neuronal mechanisms, with limits on extrapolation to human appetite regulation.)
6. Raun K et al. Liraglutide, a long-acting glucagon-like peptide-1 analog, reduces body weight and food intake in obese candy-fed rats, whereas a dipeptidyl peptidase-IV inhibitor, vildagliptin, does not.. *Diabetes*, 2007. PMID 17192459 DOI 10.2337/db06-0565 (Verified rat dose, subcutaneous route, twice-daily frequency, treatment duration, food intake, and body-composition outcomes.)
7. He L et al. Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials.. *JAMA internal medicine*, 2022. PMID 35344001 DOI 10.1001/jamainternmed.2022.0338 (Class-level relative risks for gallbladder or biliary disease across 76 randomized trials.)
8. Bjerre Knudsen L et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation.. *Endocrinology*, 2010. PMID 20203154 DOI 10.1210/en.2009-1272 (Rodent C-cell findings, species differences, and unresolved long-term human thyroid relevance.)
9. Sisson EM et al. Liraglutide: clinical pharmacology and considerations for therapy.. *Pharmacotherapy*, 2011. PMID 21923591 DOI 10.1592/phco.31.9.896 (Albumin binding, prolonged absorption, pharmacology, and approximately 13-hour elimination half-life.)
10. van Can J et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults.. *International journal of obesity (2005)*, 2014. PMID 23999198 DOI 10.1038/ijo.2013.162 (Human mechanistic regimens, appetite, energy intake, gastric emptying, and lack of increased energy expenditure.)
11. Sun F et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis.. *Diabetes research and clinical practice*, 2015. PMID 26358202 DOI 10.1016/j.diabres.2015.07.015 (Modest resting heart-rate increases with liraglutide in diabetes trials.)
12. Fujioka K et al. Early Weight Loss with Liraglutide 3.0 mg Predicts 1-Year Weight Loss and is Associated with Improvements in Clinical Markers.. *Obesity (Silver Spring, Md.)*, 2016. PMID 27804269 DOI 10.1002/oby.21629 (Predictive value of at least 4 percent weight loss at week 16 after initiation.)
13. Batsis JA et al. Effect of Incretin-Based and Nonpharmacologic Weight Loss on Body Composition : A Systematic Review.. *Annals of internal medicine*, 2026. PMID 41996180 DOI 10.7326/ANNALS-25-00478 (Heterogeneous body-composition outcomes across 35 studies and limitations of treating different muscle-related indices as equivalent.)
14. Rutledge C et al. Liraglutide Protects Against Diastolic Dysfunction and Improves Ventricular Protein Translation.. *Cardiovascular drugs and therapy*, 2024. PMID 37382868 DOI 10.1007/s10557-023-07482-9 (Cardiac and lean-muscle findings in an angiotensin II mouse model; journal publication year corrected from online-first year.)
15. La Vignera S et al. Incretin-Based Therapies in Sports: Pharmacological Mechanisms, Performance-Enhancing Potential, and Anti-Doping Implications-A Narrative Review.. *International journal of molecular sciences*, 2026. PMID 42511463 DOI 10.3390/ijms27146116 (Published 2026 account of incretin anti-doping status and uncertain human performance benefits; not an official WADA ruling.)
16. Alhalabi H et al. In vitro metabolic profiling of weight-loss-inducing amylin receptor agonists in the context of preventive doping research.. *Journal of pharmaceutical and biomedical analysis*, 2026. PMID 41702251 DOI 10.1016/j.jpba.2026.117418 (Background statement reporting semaglutide monitoring since 2024; does not establish liraglutide monitoring or prohibition.)

AOD-9604

hGH fragment 177-191 analog

Modified GH C-terminal fragment | Module 2 · Recomposition | Goals: Fat loss | Route: SC

WADA prohibited

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

WHAT IT IS

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

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

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

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

MECHANISM

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

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

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

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

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

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

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

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

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

EVIDENCE · GRADE C

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

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

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

CYCLE LENGTH

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

TITRATION

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

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

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

STACKING

+ CJC-1295

Proposed pairing, not demonstrated synergy. The rationale combines a GH-axis agent with a fragment intended to affect lipid metabolism through another pathway. No controlled human study establishing an incremental AOD-9604 benefit was identified. Lack of an IGF-1 rise with AOD-9604 alone cannot establish the endocrine profile of the combination. Mechanistic complementarity remains a hypothesis rather than an outcome.

+ Ipamorelin

Proposed pairing with no established human combination benefit. A GH secretagogue and a GH-derived fragment need not share the same target, but distinct targets do not establish compatible exposures or additive fat loss. No controlled combination data were identified that quantify body composition, glucose effects or longer-term safety. A dosing convention cannot supply those missing measurements.

+ BPC-157

Proposed tissue-repair pairing without a supporting human combination trial. The cited rabbit experiment tested AOD-9604 with hyaluronic acid, not BPC-157 (PMID 26275694). Its results cannot establish synergy between these peptides. Differences in injury model,

– HGH Fragment 176-191

Identity and duplication concern. Commercial fragment names overlap, but they do not prove chemical equivalence. Exact sequence, terminal chemistry, salt form and disulfide state require verification. If both preparations contain the same active peptide, coadministration duplicates exposure. If they differ, there is still no established complementary benefit. The analytical literature cannot authenticate a preparation from its label alone (PMID 25208511).

– IGF-1 LR3

No established combination benefit or safety profile. AOD-9604's lack of a significant IGF-1 increase in summarized trials does not neutralize another agent's pharmacology. An IGF-1 analogue introduces a separate growth-factor exposure requiring independent assessment. The AOD-9604 receptor experiments cannot justify a claim that the combination preserves the fragment's proposed metabolic separation (PMID 11673763).

– Tesamorelin

No controlled evidence establishes an AOD-9604 contribution to this combination. Evidence supporting another agent in a defined indication does not transfer to the added fragment. Concurrent exposure also complicates interpretation of laboratory changes, adverse effects and weight outcomes.

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

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

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

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

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

BUYING NOTES

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

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

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

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

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

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

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

COMMON MISTAKES

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

hydration and measurement variation without an appropriate comparison.

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

REFERENCES

1. Heffernan MA et al. Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment.. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 2001. PMID 11673763 DOI 10.1038/sj.ijo.0801740 (Direct AOD-9604 rodent metabolic experiments and in vitro GH receptor competition and proliferation assays. Does not establish human efficacy or comprehensive absence of growth-related risk.)
2. Heffernan M et al. The effects of human GH and its lipolytic fragment (AOD9604) on lipid metabolism following chronic treatment in obese mice and beta(3)-AR knock-out mice.. *Endocrinology*, 2001. PMID 11713213 DOI 10.1210/endo.142.12.8522 (Beta-3 receptor expression and knockout experiments. Supports indirect pathway involvement rather than demonstrated direct beta-3 receptor agonism.)
3. Ng FM et al. Molecular and cellular actions of a structural domain of human growth hormone (AOD9401) on lipid metabolism in Zucker fatty rats.. *Journal of molecular endocrinology*, 2000. PMID 11116208 DOI 10.1677/jme.0.0250287 (Related AOD9401 fragment research involving lipid enzymes, adipocyte size and weight gain. Retained with explicit separation from direct AOD-9604 evidence.)
4. Ng FM et al. Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone.. *Hormone research*, 2000. PMID 11146367 DOI 10.1159/000053183 (AOD-9604 at 500 mcg/kg orally once daily for 19 days in obese Zucker rats. Reports reduced weight gain and preserved insulin sensitivity in the experimental model.)
5. Kwon DR et al. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model.. *Annals of clinical and laboratory science*, 2015. PMID 26275694 (Rabbit osteoarthritis experiment using 0.25 mg AOD-9604 per knee intra-articularly weekly during post-induction weeks 4 through 7. The combination arm included 6 mg hyaluronic acid per knee on that schedule.)
6. Cox HD et al. Detection and in vitro metabolism of AOD9604.. *Drug testing and analysis*, 2015. PMID 25208511 DOI 10.1002/dta.1715 (Compound identity, analytical characterization and in vitro metabolism. Publication year follows PubMed's journal publication date rather than its earlier electronic publication date.)
7. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Secondary overview of unsuccessful obesity development and non-clinical practices. Reports 1 mg orally daily for 12 weeks and forum-derived subcutaneous daily totals. Its intravenous unit omission and current Category 2 claim were not adopted.)
8. Rahman OF et al. Therapeutic Peptides in Orthopaedics: Applications, Challenges, and Future Directions.. *Journal of the American Academy of Orthopaedic Surgeons. Global research & reviews*, 2026. PMID 41490200 DOI 10.5435/JAAOSGlobal-D-25-00236 (Narrative orthopaedic research context. Does not constitute a human AOD-9604 combination trial or establish clinical joint-repair efficacy.)
9. Wu Z et al. Antilipogenic action of synthetic C-terminal sequence 177-191 of human growth hormone.. *Biochemistry and molecular biology international*, 1993. PMID 8358331 (Related GH fragment inhibited lipogenesis without significantly increasing glycerol release in the reported rat adipose assay. Supports distinguishing lipogenesis from lipolysis.)
10. Wade JD et al. Effect of C-terminal chain shortening on the insulin-antagonistic activity of human growth hormone 177--191.. *Acta endocrinologica*, 1982. PMID 6751009 DOI 10.1530/acta.0.1010010 (Insulin-antagonistic activity of chemically modified GH fragments in rats. Does not show that ordinary AOD-9604 handling generates those derivatives.)
11. Orlovius AK et al. AOD-9604 does not influence the WADA hGH isoform immunoassay.. *Drug testing and analysis*, 2013. PMID 24124033 DOI 10.1002/dta.1557 (Analytical anti-doping context only. Does not determine current prohibited status, human efficacy or a permissible exposure pattern.)
12. Mazzarino M et al. Rapid and harmonized analytical workflow for the determination of peptidic and non-peptidic doping agents in dried and liquid blood matrices.. *The Analyst*, 2026. PMID 42328738 DOI 10.1039/d6an00455e (Matrix-dependent analytical stability, including AOD-9604 degradation in serum and plasma. Does not establish reconstitution instructions or a pharmaceutical beyond-use date.)
13. Ogru E et al. The conformational and biological analysis of a cyclic anti-obesity peptide from the C-terminal domain of human growth hormone.. *The journal of peptide research : official journal of the American Peptide Society*, 2000. PMID 11152298 DOI 10.1034/j.1399-3011.2000.00771.x (Structural characterization of a related 15-residue cyclic fragment. Does not test shaking, routine storage, or a complete AOD-9604 preparation protocol.)
14. Wilding J et al. AOD-9604 Metabolic.. *Current opinion in investigational drugs (London, England : 2000)*, 2004. PMID 15134286 (Historical development review describing early human research. FDA corroborates its study using 25, 50 or 100 mcg/kg intravenously at weekly study visits across four periods.)

HGH Fragment 176-191

Frag 176-191

GH C-terminal fragment | Module 2 · Recomposition | Goals: Fat loss | Route: SC | WADA prohibited

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

WHAT IT IS

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

MECHANISM

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

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

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

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

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

EVIDENCE · GRADE C

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

STACKING

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

– AOD-9604

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

– Semaglutide

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

– Tirzepatide

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

– Tesamorelin

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

	measurements have not been characterized for native Frag.
– CJC-1295	No validated combination regimen exists. Growth hormone axis stimulation complicates interpretation of metabolic symptoms, and native Frag cannot be assumed metabolically neutral.
– Ipamorelin	No demonstrated synergy or clinical interaction dataset supports this pairing. Receptor selectivity of one component does not establish the tolerability of combined exposure.
– GHRP-6	Appetite and endocrine effects create additional variables without an established combination benefit. The original claim of a predictable opposing effect was too categorical.
– IGF-1 LR3	No human combination evidence supports this pairing. Additional IGF-related activity introduces metabolic and proliferative uncertainty, without evidence that native Frag offsets those risks.

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

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

STORAGE

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

```
Concentration arithmetic can be explained without establishing an administration regimen.
Hypothetical laboratory example: 5 mg of verified peptide in a final solution volume of 2 mL equals
2.5 mg/mL, or 2500 mcg/mL. These numbers describe an illustrative concentration, not a studied
dose, administration route, or frequency.

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

BUYING NOTES

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

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

COMMON MISTAKES

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

REFERENCES

1. Ng FM et al. Hyperglycemic action of synthetic C-terminal fragments of human growth hormone.. *The American journal of physiology*, 1978. PMID 645904 DOI 10.1152/ajpendo.1978.234.5.E521 (Direct experiments including native hGH 176-191 in normal rats. Reports transient hyperglycaemia, increased insulin, and reduced insulin sensitivity. Does not establish human risk magnitude or fat loss efficacy.)
2. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Related-compound context: summarizes the AOD9604 human obesity programme, its unsuccessful primary endpoint, and published safety reporting. Its naming convention does not establish identity with native Frag, and current regulatory status requires the FDA source.)
3. Heffernan MA et al. Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment.. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 2001. PMID 11673763 DOI 10.1038/sj.ijo.0801740 (Related-compound context: AOD9604 mouse metabolism and laboratory growth hormone receptor assays. Does not establish receptor behavior or metabolic neutrality of native hGH 176-191 in humans.)
4. Heffernan M et al. The effects of human GH and its lipolytic fragment (AOD9604) on lipid metabolism following chronic treatment in obese mice and beta(3)-AR knock-out mice.. *Endocrinology*, 2001. PMID 11713213 DOI 10.1210/endo.142.12.8522 (Related-compound context: AOD9604 effects on beta3 receptor expression and differing acute and chronic responses in receptor-knockout mice. Does not identify a native Frag receptor.)
5. Ng FM et al. Molecular and cellular actions of a structural domain of human growth hormone (AOD9401) on lipid metabolism in Zucker fatty rats.. *Journal of molecular endocrinology*, 2000. PMID 11116208 DOI 10.1677/jme.0.0250287 (Identifies AOD9401 as hGH 177-191 and reports adipose enzyme and rat metabolic findings. Retained to distinguish this fifteen-residue peptide from native Frag and AOD9604.)
6. Ng FM et al. Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone.. *Hormone research*, 2000. PMID 11146367 DOI 10.1159/000053183 (Related AOD9604 study: 500 mcg/kg orally once daily for 19 days in obese Zucker rats. Reports reduced weight gain and preserved insulin sensitivity, not a native Frag or human regimen.)
7. Heffernan MA et al. Effects of oral administration of a synthetic fragment of human growth hormone on lipid metabolism.. *American journal of physiology. Endocrinology and metabolism*, 2000. PMID 10950816 DOI 10.1152/ajpendo.2000.279.3.E501 (Related AOD9401 study in obese mice and isolated rodent and human adipose tissue. Supports attribution correction and the distinction between human tissue experiments and clinical trials.)
8. Cox HD et al. Detection and in vitro metabolism of AOD9604.. *Drug testing and analysis*, 2015. PMID 25208511 DOI 10.1002/dta.1715 (Defines AOD9604 as hGH 177-191 with an additional N-terminal tyrosine. Reports laboratory metabolism, not a human elimination half-life for native Frag.)
9. Kwon DR et al. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model.. *Annals of clinical and laboratory science*, 2015. PMID 26275694 (Related AOD9604 rabbit study: 0.25 mg per treated knee, alone or with 6 mg hyaluronic acid, intra-articularly weekly during weeks 4 through 7 after collagenase. Does not establish native Frag or human joint repair.)
10. Habibullah MM et al. Human Growth Hormone Fragment 176-191 Peptide Enhances the Toxicity of Doxorubicin-Loaded Chitosan Nanoparticles Against MCF-7 Breast Cancer Cells.. *Drug design, development and therapy*, 2022. PMID 35783198 DOI 10.2147/DDDT.S367586 (Computational and cultured-cell study using material described as hGH fragment 176-191 in a nanoparticle formulation. Does not establish human anticancer efficacy, fat loss, or safety.)

CJC-1295

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

GHRH analog | Module 2 · Recomposition | Goals: Hypertrophy, Recovery, Sleep | Route: SC

WADA prohibited

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

WHAT IT IS

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

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

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

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

MECHANISM

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

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

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

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

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

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

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

EVIDENCE · GRADE B

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

STACKING

+ Ipamorelin

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

+ GHRP-2

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

+ BPC-157

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

+ Semaglutide

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

– Sermorelin

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

– Tesamorelin

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

– IGF-1 LR3

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

SAFETY

COMMON EFFECTS

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

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

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

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

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

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

BUYING NOTES

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

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

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

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

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

COMMON MISTAKES

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

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

REFERENCES

1. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Two small randomized human studies, subcutaneous administration, pharmacokinetics, prolonged GH and IGF-1 responses, selected reported dose levels and short-term tolerability. The publication year is 2006; electronic publication occurred in 2005. Does not establish athletic benefits or long-term safety.)
2. Ionescu M et al. Pulsatile secretion of growth hormone (GH) persists during continuous stimulation by CJC-1295, a long-acting GH-releasing hormone analog.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 17018654 DOI 10.1210/jc.2006-1702 (Single-administration human study showing preserved GH pulsatility and increased trough GH and IGF-1. Supports the study doses and sampling interval. The lack of a significant dose-group difference does not establish a plateau. IGF-1 changes did not correlate with measured GH secretion parameters.)
3. Jetté L et al. Human growth hormone-releasing factor (hGRF)1-29-albumin bioconjugates activate the GRF receptor on the anterior pituitary in rats: identification of CJC-1295 as a long-lasting GRF analog.. *Endocrinology*, 2005. PMID 15817669 DOI 10.1210/en.2004-1286 (Molecular design, albumin attachment, in vitro stability, GH secretion assays and prolonged activity in normal rats. Distinguishes plasma detection beyond 72 hours from the separately demonstrated albumin-associated signal. This was not a deficiency-restoration experiment.)
4. Alba M et al. Once-daily administration of CJC-1295, a long-acting growth hormone-releasing hormone (GHRH) analog, normalizes growth in the GHRH knockout mouse.. *American journal of physiology. Endocrinology and metabolism*, 2006. PMID 16822960 DOI 10.1152/ajpendo.00201.2006 (Per-animal dose, experimental intervals, growth and body composition findings, and pituitary changes in GHRH-knockout mice. FDA's review of this study clarifies the change from subcutaneous to intraperitoneal administration. Does not establish enhancement or tumor risk in humans.)
5. Henninge J et al. Identification of CJC-1295, a growth-hormone-releasing peptide, in an unknown pharmaceutical preparation.. *Drug testing and analysis*, 2010. PMID 21204297 DOI 10.1002/dta.233 (Analytical identification of a 29-amino-acid amidated peptide consistent with material marketed as CJC-1295, plus historical WADA S2 classification. Does not establish that this material was the albumin-binding clinical molecule or support universal detection claims.)
6. Tewari K et al. Peptide Supplements and Their Therapeutic Applications in Sports Medicine.. *The American journal of sports medicine*, 2026. PMID 42578445 DOI 10.1177/03635465261464420 (Scoping review including CJC-1295. Supports the predominance of animal research across the included literature and inadequate human evidence for musculoskeletal claims. Pooled findings and risks from other compounds are not CJC-1295-specific estimates.)
7. Jessup SK et al. Blockade of endogenous growth hormone-releasing hormone receptors dissociates nocturnal growth hormone secretion and slow-wave sleep.. *European journal of endocrinology*, 2004. PMID 15538933 DOI 10.1530/eje.0.1510561 (GHRH antagonist experiment separating GH suppression from measured slow-wave sleep. Provides indirect context for evaluating sleep claims. It did not test CJC-1295 and cannot determine its sleep effects.)
8. Villegas Meza AD et al. Injectable Peptides in Sports Medicine: A Structured Narrative Review of Evidence, Safety, and Antidoping Implications.. *JBJS reviews*, 2026. PMID 42160466 DOI 10.2106/JBJS.RVW.26.00027 (Investigational status of GH-axis secretagogues for sports medicine, uncertain safety, product quality concerns and antidoping implications. Its evidence classification and indication-specific conclusions should not be treated as universal approval determinations.)
9. Sackmann-Sala L et al. Activation of the GH/IGF-1 axis by CJC-1295, a long-acting GHRH analog, results in serum protein profile changes in normal adult subjects.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and*

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

Ipamorelin

Selective ghrelin receptor agonist (GHRP) | Module 2 · Recomposition | Goals: Hypertrophy, Recovery, Sleep | Route: SC | WADA prohibited

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

WHAT IT IS

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

MECHANISM

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

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

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

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

EVIDENCE · GRADE C

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

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

CYCLE LENGTH

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

TITRATION

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

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

STACKING

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

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No approved ipamorelin presentation or standardized vial strength was identified. A labeled mass is not independent confirmation of peptide content, salt composition or usable concentration. Salt, water content and assay conventions can affect how reported mass is interpreted.
SOLVENT	No approved reconstitution solvent or validated multidose preparation procedure was identified in the cited human studies. Sterile water and bacteriostatic water are not interchangeable evidence of formulation compatibility. A preservative does not establish peptide stability, remove endotoxin or make an unverified powder suitable for administration.
STORAGE	No formulation-specific post-reconstitution stability or beyond-use period was established by the references reviewed. Storage requirements depend on formulation, container, sterility assurance and validated stability data. Refrigeration or freezing does not independently establish suitability, and repeated freezing may affect peptide preparations. Visible cloudiness or particles indicate a problem, but a clear solution can still contain contaminants or degraded material.

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

BUYING NOTES

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

COMMON MISTAKES

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

REFERENCES

1. Raun K et al. Ipamorelin, the first selective growth hormone secretagogue. *European journal of endocrinology*. 1998. PMID 9849822 DOI 10.1530/eje.0.1390552 (Peptide sequence, antagonist pharmacology, rat pituitary activity and swine endocrine

selectivity. Prolactin remained unaffected with all tested secretagogues.)

2. Gobburu JV et al. Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers.. *Pharmaceutical research*, 1999. PMID 10496658 DOI 10.1023/a:1018955126402 (Single-dose intravenous human dose-ranging study, pharmacokinetics and acute GH response. Does not establish subcutaneous dosing or performance outcomes.)
3. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Randomized postoperative ileus trial, intravenous regimen, enrollment and analysis populations, overall adverse-event rates and nonsignificant efficacy comparisons.)
4. Johansen PB et al. Ipamorelin, a new growth-hormone-releasing peptide, induces longitudinal bone growth in rats.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 1999. PMID 10373343 DOI 10.1054/ghir.1999.9998 (Divided daily subcutaneous doses in female rats, longitudinal bone growth without increased total IGF-I and modestly reduced subsequent ipamorelin responsiveness.)
5. Andersen NB et al. The growth hormone secretagogue ipamorelin counteracts glucocorticoid-induced decrease in bone formation of adult rats.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2001. PMID 11735244 DOI 10.1054/ghir.2001.0239 (Three-month subcutaneous rat regimen, muscle tetanic tension and periosteal bone formation in a glucocorticoid model.)
6. Lall S et al. Growth hormone (GH)-independent stimulation of adiposity by GH secretagogues.. *Biochemical and biophysical research communications*, 2001. PMID 11162489 DOI 10.1006/bbrc.2000.4065 (Mouse evidence of increased adiposity independent of normal GH production, with food-intake and leptin findings.)
7. Tewari K et al. Peptide Supplements and Their Therapeutic Applications in Sports Medicine.. *The American journal of sports medicine*, 2026. PMID 42578445 DOI 10.1177/03635465261464420 (Scoping review including ipamorelin. The predominance of animal publications and limited human outcomes describe the review's combined peptide literature.)
8. Semenistaya E et al. Determination of growth hormone releasing peptides metabolites in human urine after nasal administration of GHRP-1, GHRP-2, GHRP-6, Hexarelin, and Ipamorelin.. *Drug testing and analysis*, 2015. PMID 25869809 DOI 10.1002/dta.1787 (Documents nasal ipamorelin exposure in one human volunteer during analytical research, contradicting the claim that all human exposure was intravenous.)
9. Johansen PB et al. Pharmacokinetic evaluation of ipamorelin and other peptidyl growth hormone secretagogues with emphasis on nasal absorption.. *Xenobiotica; the fate of foreign compounds in biological systems*, 1998. PMID 9879640 DOI 10.1080/004982598238976 (NNC 26-0161 alias and rat pharmacokinetics, including approximately 20 percent nasal bioavailability.)
10. Svensson J et al. The GH secretagogues ipamorelin and GH-releasing peptide-6 increase bone mineral content in adult female rats.. *The Journal of endocrinology*, 2000. PMID 10828840 DOI 10.1677/joe.0.1650569 (Continuous subcutaneous rat exposure for 12 weeks. Greater bone mineral content reflected larger bone dimensions without increased volumetric density.)
11. Frieboes RM et al. Growth hormone-releasing peptide-6 stimulates sleep, growth hormone, ACTH and cortisol release in normal man.. *Neuroendocrinology*, 1995. PMID 7617137 DOI 10.1159/000126883 (Human GHRP-6 sleep and hormone findings. Included as a clearly identified comparator, not evidence that ipamorelin improves sleep.)
12. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Broader review of GH-axis peptides, unvalidated self-administration practices, adverse-effect categories and uncertainty surrounding combinations.)
13. Sigalos JT et al. The Safety and Efficacy of Growth Hormone Secretagogues.. *Sexual medicine reviews*, 2018. PMID 28400207 DOI 10.1016/j.sxmr.2017.02.004 (Class-level feedback physiology, glucose and insulin-sensitivity concerns, and limitations of long-term cancer and mortality evidence.)
14. Krug O et al. Analysis of new growth promoting black market products.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2018. PMID 29864719 DOI 10.1016/j.ghir.2018.05.001 (Analytical identification of glycine-extended secretagogues, including Gly-Ipamorelin. Does not establish a general contamination or mislabeling prevalence.)

GHRP-2 (Pralmorelin)

Pralmorelin

Ghrelin receptor agonist | Module 2 · Recomposition | Goals: Hypertrophy | Route: SC

WADA prohibited

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

WHAT IT IS

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

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

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

MECHANISM

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

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

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

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

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

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

EVIDENCE · GRADE A

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

Pralmorelin is approved in Japan for diagnosis of GH deficiency. The adult diagnostic regimen is a single 100 mcg IV administration, also documented in the validation study (PMID 17609397). This approval does not cover chronic physique, performance, anti-aging or weight-management treatment. No FDA-approved therapeutic indication for GHRP-2 was identified. FDA specifically flags injectable and nasal compounded GHRP-2 for potential significant safety risks. Regulatory authorization, access and compounding rules are separate questions and vary by jurisdiction. [FDA compounding safety information](https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks).

WADA

Prohibited at all times, both in and out of competition, under S2.2.4, Growth Hormone Releasing Factors. GHRP-2, also named pralmorelin, is explicitly listed among GH-releasing peptides. Diagnostic approval does not remove anti-doping obligations. Analytical detection research exists, but detection timing does not define permission to use the substance (PMID 20552695). [WADA Prohibited List](https://www.wada-ama.org/en/prohibited-list).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Documented human routes include IV bolus for diagnostic testing, IV infusion for physiological experiments, SC infusion, SC bolus, intranasal administration and oral administration. The supporting records include PMID 17609397, PMID 10372723, PMID 15126555, PMID 11322505, PMID 9390009 and PMID 14513874. These routes have different absorption and exposure characteristics. Activity after oral or nasal administration does not make their doses interchangeable with IV or SC doses. Trial formulations also cannot be assumed equivalent to an unidentified research preparation.

HALF-LIFE

The Japanese pralmorelin hydrochloride diagnostic injection label reports a terminal elimination half-life of approximately 0.42 to 0.69 hours after IV administration in healthy men. This is approximately 25 to 41 minutes. It is distinct from GH peak timing and does not establish SC or intranasal kinetics. [Japanese diagnostic injection label, July 2025] (https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/200022_7223407D2023_1_01).

TIMING

The diagnostic validation used overnight fasting before testing (PMID 17609397). Historical GHRP research describes reduced GH responses under some glucose, fatty-acid and glucocorticoid conditions (PMID 9186261). Appetite experiments included meals during infusion, showing that fasting is not a universal feature of every research design (PMID 16861611). No controlled evidence identified here establishes bedtime or workout timing as superior for muscle outcomes. A timing rationale based on normal GH rhythms remains an extrapolation.

CYCLE LENGTH

Thirty days is the duration of a verified continuous SC infusion study in older adults, not the maximum documented adult exposure (PMID 15126555). A separate severe-anorexia case report describes one year of intranasal administration (PMID 26401470). Pediatric studies extended to 12 months orally and up to 24 months intranasally (PMID 14513874, PMID 9390009). Their longer duration does not validate repeated exposure in healthy adults. Non-clinical cycles of 8 to 12 weeks are conventions without demonstrated performance efficacy or an established safety boundary.

TITRATION

The cited studies used prespecified experimental doses rather than a validated symptom-guided escalation protocol. Continuous SC infusion at 0.1 versus 1 mcg/kg per hour for 270 minutes produced different appetite and GH responses (PMID 16861611). One acute comparison described a single 2 mcg/kg IV dose as maximally effective for GH in that experimental context (PMID 10195374). That wording does not establish a universal ceiling across routes, populations or exposure patterns. It also does not prove that every higher dose produces only adverse effects.

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

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

STACKING

+ CJC-1295

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

+ Sermorelin

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

+ Tesamorelin

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

– GHRP-6

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

– Hexarelin

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

– Semaglutide

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

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL	No universal research-vial strength or formulation is established. Package mass is a content claim, not evidence of identity, potency or sterility. The Japanese diagnostic formulation contains 100 mcg per vial according to its pralmorelin hydrochloride injection label. Its specifications cannot be transferred to another preparation.
SOLVENT	The Japanese pralmorelin hydrochloride diagnostic injection label specifies 10 mL of physiological saline for preparation immediately before administration. It does not validate bacteriostatic water, repeated vial entry or extended storage for unrelated research formulations.
STORAGE	The Japanese diagnostic label specifies storage at or below 10 C, avoiding freezing. No formulation-specific evidence reviewed here validates freezing research powders or keeping reconstituted research material for four weeks. A clear solution can still be contaminated or degraded. Appearance alone does not establish suitability, and preservative content does not substitute for validated stability and sterility data.

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

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

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

BUYING NOTES

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

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

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

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

COMMON MISTAKES

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

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

REFERENCES

1. Bowers CY et al. History to the discovery of ghrelin.. *Methods in enzymology*, 2012. PMID 22975043 DOI 10.1016/B978-0-12-381272-8.00001-5 (Historical development of growth hormone releasing peptides before the discovery of ghrelin.)
2. Chihara K et al. A simple diagnostic test using GH-releasing peptide-2 in adult GH deficiency.. *European journal of endocrinology*, 2007. PMID 17609397 DOI 10.1530/EJE-07-0066 (Diagnostic validation, assay-dependent interpretation and a single 100 mcg IV bolus after overnight fasting, as reported in PMID 17609397.)
3. McKee KK et al. Molecular analysis of rat pituitary and hypothalamic growth hormone secretagogue receptors.. *Molecular endocrinology (Baltimore, Md.)*, 1997. PMID 9092793 DOI 10.1210/mend.11.4.9908 (Rat receptor cloning, seven-transmembrane structure and pituitary and hypothalamic expression.)
4. Gondo RG et al. Growth hormone-releasing peptide-2 stimulates GH secretion in GH-deficient patients with mutated GH-releasing hormone receptor.. *The Journal of clinical endocrinology and metabolism*, 2001. PMID 11443201 DOI 10.1210/jcem.86.7.7694 (Residual GH responsiveness in GHRH-receptor deficiency and limitations on interpreting dependence on intact GHRH signaling.)
5. Van den Berghe G et al. The somatotropic axis in critical illness: effect of continuous growth hormone (GH)-releasing hormone and GH-releasing peptide-2 infusion.. *The Journal of clinical endocrinology and metabolism*, 1997. PMID 9024260 DOI 10.1210/jcem.82.2.3736 (Endocrine responses to GHRP-2 and GHRH in critical illness, including additional GH and IGF-I responses with their combination.)
6. Bowers CY et al. Sustained elevation of pulsatile growth hormone (GH) secretion and insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3), and IGFBP-5 concentrations during 30-day continuous subcutaneous infusion of GH-releasing peptide-2 in older men and women.. *The Journal of clinical endocrinology and metabolism*, 2004. PMID 15126555 DOI 10.1210/jc.2003-031799 (Thirty-day hormone responses, normal screening tests and separate GHRH combination experiments. Continuous SC exposure was 1 mcg/kg per hour for 30 days, reported in PMID 15126555.)
7. Ghigo E et al. Growth hormone-releasing peptides.. *European journal of endocrinology*, 1997. PMID 9186261 DOI 10.1530/eje.0.1360445 (Historical review of receptor distinction, proposed hypothalamic actions, routes, response modifiers and partial desensitization.)
8. Argente J et al. Growth hormone-releasing peptides: clinical and basic aspects.. *Hormone research*, 1996. PMID 8950613 DOI 10.1159/000185015 (GHRP-2 interaction with GHRH 1-29 NH2 and separately identified GHRP-6 experiments involving rat hypothalamic gene expression.)
9. Shah N et al. Tripartite neuroendocrine activation of the human growth hormone (GH) axis in women by continuous 24-hour GH-releasing peptide infusion: pulsatile, entropic, and nyctohemeral mechanisms.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 10372723 DOI 10.1210/jcem.84.6.5687 (Changes in GH burst mass, amplitude and basal secretion during continuous IV infusion at 1 mcg/kg per hour for 24 hours, reported in PMID 10372723.)
10. Arvat E et al. Effects of GHRP-2 and hexarelin, two synthetic GH-releasing peptides, on GH, prolactin, ACTH and cortisol levels in man. Comparison with the effects of GHRH, TRH and hCRH.. *Peptides*, 1997. PMID 9285939 DOI 10.1016/s0196-9781(97)00016-8 (Acute endocrine comparisons using single IV administrations of 1 or 2 mcg/kg, reported in PMID 9285939.)
11. Laferrère B et al. Obese subjects respond to the stimulatory effect of the ghrelin agonist growth hormone-releasing peptide-2 on food intake.. *Obesity (Silver Spring, Md.)*, 2006. PMID 16861611 DOI 10.1038/oby.2006.121 (Randomized appetite experiment using continuous SC infusion at 0.1 or 1 mcg/kg per hour for 270 minutes per condition, reported in PMID 16861611.)
12. Li G et al. Growth hormone releasing peptide-2, a ghrelin agonist, attenuates lipopolysaccharide-induced acute lung injury in rats.. *The Tohoku journal of experimental medicine*, 2010. PMID 20805679 DOI 10.1620/tjem.222.7 (Rat lung injury and NF-kappaB findings after a single 100 mcg/kg SC pretreatment administration, reported in PMID 20805679.)
13. Xu XB et al. GH-releasing peptides improve cardiac dysfunction and cachexia and suppress stress-related hormones and cardiomyocyte apoptosis in rats with heart failure.. *American journal of physiology. Heart and circulatory physiology*, 2005. PMID

15951341 DOI 10.1152/ajpheart.01042.2004 (Rat cardiac findings in a study including GHRP-2 at 100 mcg/kg SC twice daily for three weeks, reported in PMID 15951341.)

14. Kinoshita Y et al. The arginine and GHRP-2 tests as alternatives to the insulin tolerance test for the diagnosis of adult GH deficiency in Japanese patients: a comparison.. *Endocrine journal*, 2013. PMID 23079545 DOI 10.1507/endocrj.ej12-0230 (Diagnostic comparison in 71 patients, with GHRP-2 sensitivity of 81.3 percent and specificity of 94.5 percent under the study's criteria.)
15. Laferrère B et al. Growth hormone releasing peptide-2 (GHRP-2), like ghrelin, increases food intake in healthy men.. *The Journal of clinical endocrinology and metabolism*, 2005. PMID 15699539 DOI 10.1210/jc.2004-1719 (Increased food intake in seven men during continuous SC infusion at 1 mcg/kg per hour for 270 minutes, reported in PMID 15699539.)
16. Pihoker C et al. Treatment effects of intranasal growth hormone releasing peptide-2 in children with short stature.. *The Journal of endocrinology*, 1997. PMID 9390009 DOI 10.1677/joe.0.1550079 (Uncontrolled pediatric growth study using 5 to 15 mcg/kg intranasally twice daily initially, then three times daily, reported in PMID 9390009.)
17. Mericq V et al. Changes in appetite and body weight in response to long-term oral administration of the ghrelin agonist GHRP-2 in growth hormone deficient children.. *Journal of pediatric endocrinology & metabolism : JPEM*, 2003. PMID 14513874 DOI 10.1515/jpem.2003.16.7.981 (Appetite and BMI observations in ten children receiving 900 mcg/kg orally twice daily for 12 months, reported in PMID 14513874.)
18. Johansen PB et al. Pharmacokinetic evaluation of ipamorelin and other peptidyl growth hormone secretagogues with emphasis on nasal absorption.. *Xenobiotica; the fate of foreign compounds in biological systems*, 1998. PMID 9879640 DOI 10.1080/004982598238976 (Rat pharmacokinetics and nasal absorption. Does not establish human route-specific pharmacokinetics.)
19. Liu X et al. Regulation of ghrelin gene expression in stomach and feeding response to a ghrelin analogue in two strains of rats.. *Peptides*, 2004. PMID 15572207 DOI 10.1016/j.peptides.2004.08.020 (GHRP-2 feeding responses differed with rat strain, feeding state and preferred diet.)
20. Gupta D et al. β1-adrenergic receptors mediate plasma acyl-ghrelin elevation and depressive-like behavior induced by chronic psychosocial stress.. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 2019. PMID 30758330 DOI 10.1038/s41386-019-0334-7 (Chronic GHRP-2 did not improve depressive-like behavior in the mouse social-defeat experiment.)
21. Okano M et al. Determination of growth hormone secretagogue pralmorelin (GHRP-2) and its metabolite in human urine by liquid chromatography/electrospray ionization tandem mass spectrometry.. *Rapid communications in mass spectrometry : RCM*, 2010. PMID 20552695 DOI 10.1002/rcm.4619 (Analytical detection of pralmorelin and a metabolite in human urine. Current prohibition is supported separately by WADA.)
22. Bowers CY et al. Growth hormone/insulin-like growth factor-1 response to acute and chronic growth hormone-releasing peptide-2, growth hormone-releasing hormone 1-44NH2 and in combination in older men and women with decreased growth hormone secretion.. *Endocrine*, 2001. PMID 11322505 DOI 10.1385/ENDO:14:1:079 (Acute and repeated-exposure experiments in older adults, including a single 10 mcg/kg SC bolus reported in PMID 11322505.)
23. Arvat E et al. Tyr-Ala-Hexarelin, a synthetic octapeptide, possesses the same endocrine activities of Hexarelin and GHRP-2 in humans.. *Journal of endocrinological investigation*, 1999. PMID 10195374 DOI 10.1007/BF03350886 (Acute endocrine comparison describing a single 2 mcg/kg IV GHRP-2 dose as maximally effective in that context, reported in PMID 10195374.)
24. Haruta I et al. One-year intranasal application of growth hormone releasing peptide-2 improves body weight and hypoglycemia in a severely emaciated anorexia nervosa patient.. *Journal of cachexia, sarcopenia and muscle*, 2015. PMID 26401470 DOI 10.1002/jcsm.12028 (One-year adult intranasal case report with weight, appetite and reported strength improvements. Does not establish causality or efficacy in trained adults.)
25. Hu R et al. Effects of GHRP-2 and Cysteamine Administration on Growth Performance, Somatotropic Axis Hormone and Muscle Protein Deposition in Yaks (Bos grunniens) with Growth Retardation.. *PloS one*, 2016. PMID 26894743 DOI 10.1371/journal.pone.0149461 (Direct animal skeletal-muscle findings, including increased fiber diameter and area in growth-retarded yaks.)
26. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Contemporary review of evidence limitations, GH-axis adverse-effect concerns and uncertain composition and dosing in non-clinical exposure.)

GHRP-6

Ghrelin receptor agonist | Module 2 · Recomposition | Goals: Hypertrophy | Route: SC

WADA prohibited

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

WHAT IT IS

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

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

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

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

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

MECHANISM

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

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

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

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

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

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

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

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

EVIDENCE · GRADE C

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

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

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

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

STACKING

+ CJC-1295	Mechanistic rationale only. GHRP-6 and GHRH produced acute endocrine synergy in humans, but the cited study did not test CJC-1295 (PMID	**– GHRP-2**	Overlapping secretagogue mechanisms and untested combined exposure provide no demonstrated advantage. GHRP-2 can stimulate prolactin,

	2108187). GHRH antagonist data support interaction between the two signaling systems (PMID 9543138). They do not establish the magnitude, duration or clinical benefit of this specific combination. Its adverse effects cannot be calculated by adding the profiles of the individual compounds.
+ Sermorelin	Sermorelin belongs to the GHRH signaling pathway, making endocrine interaction plausible. However, the cited Bowers synergy experiment used GHRH-(1-44)-NH2, not a chronic sermorelin regimen (PMID 2108187). The diagnostic combination study likewise does not establish a training protocol (PMID 11030292). Claims of a more physiological pulse, lower total exposure or fewer adverse effects require direct comparative evidence.
+ Tesamorelin	Interaction is plausible through GHRH receptor stimulation, but no direct GHRP-6 plus tesamorelin fitness trial was identified. Evidence for GHRP-6 plus another GHRH preparation cannot establish this combination's effectiveness (PMID 2108187). Potentially greater growth hormone and IGF-1 exposure raises metabolic concerns. Neither those concerns nor possible benefits have been quantified for this pair.
	ACTH and cortisol in acute human experiments (PMID 9285939). That study did not test coadministration with GHRP-6. Claims that the combination doubles hormonal adverse effects or cannot increase growth hormone are unsupported. The practical limitation is absent combination evidence, not a proven arithmetic rule.
– Hexarelin	Hexarelin has overlapping endocrine effects, including prolactin, ACTH and cortisol responses (PMID 9285939). An overnight study also found reduced slow-wave sleep and increased endocrine secretion (PMID 15177700). Those are findings for hexarelin, not measured outcomes of a GHRP-6 combination. No established physique benefit offsets the uncertainty of combined exposure.
– IGF-1 LR3	No human evidence supporting this combination was identified. Direct IGF-1 receptor stimulation would add a different exposure to secretagogue-driven endocrine signaling. Potential hypoglycemic and growth-signaling effects require separate evaluation. Neither an unlimited response nor a quantified cancer risk has been demonstrated.

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

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

STORAGE

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

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

concentration calculator cannot verify the label claim, correct an unknown net-content assay, determine sterility or establish peptide stability. It also cannot convert intravenous pharmacology into subcutaneous pharmacology.

BUYING NOTES

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

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

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

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

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

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

COMMON MISTAKES

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

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

REFERENCES

1. Bowers CY et al. Growth hormone (GH)-releasing peptide stimulates GH release in normal men and acts synergistically with GH-releasing hormone.. *The Journal of clinical endocrinology and metabolism*, 1990. PMID 2108187 DOI 10.1210/jcem-70-4-975 (Acute intravenous endocrine dose response in 18 men, synergy with GHRH-(1-44)-NH2, and prolactin and cortisol responses. Does not establish muscle gain or chronic combination efficacy.)
2. Bowers CY et al. The growth hormone-releasing activity of a synthetic hexapeptide in normal men and short statured children after oral administration.. *The Journal of clinical endocrinology and metabolism*, 1992. PMID 1730807 DOI 10.1210/jcem.74.2.1730807 (Oral endocrine activity, route-specific hormone timing, comparison with intravenous activity, and an older immunoreactive peptide half-life estimate. The relative activity estimate is not universal absolute bioavailability.)
3. Cabrales A et al. Pharmacokinetic study of Growth Hormone-Releasing Peptide 6 (GHRP-6) in nine male healthy volunteers.. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 2013. PMID 23099431 DOI 10.1016/j.ejps.2012.10.006 (Single intravenous pharmacokinetic study, peptide sequence and molecular weight, distribution and elimination half-life estimates. Publication year follows PubMed pubdate, with online publication in 2012.)
4. Pandya N et al. Growth hormone (GH)-releasing peptide-6 requires endogenous hypothalamic GH-releasing hormone for maximal GH stimulation.. *The Journal of clinical endocrinology and metabolism*, 1998. PMID 9543138 DOI 10.1210/jcem.83.4.4711 (GHRH antagonist suppression of most, but not all, of the acute GHRP-6 growth hormone response in nine healthy men.)
5. Jaffe CA et al. Effects of a prolonged growth hormone (GH)-releasing peptide infusion on pulsatile GH secretion in normal men.. *The Journal of clinical endocrinology and metabolism*, 1993. PMID 7903313 DOI 10.1210/jcem.77.6.7903313 (A 34-hour infusion increased pulse amplitude and IGF-1 without changing pulse frequency. Response to an additional GHRP challenge decreased, qualifying claims about preserved responsiveness.)
6. Frieboes RM et al. Growth hormone-releasing peptide-6 stimulates sleep, growth hormone, ACTH and cortisol release in normal man.. *Neuroendocrinology*, 1995. PMID 7617137 DOI 10.1159/000126883 (Four intravenous administrations during an experimental night increased growth hormone, ACTH, cortisol and stage 2 sleep. Slow-wave sleep did not increase.)
7. Ghigo E et al. Growth hormone-releasing peptides.. *European journal of endocrinology*, 1997. PMID 9186261 DOI 10.1530/eje.0.1360445 (Historical class review of routes, hypothalamic and pituitary mechanisms, metabolic modulation, age-related responses, naloxone findings and partial desensitization. Class statements require compound-specific qualification.)
8. Semenistaya E et al. Determination of growth hormone releasing peptides metabolites in human urine after nasal administration of GHRP-1, GHRP-2, GHRP-6, Hexarelin, and Ipamorelin.. *Drug testing and analysis*, 2015. PMID 25869809 DOI 10.1002/dta.1787 (Analytical identification of growth hormone releasing peptides and metabolites in human urine. Retained solely for detectability, without clearance windows or testing-evasion guidance.)
9. Lengyel AM et al. Novel mechanisms of growth hormone regulation: growth hormone-releasing peptides and ghrelin.. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas*, 2006. PMID 16906274 DOI 10.1590/s0100-879x2006000800002 (Discovery of the ghrelin receptor pathway, interaction with GHRH, hypothalamic participation and intracellular signaling. Supports mechanism, not a fitness dosing protocol.)
10. Hayashi S et al. Intranasal administration of His-D-Trp-Ala-Trp-D-Phe-LysNH2 (growth hormone releasing peptide) increased plasma growth hormone and insulin-like growth factor-I levels in normal men.. *Endocrinologia japonica*, 1991. PMID 1915110 DOI 10.1507/endocrj1954.38.15 (Intranasal dose-related endocrine responses and increased IGF-1 after seven consecutive administrations in six men. Does not establish long-term treatment outcomes.)
11. Ghigo E et al. Growth hormone-releasing activity of growth hormone-releasing peptide-6 is maintained after short-term oral pretreatment with the hexapeptide in normal aging.. *European journal of endocrinology*, 1994. PMID 7952160 DOI 10.1530/eje.0.1310499 (Four days of repeated oral exposure in seven elderly women preserved growth hormone responsiveness without significantly increasing IGF-1.)
12. Cibrián D et al. Use of growth-hormone-releasing peptide-6 (GHRP-6) for the prevention of multiple organ failure. *Clinical science (London, England : 1979)*, 2006. PMID 16417467 DOI 10.1042/CS20050374 (Cell experiments and rat ischemia-reperfusion injury

findings, including intraperitoneal pretreatment and reductions in selected injury markers. Does not establish human organ protection.)

13. Wang L et al. Growth hormone releasing peptide-6 (GHRP-6) ameliorates acute lung injury and its subsequent evolvement to interstitial fibrosis.. *International immunopharmacology*, 2026. PMID 41534456 DOI 10.1016/j.intimp.2026.116204 (Mouse models of acute lung injury and subsequent fibrotic changes. Findings remain preclinical.)
14. Zhao X et al. Growth hormone-releasing peptide 6 (GHRP-6) hydrogel for acute kidney injury therapy via metabolic regulation.. *Journal of nanobiotechnology*, 2025. PMID 41327290 DOI 10.1186/s12951-025-03888-9 (A self-assembling GHRP-6 hydrogel in experimental kidney injury, tubular-cell metabolism and mTOR-P70 signaling. Formulation-specific preclinical findings.)
15. Yokota-Nakagi N et al. Estradiol Replacement Improves High-Fat Diet-Induced Obesity by Suppressing the Action of Ghrelin in Ovariectomized Rats.. *Nutrients*, 2020. PMID 32224927 DOI 10.3390/nu12040907 (GHRP-6 increased high-fat diet intake and arcuate nucleus activation in placebo-treated ovariectomized rats, with different responses after estradiol replacement.)
16. Popovic V et al. GH-releasing hormone and GH-releasing peptide-6 for diagnostic testing in GH-deficient adults.. *Lancet (London, England)*, 2000. PMID 11030292 DOI 10.1016/S0140-6736(00)02755-0 (Acute diagnostic testing in 125 patients and 125 healthy controls. Supports diagnostic investigation, not marketing approval or chronic recomposition treatment.)
17. Frieboes RM et al. Effects of growth hormone-releasing peptide-6 on the nocturnal secretion of GH, ACTH and cortisol and on the sleep EEG in man: role of routes of administration.. *Journal of neuroendocrinology*, 1999. PMID 10336729 DOI 10.1046/j.1365-2826.1999.00364.x (Different nocturnal endocrine and sleep responses across oral, intranasal and sublingual preparations. Demonstrates limitations of generalizing across routes and formulations.)
18. Arvat E et al. Effects of GHRP-2 and hexarelin, two synthetic GH-releasing peptides, on GH, prolactin, ACTH and cortisol levels in man. Comparison with the effects of GHRH, TRH and hCRH.. *Peptides*, 1997. PMID 9285939 DOI 10.1016/s0196-9781(97)00016-8 (Endocrine effects of GHRP-2 and hexarelin as related-compound context. Does not test either compound combined with GHRP-6.)
19. Frieboes RM et al. Hexarelin decreases slow-wave sleep and stimulates the secretion of GH, ACTH, cortisol and prolactin during sleep in healthy volunteers.. *Psychoneuroendocrinology*, 2004. PMID 15177700 DOI 10.1016/S0306-4530(03)00152-5 (Hexarelin-specific sleep and endocrine effects. Retained as qualified related-compound context, not evidence from a GHRP-6 combination trial.)
20. Nascif SO et al. Decreased ghrelin-induced GH release in thyrotoxicosis: comparison with GH-releasing peptide-6 (GHRP-6) and GHRH.. *Pituitary*, 2007. PMID 17410412 DOI 10.1007/s11102-007-0005-2 (Acute endocrine comparison in thyrotoxicosis and healthy controls. GHRP-6 did not increase glucose during this experiment, which does not exclude chronic metabolic effects.)
21. Sigalos JT et al. The Safety and Efficacy of Growth Hormone Secretagogues.. *Sexual medicine reviews*, 2018. PMID 28400207 DOI 10.1016/j.sxmr.2017.02.004 (Human secretagogue literature review identifying limited rigorous long-term evidence, glucose and insulin-sensitivity concerns, and unresolved cancer and mortality outcomes. Class findings are not automatically GHRP-6 findings.)

Hexarelin

Examorelin

Ghrelin receptor agonist | Module 2 · Recomposition | Goals: Hypertrophy | Route: SC

WADA prohibited

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

WHAT IT IS

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

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

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

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

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

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

MECHANISM

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

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

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

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

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

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

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

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

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

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

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

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

EVIDENCE · GRADE C

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

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

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

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

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

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

STACKING

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

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

SOLVENT

No validated hexarelin-specific clinical reconstitution solvent, preservative concentration or multidose procedure was established by the retrieved records. General practices used with other

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

STORAGE

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

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

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

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

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

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

BUYING NOTES

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

COMMON MISTAKES

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

REFERENCES

1. Imbimbo BP et al. Growth hormone-releasing activity of hexarelin in humans. A dose-response study.. *European journal of clinical pharmacology*, 1994. PMID 7957536 DOI 10.1007/BF00191964 (Human double-blind rising-dose pharmacology, placebo

placement, peak versus integrated growth hormone responses, modeled ED50 estimates and growth hormone response timing. The reported hormone half-life is not a measured hexarelin elimination half-life.)

2. Ghigo E et al. Growth hormone-releasing activity of hexarelin, a new synthetic hexapeptide, after intravenous, subcutaneous, intranasal, and oral administration in man.. *The Journal of clinical endocrinology and metabolism*, 1994. `PMID 8126144` `DOI 10.1210/jcem.78.3.8126144` (Human four-route pharmacology, documented experimental exposures, dose-related responses and biological bioavailability estimated from growth hormone release. Does not establish direct systemic peptide bioavailability or universal route equivalence.)

3. Massoud AF et al. Hexarelin-induced growth hormone, cortisol, and prolactin release: a dose-response study.. *The Journal of clinical endocrinology and metabolism*, 1996. `PMID 8954038` `DOI 10.1210/jcem.81.12.8954038` (Acute growth hormone, prolactin and cortisol dose-response relationships. Documents the specific low-exposure intravenous GHRH(1-29)-NH2 combination, including prolactin elevation and no measured cortisol rise under that condition.)

4. Rahim A et al. Growth hormone status during long-term hexarelin therapy.. *The Journal of clinical endocrinology and metabolism*, 1998. `PMID 9589671` `DOI 10.1210/jcem.83.5.4812` (Adult 16-week subcutaneous regimen, reversible attenuation of stimulated growth hormone release, unchanged IGF-1 and body-composition endpoints, and an increase in one bone formation marker. Does not establish a cycling recommendation.)

5. Rahim A et al. Does desensitization to hexarelin occur?. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 1998. `PMID 10990150` `DOI 10.1016/s1096-6374(98)80039-7` (Identifies 12 healthy elderly participants and reports the adult 16-week response attenuation and recovery. Related to the chronic-treatment findings, rather than an independent replication.)

6. Rahim A et al. The effect of chronic hexarelin administration on the pituitary-adrenal axis and prolactin.. *Clinical endocrinology*, 1999. `PMID 10341859` `DOI 10.1046/j.1365-2265.1999.00609.x` (Pituitary-adrenal and prolactin findings during the adult repeated-treatment regimen. No significant increase in urinary free cortisol or prolactin response area, with reduced cortisol response area during treatment.)

7. Maccario M et al. Impact of two or three daily subcutaneous injections of hexarelin, a synthetic growth hormone (GH) secretagogue, on 24-h GH, prolactin, adrenocorticotropin and cortisol secretion in humans.. *European journal of endocrinology*, 2002. `PMID 11888836` `DOI 10.1530/eje.0.1460310` (Six-man, 24-hour study comparing two and three daily subcutaneous administrations. Both increased growth hormone secretion similarly without changing IGF-1 or integrated prolactin, ACTH and cortisol secretion.)

8. Laron Z et al. Intranasal administration of the GHRP hexarelin accelerates growth in short children.. *Clinical endocrinology*, 1995. `PMID 8548949` `DOI 10.1111/j.1365-2265.1995.tb02929.x` (Eight-child intranasal treatment study lasting up to 8 months, with reported increases in IGF-1 and linear growth velocity.)

9. Klinger B et al. Desensitization from long-term intranasal treatment with hexarelin does not interfere with the biological effects of this growth hormone-releasing peptide in short children.. *European journal of endocrinology*, 1996. `PMID 8766941` `DOI 10.1530/eje.0.1340716` (Seven-child prospective report covering 6 to 10 months of intranasal treatment. Growth velocity increased despite attenuated growth hormone challenge responses. Does not validate an adult performance regimen.)

10. Sigalos JT et al. The Safety and Efficacy of Growth Hormone Secretagogues.. *Sexual medicine reviews*, 2018. `PMID 28400207` `DOI 10.1016/j.sxmr.2017.02.004` (Clinical secretagogue review providing context on pediatric hexarelin research, limited long-term evidence and unresolved glucose and long-term safety questions. Class findings are not treated as hexarelin-specific event rates.)

11. Arvat E et al. Arginine and growth hormone-releasing hormone restore the blunted growth hormone-releasing activity of hexarelin in elderly subjects.. *The Journal of clinical endocrinology and metabolism*, 1994. `PMID 7962341` `DOI 10.1210/jcem.79.5.7962341` (Age-related differences in hexarelin responses and potentiation by GHRH or arginine under specific acute experimental conditions. Supports population-dependent endocrine responses.)

12. Massoud AF et al. The effect of repeated administration of hexarelin, a growth hormone releasing peptide, and growth hormone releasing hormone on growth hormone responsivity.. *Clinical endocrinology*, 1996. `PMID 8762732` `DOI 10.1046/j.1365-2265.1996.722543.x` (Acute synergy with GHRH(1-29)-NH2 in six men, altered responses to repeat challenges and loss of statistically demonstrable synergy after repeated combined administration.)

13. Maghnie M et al. The growth hormone response to hexarelin in patients with different hypothalamic-pituitary abnormalities.. *The Journal of clinical endocrinology and metabolism*, 1998. `PMID 9814463` `DOI 10.1210/jcem.83.11.5242` (Growth hormone responses in patients with imaging-characterized hypothalamic-pituitary abnormalities, supporting the importance of residual anatomical and vascular connections.)

14. Maccario M et al. Metabolic modulation of the growth hormone-releasing activity of hexarelin in man.. *Metabolism: clinical and experimental*, 1995. `PMID 7854159` `DOI 10.1016/0026-0495(95)90300-3` (Oral glucose and lipid-heparin infusion reduced hexarelin-stimulated growth hormone in healthy men. These challenge experiments do not establish a meal-timing strategy for training outcomes.)

15. Arvat E et al. Modulation of growth hormone-releasing activity of hexarelin in man.. *Neuroendocrinology*, 1995. `PMID 7731498` `DOI 10.1159/000126827` (Human interactions with GHRH, somatostatin and neuroactive interventions. Somatostatin blunted the hexarelin response under the studied conditions.)

16. Massoud AF et al. Interaction of the growth hormone releasing peptide hexarelin with somatostatin.. *Clinical endocrinology*, 1997. `PMID 9425393` `DOI 10.1046/j.1365-2265.1997.3121128.x` (Somatostatin infusion and withdrawal studies, including inhibition of separate and combined secretagogue responses. Does not support complete escape from inhibitory control.)

17. Korbonits M et al. The growth hormone secretagogue hexarelin stimulates the hypothalamo-pituitary-adrenal axis via arginine vasopressin.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 10404825 DOI 10.1210/jcem.84.7.5811 (Human ACTH, cortisol, growth hormone and prolactin responses, a small appetite increase, and CRH-desmopressin interaction findings consistent with a possible vasopressin contribution.)

18. Massoud AF et al. Hexarelin induced growth hormone release is influenced by exogenous growth hormone.. *Clinical endocrinology*, 1995. PMID 8548947 DOI 10.1111/j.1365-2265.1995.tb02927.x (Reduced hexarelin-stimulated growth hormone response after recombinant growth hormone pretreatment in healthy men. Supports feedback sensitivity without establishing chronic combination outcomes.)

19. Ghigo E et al. Effects of recombinant human insulin-like growth factor I administration on growth hormone (GH) secretion, both spontaneous and stimulated by GH-releasing hormone or hexarelin, a peptidyl GH secretagogue, in humans.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 9920097 DOI 10.1210/jcem.84.1.5386 (Recombinant human IGF-1 feedback on stimulated growth hormone in eight women under fed experimental conditions. The compound studied was not IGF-1 LR3.)

20. Loche S et al. Acute administration of hexarelin stimulates GH secretion during day and night in normal men.. *Clinical endocrinology*, 1997. PMID 9156035 DOI 10.1046/j.1365-2265.1997.1240940.x (Morning-versus-sleep endocrine responses in eight men. Similar growth hormone peaks but greater integrated response during sleep, associated with slower hormone disappearance.)

21. Laron Z et al. Growth hormone releasing activity by intranasal administration of a synthetic hexapeptide (hexarelin).. *Clinical endocrinology*, 1994. PMID 7955465 DOI 10.1111/j.1365-2265.1994.tb02589.x (Intranasal and intravenous diagnostic testing in children with short stature and two growth hormone deficient adults. Provides route-specific hormone peak timing, not universal dose equivalence.)

22. Tolis G et al. Growth hormone release by the novel GH releasing peptide hexarelin in patients with homozygous beta-thalassemia.. *Journal of pediatric endocrinology & metabolism : JPEM*, 1997. PMID 9364340 DOI 10.1515/jpem.1997.10.1.35 (Documents investigation of growth hormone release in beta-thalassemia. Included to define the human research populations, not to establish adult training benefits.)

23. Popovic V et al. Absence of desensitization by hexarelin to subsequent GH releasing hormone-mediated GH secretion in patients with anorexia nervosa.. *Clinical endocrinology*, 1997. PMID 9231048 DOI 10.1046/j.1365-2265.1997.1650982.x (Documents an endocrine interaction study in anorexia nervosa. Population-specific findings should not be generalized into universal secretagogue adaptation rules.)

24. Gasperi M et al. Low dose hexarelin and growth hormone (GH)-releasing hormone as a diagnostic tool for the diagnosis of GH deficiency in adults: comparison with insulin-induced hypoglycemia test.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 10443652 DOI 10.1210/jcem.84.8.5904 (Adult diagnostic research comparing a hexarelin-GHRH challenge with insulin-induced hypoglycemia. Diagnostic performance is distinct from treatment efficacy.)

25. Bodart V et al. CD36 mediates the cardiovascular action of growth hormone-releasing peptides in the heart.. *Circulation research*, 2002. PMID 11988484 DOI 10.1161/01.res.0000016164.02525.b4 (Identification of CD36 as a cardiac hexarelin-binding protein and CD36-dependent increases in coronary perfusion pressure in isolated hearts. This is a preclinical vascular finding.)

26. Mao Y et al. The cardiovascular action of hexarelin.. *Journal of geriatric cardiology : JGC*, 2014. PMID 25278975 DOI 10.11909/j.issn.1671-5411.2014.03.007 (Review of GHSR-related and CD36-related cardiovascular mechanisms. Provides context for the largely experimental cardiovascular literature without establishing clinical efficacy.)

27. Locatelli V et al. Growth hormone-independent cardioprotective effects of hexarelin in the rat.. *Endocrinology*, 1999. PMID 10465272 DOI 10.1210/endo.140.9.6948 (Protection against experimental ischemia-reperfusion injury in hearts from hypophysectomized rats, supporting an effect independent of pituitary growth hormone release.)

28. De Gennaro-Colonna V et al. Endocrine, metabolic and cardioprotective effects of hexarelin in obese Zucker rats.. *The Journal of endocrinology*, 2000. PMID 10974647 DOI 10.1677/joe.0.1660529 (Rat subcutaneous exposure, cardiac findings, failure to improve somatotropic function in obese animals and increased glucose and insulin in the obese group.)

29. Mao Y et al. Hexarelin treatment in male ghrelin knockout mice after myocardial infarction.. *Endocrinology*, 2013. PMID 23861368 DOI 10.1210/en.2013-1291 (Mouse myocardial infarction research involving ghrelin knockout animals. Defines a preclinical cardiovascular model rather than human efficacy evidence.)

30. Mao Y et al. One dose of oral hexarelin protects chronic cardiac function after myocardial infarction.. *Peptides*, 2014. PMID 24747279 DOI 10.1016/j.peptides.2014.04.004 (Preclinical investigation of oral hexarelin after myocardial infarction. Does not validate oral treatment for human cardiovascular disease.)

31. McDonald H et al. Hexarelin targets neuroinflammatory pathways to preserve cardiac morphology and function in a mouse model of myocardial ischemia-reperfusion.. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, 2020. PMID 32403043 DOI 10.1016/j.biopha.2020.110165 (Mouse ischemia-reperfusion research examining cardiac morphology, function and neuroinflammatory pathways. Findings remain model-specific.)

32. Huang J et al. The Growth Hormone Secretagogue Hexarelin Protects Rat Cardiomyocytes From in vivo Ischemia/Reperfusion Injury Through Interleukin-1 Signaling Pathway.. *International heart journal*, 2017. PMID 28321024 DOI 10.1536/ihj.16-241 (Rat ischemia-reperfusion research involving interleukin-1 signaling. Supports the existence of experimental cardiac mechanisms, not a clinical protocol.)

33. Agbo E et al. Modulation of PTEN by hexarelin attenuates coronary artery ligation-induced heart failure in rats.. *Turkish journal of medical sciences*, 2019. PMID 31091855 DOI 10.3906/sag-1812-49 (Rat coronary-ligation heart failure research involving PTEN modulation. Does not establish efficacy or safety in human heart failure.)

34. Pang J et al. Hexarelin suppresses high lipid diet and vitamin D3-induced atherosclerosis in the rat.. *Peptides*, 2010. PMID 19931584 DOI 10.1016/j.peptides.2009.11.007 (Experimentally induced rat atherosclerosis model. Defines preclinical vascular evidence rather than cardiovascular prevention in humans.)

35. Jiang B et al. Hexarelin attenuates abdominal aortic aneurysm formation by inhibiting SMC phenotype switch and inflammasome activation.. *Microvascular research*, 2022. PMID 34856183 DOI 10.1016/j.mvr.2021.104280 (Preclinical abdominal aortic aneurysm research involving smooth muscle phenotype and inflammasome pathways. The PubMed publication year is 2022 despite the 2021 DOI component.)

36. Mosa R et al. Hexarelin, a Growth Hormone Secretagogue, Improves Lipid Metabolic Aberrations in Nonobese Insulin-Resistant Male MKR Mice.. *Endocrinology*, 2017. PMID 28977588 DOI 10.1210/en.2017-00168 (Intraperitoneal treatment in MKR mice, with reported improvements in metabolic tolerance, triglycerides and body composition.)

37. Demers A et al. Hexarelin Signaling to PPARgamma in Metabolic Diseases.. *PPAR research*, 2008. PMID 18288286 DOI 10.1155/2008/364784 (Mechanistic review of hexarelin-related metabolic signaling and PPARgamma. Supports proposed pathways, not established adult recomposition outcomes.)

38. Cella SG et al. Sixteen weeks of hexarelin therapy in aged dogs: effects on the somatotropic axis, muscle morphology, and bone metabolism.. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 1996. PMID 8914494 DOI 10.1093/gerona/51a.6.b439 (Aged-dog treatment and interruption periods, changing endocrine responsiveness and improvement in selected muscle indices in three of six animals. Does not validate human cycling.)

39. Rigamonti AE et al. Six-week treatment with hexarelin in young dogs: evaluation of the GH responsiveness to acute hexarelin or GHRH administration, and of the orexigenic effect of hexarelin.. *European journal of endocrinology*, 1999. PMID 10474131 DOI 10.1530/eje.0.1410313 (Verified repeated subcutaneous dog exposure, changing growth hormone responsiveness and a different time course for appetite effects.)

40. Torsello A et al. Hexarelin stimulation of growth hormone release and mRNA levels in an infant and adult rat model of impaired GHRH function.. *Neuroendocrinology*, 1997. PMID 9067986 DOI 10.1159/000127168 (Age-dependent rat endocrine responses, including suppressed challenge responses after repeated exposure in young-adult animals. Does not establish uniform adaptation across ages.)

41. Pierno S et al. Growth hormone secretagogues modulate the electrical and contractile properties of rat skeletal muscle through a ghrelin-specific receptor.. *British journal of pharmacology*, 2003. PMID 12788817 DOI 10.1038/sj.bjp.0705284 (Direct skeletal muscle mechanistic research and failure of chronic secretagogue treatment to restore electrical and contractile properties in aged rats. Adds relevant non-hypertrophy muscle evidence.)

42. Agbo E et al. Hexarelin protects cardiac H9C2 cells from angiotensin II-induced hypertrophy via the regulation of autophagy.. *Die Pharmazie*, 2019. PMID 31526442 DOI 10.1691/ph.2019.9324 (Cultured cardiac-cell research on autophagy and hypertrophy. Classified as mechanistic cell evidence, not an animal or human outcome trial.)

43. Filigheddu N et al. Hexarelin protects H9c2 cardiomyocytes from doxorubicin-induced cell death.. *Endocrine*, 2001. PMID 11322493 DOI 10.1385/ENDO:14:1:113 (Cultured cardiomyocyte injury research. Does not establish prevention of chemotherapy-associated cardiotoxicity in patients.)

44. Brywe KG et al. Growth hormone-releasing peptide hexarelin reduces neonatal brain injury and alters Akt/glycogen synthase kinase-3beta phosphorylation.. *Endocrinology*, 2005. PMID 16081643 DOI 10.1210/en.2005-0389 (Neonatal rat brain-injury research and associated signaling findings. Provides animal evidence for that injury model, not adult cognitive benefit.)

45. Meanti R et al. Protective Effects of Hexarelin and JMV2894 in a Human Neuroblastoma Cell Line Expressing the SOD1-G93A Mutated Protein.. *International journal of molecular sciences*, 2023. PMID 36674509 DOI 10.3390/ijms24020993 (Human-derived cell-line research involving mutant SOD1. The word human describes the cell line and does not make this a human clinical study.)

46. Roumi M et al. Kinetics and disposition of hexarelin, a peptidic growth hormone secretagogue, in rats.. *Drug metabolism and disposition: the biological fate of chemicals*, 2000. PMID 10611139 (Rat peptide pharmacokinetics, terminal half-life, clearance, distribution and excretion. Does not establish human half-life or stability of a reconstituted preparation. No DOI was returned by PubMed esummary.)

47. Roumi M et al. Radioimmunoassay for hexarelin, a peptidic growth hormone secretagogue, and its pharmacokinetic studies.. *Peptides*, 1995. PMID 8545255 DOI 10.1016/0196-9781(95)02022-o (Dog pharmacokinetic measurements using a hexarelin radioimmunoassay, including an approximately 120-minute intravenous terminal half-life.)

48. Westberg C et al. Hexarelin--evaluation of factors influencing oral bioavailability and ways to improve absorption.. *The Journal of pharmacy and pharmacology*, 2001. PMID 11578108 DOI 10.1211/0022357011776540 (Experimental intestinal degradation, lysine deamidation and low permeability relevant to oral absorption. Does not provide a validated storage specification.)

49. Semenistaya E et al. Determination of growth hormone releasing peptides metabolites in human urine after nasal administration of GHRP-1, GHRP-2, GHRP-6, Hexarelin, and Ipamorelin.. *Drug testing and analysis*, 2015. PMID 25869809 DOI 10.1002/dta.1787 (Analytical identification of peptide-related substances in human urine. Included only to establish detectability, without clearance intervals or testing-evasion guidance.)

Sermorelin

GRF 1-29, Geref

GHRH analog | Module 2 · Recomposition | Goals: Hypertrophy, Sleep | Route: SC | WADA prohibited

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

WHAT IT IS

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

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

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

MECHANISM

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

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

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

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

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

EVIDENCE · GRADE B

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

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

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

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

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

REGULATORY STATUS AND SPORT

STATUS

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

WADA

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

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

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

HALF-LIFE

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

TIMING

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

CYCLE LENGTH

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

TITRATION

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

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

STACKING

+ GHRP-6

An acute human experiment demonstrated synergistic GH release with GHRP-6 and GHRH(1-44)-NH2 (Bowers 1990, PMID 2108187). It did not test sermorelin. Different receptor pathways provide a mechanistic rationale for interaction, but an acute GH peak does not establish better physique outcomes. The study also observed prolactin and cortisol increases with the highest GHRP exposure. It does not validate chronic SC combination treatment.

+ GHRP-2

A review describes strong GH release with GHRP-2, but its explicitly described combination experiment used GHRP-1 with GHRH(1-44)-NH2 (Bowers 1993,

– CJC-1295

Both compounds engage GHRH-receptor signaling, and the retrieved evidence does not demonstrate a benefit from combining them. Longer exposure can complicate interpretation of GH and IGF-I responses. Receptor overlap does not prove that GH becomes continuously secreted or that every combination necessarily raises IGF-I. The concern is unvalidated overlapping exposure.

– Tesamorelin

Another GHRH-receptor agonist adds overlapping pharmacology. No comparative or combination trial establishing an advantage for sermorelin plus tesamorelin was identified. Benefits established for a different

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

SAFETY

COMMON EFFECTS

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

SERIOUS SIGNALS

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

CONTRAINDICATIONS

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

STOP RULES

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

RECONSTITUTION AND STORAGE

TYPICAL VIAL

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

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

SOLVENT

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

STORAGE

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

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

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

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

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

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

BUYING NOTES

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

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

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

Preblended preparations create additional uncertainty because each component requires its own identity and content assessment. They also make attribution of effects and adverse reactions more difficult. The narrative review identifies uncertainty in composition, dose, and combination practices as recurring problems in unregulated supply chains (Dominikowski 2026, PMID 42395176). An analytical certificate cannot substitute for evidence that the proposed clinical use works.

COMMON MISTAKES

- Treating historical pediatric approval as proof of adult hypertrophy. The relevant older-men study found no DEXA muscle or fat change (PMID 9005976).
- Reporting the Vittone results as three improved strength measures. Two strength measures improved, plus a separate endurance test, in an uncontrolled study (PMID 9005976).
- Treating modified GHRH analogs as identical to sermorelin. The norleucine-substituted and PEG-conjugated compounds have separate identities and evidence (PMIDs 9360512 and 16061831).
- Converting IV sleep-laboratory findings into a claim that bedtime SC sermorelin improves sleep. Preparation, route, timing, population, and outcome differ.
- Reading greater GH release as demonstrated muscle gain. Integrated GH, IGF-I, strength, and body composition are separate endpoints.
- Calling a study's statistically nonsignificant result proof of no biological effect. Small samples can miss effects, and statistical thresholds do not define individual dosing thresholds.
- Reading the non-clinical range as trial-derived dosing. The reported 200 to 500 mcg SC once nightly is commonly cited in non-clinical use; not validated in trials.
- Copying a measured volume between preparations. Delivered mass depends on concentration, while vial contents and final solution volume are different quantities.
- Assuming retained feedback guarantees protection from excessive growth signaling. Feedback influences responses but does not establish a clinical safety ceiling.
- Calling two GHRH agonists a proven synergy. Receptor overlap alone does not demonstrate a beneficial combination.
- Assuming the FDA withdrawal determination approved contemporary compounding practices or adult performance uses. Those conclusions do not follow from the notice.
- Ignoring sports rules because the peptide is short-lived or prescribed. Sermorelin remains explicitly prohibited under WADA S2.2.4.

REFERENCES

1. Corpas E et al. Growth hormone (GH)-releasing hormone-(1-29) twice daily reverses the decreased GH and insulin-like growth factor-I levels in old men.. *The Journal of clinical endocrinology and metabolism*, 1992. PMID 1379256 DOI 10.1210/jcem.75.2.1379256 (Small adult crossover study of GH and IGF-I responses. Does not demonstrate improved body composition.)
2. Vittone J et al. Effects of single nightly injections of growth hormone-releasing hormone (GHRH 1-29) in healthy elderly men.. *Metabolism: clinical and experimental*, 1997. PMID 9005976 DOI 10.1016/s0026-0495(97)90174-8 (Uncontrolled adult study with increased nocturnal GH, unchanged IGF-I and DEXA body composition, and limited functional findings.)
3. Thorner M et al. Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. Geref International Study Group.. *The Journal of clinical endocrinology and metabolism*, 1996. PMID 8772599 DOI 10.1210/jcem.81.3.8772599 (Open-label pediatric growth study. Distinguishes 110 enrolled children from 86 eligible for efficacy analysis.)
4. Prakash A et al. Sermorelin: a review of its use in the diagnosis and treatment of children with idiopathic growth hormone deficiency.. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 1999. PMID 18031173 DOI 10.2165/00063030-199912020-00007 (Historical diagnostic and pediatric treatment evidence, diagnostic limitations, and documented flushing and injection-site pain.)
5. Soule S et al. Incorporation of D-Ala2 in growth hormone-releasing hormone-(1-29)-NH2 increases the half-life and decreases metabolic clearance in normal men.. *The Journal of clinical endocrinology and metabolism*, 1994. PMID 7962295 DOI 10.1210/jcem.79.4.7962295 (Human IV pharmacokinetics, including a 4.3-minute disappearance half-time for the unmodified fragment.)
6. Kerkhofs M et al. Sleep-promoting effects of growth hormone-releasing hormone in normal men.. *The American journal of physiology*, 1993. PMID 8476038 DOI 10.1152/ajpendo.1993.264.4.E594 (Timing-dependent effects of IV GHRH on laboratory sleep. Does not validate SC sermorelin for sleep improvement.)
7. Bowers CY et al. Growth hormone (GH)-releasing peptide stimulates GH release in normal men and acts synergistically with GH-releasing hormone.. *The Journal of clinical endocrinology and metabolism*, 1990. PMID 2108187 DOI 10.1210/jcem-70-4-975 (Acute GHRP-6 interaction with GHRH(1-44)-NH2, not sermorelin. Includes cortisol, prolactin, and flushing observations.)
8. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Narrative synthesis of evidence limitations, class concerns, and uncertainty in non-clinical dosing and supply chains.)

9. Mayo KE et al. Regulation of the pituitary somatotroph cell by GHRH and its receptor.. *Recent progress in hormone research*, 2000. PMID 11036940 (GHRH receptor biology and regulation of pituitary somatotroph function.)

10. Wilton P et al. Pharmacokinetics of growth hormone-releasing hormone(1-29)-NH2 and stimulation of growth hormone secretion in healthy subjects after intravenous or intranasal administration.. *Acta paediatrica (Oslo, Norway : 1992). Supplement*, 1993. PMID 8329825 DOI 10.1111/j.1651-2227.1993.tb12827.x (Human IV and intranasal experiments, low intranasal bioavailability, and GH elevation lasting longer than circulating peptide exposure.)

11. Rafferty B et al. Growth hormone-releasing factor analogue (hGRF1-29NH2): immunoreactive-GRF plasma levels after intravenous and subcutaneous administration.. *The Journal of endocrinology*, 1985. PMID 2866222 DOI 10.1677/joe.0.107r005 (Rat pharmacokinetics and low SC systemic exposure. Does not establish a human bioavailability correction.)

12. Khorram O et al. Effects of [norleucine27]growth hormone-releasing hormone (GHRH) (1-29)-NH2 administration on the immune system of aging men and women.. *The Journal of clinical endocrinology and metabolism*, 1997. PMID 9360512 DOI 10.1210/jcem.82.11.4363 (Endocrine and immune laboratory responses to a modified GHRH analog, explicitly distinguished from sermorelin.)

13. Guldner J et al. Reduced efficacy of growth hormone-releasing hormone in modulating sleep endocrine activity in the elderly.. *Neurobiology of aging*, 1997. PMID 9390775 DOI 10.1016/s0197-4580(97)00106-1 (Laboratory sleep responses to IV GHRH in seniors, with reduced efficacy compared with younger subjects.)

14. Antonijevic IA et al. Sexually dimorphic effects of GHRH on sleep-endocrine activity in patients with depression and normal controls - part I: the sleep eeg.. *Sleep research online : SRO*, 2000. PMID 11382894 (Different non-REM sleep responses in men and women. Does not establish efficacy for SC sermorelin.)

15. Neyzi O et al. Growth response to growth hormone-releasing hormone(1-29)-NH2 compared with growth hormone.. *Acta paediatrica (Oslo, Norway : 1992). Supplement*, 1993. PMID 8329826 DOI 10.1111/j.1651-2227.1993.tb12828.x (Randomized pediatric dose comparison using daily totals divided into three SC administrations.)

16. Rafferty B et al. Pharmacokinetic evaluation of superactive analogues of growth hormone-releasing factor (1-29)-amide.. *Peptides*, 1988. PMID 2896343 DOI 10.1016/0196-9781(88)90029-0 (Rat half-life and SC bioavailability estimates for the parent fragment and substituted analogs.)

17. Munafo A et al. Polyethylene glycol-conjugated growth hormone-releasing hormone is long acting and stimulates GH in healthy young and elderly subjects.. *European journal of endocrinology*, 2005. PMID 16061831 DOI 10.1530/eje.1.01965 (Adjacent evidence from a different, PEG-conjugated compound, including impaired glucose tolerance after repeated exposure in older participants.)

18. Bowers CY et al. GH releasing peptides--structure and kinetics.. *The Journal of pediatric endocrinology*, 1993. PMID 8374685 DOI 10.1515/jpem.1993.6.1.21 (GHRP pharmacology. The explicitly described combination experiment involved GHRP-1 and GHRH(1-44)-NH2, not sermorelin plus GHRP-2.)

Tesamorelin

Egrifta

GHRH analog | Module 2 · Recomposition | Goals: Fat loss, Hypertrophy | Route: SC daily

WADA prohibited

A stabilized GHRH analog approved to reduce excess abdominal fat in adults with HIV-associated lipodystrophy, with clinically important IGF-1 and glucose risks.

WHAT IT IS

Tesamorelin is a synthetic 44-amino-acid analog of human growth hormone-releasing hormone, GHRH. A trans-3-hexenoyl modification on its N-terminal tyrosine increases resistance to dipeptidyl peptidase-4 degradation. Preclinical studies demonstrated slower degradation and prolonged exposure compared with native GHRH, supporting its development as TH9507 (PMID 17214611).

Its approved indication is reduction of excess abdominal fat in adults with HIV-associated lipodystrophy. This is a specific clinical population, often receiving antiretroviral therapy. Approval does not establish efficacy for general weight management, athletic performance, muscle hypertrophy, cognitive enhancement, or longevity.

The original formulation and subsequent Egrifta SV and Egrifta WR formulations have different labeled doses, preparation requirements, and pharmacokinetics. Published trial doses must be interpreted alongside the formulation studied. A numerical dose from the historical trials cannot automatically be transferred to another presentation. Trials outside the approved indication provide preliminary evidence for selected metabolic and cognitive outcomes, with substantial limits on generalization.

MECHANISM

Established receptor action. Tesamorelin stimulates pituitary GHRH receptors, increasing endogenous GH secretion and subsequently circulating IGF-1. GHRH receptor signaling involves cAMP and calcium-dependent GH release. The drug acts through functioning pituitary somatotrophs, which explains why disruption of the hypothalamic-pituitary axis is a contraindication.

Endogenous regulation remains relevant, but it does not guarantee normal hormone concentrations. The pivotal trial reported an 81 percent IGF-1 increase (PMID 18057338). The cognition trial reported a 117 percent increase that remained within its physiological reference range (PMID 22869065). Those findings cannot establish a universal protective ceiling. Clinically excessive IGF-1 is a recognized reason to reassess treatment.

Established clinical effect, incompletely resolved tissue mechanism. GH promotes lipolysis and changes lipid handling. Tesamorelin consistently reduced visceral adipose tissue, or VAT, in HIV-associated lipodystrophy trials. The pooled phase 3 analysis found no significant change in abdominal subcutaneous adipose tissue (PMID 20554713). This supports preferential visceral effects in that population. It does not establish selective fat loss in every population or complete preservation of every other fat compartment.

Investigational liver effects. A trial in HIV-associated fatty liver disease found reduced hepatic fat after 12 months (PMID 31611038). An associated biopsy analysis identified increased oxidative phosphorylation gene expression and reduced expression of inflammation, tissue repair, and cell division pathways (PMID 32701508). These associations offer mechanistic hypotheses. They do not prove prevention of cirrhosis, liver cancer, or liver-related death.

Investigational brain effects. A 30-person substudy found increased brain GABA and other metabolite changes after 20 weeks (PMID 23689947). Neurochemical changes were not significantly associated with cognitive changes. The substudy and its parent trial represent overlapping participants, not independent replications.

Pharmacokinetic context. A population model estimated clearance near 1060 L/hour and distribution volume near 200 L (PMID 25358450). Plasma exposure is brief, while downstream endocrine effects last longer.

Clinical dosing frequency comes from studied regimens and formulation-specific labels, not from extrapolating plasma half-life alone.

EVIDENCE · GRADE A

Grade A applies to reduction of excess abdominal fat in adults with HIV-associated lipodystrophy, supported by approval and multiple randomized trials. The pooled phase 3 program included 806 participants and demonstrated sustained VAT reduction during continued treatment (PMID 20554713). Evidence for abdominal obesity without HIV, HIV-associated fatty liver disease, and cognitive outcomes is preliminary, grade B for those specific outcomes. Muscle imaging and lean-mass findings do not establish improved strength or training-induced hypertrophy. Evidence for athletic hypertrophy is grade C under this product's scale because available human findings are too indirect. No efficacy trial in healthy resistance-trained adults was identified in the targeted PubMed search.

Human data. Falutz 2007 randomized 412 adults with HIV-associated abdominal fat accumulation. VAT decreased 15.2 percent with tesamorelin and increased 5.0 percent with placebo over 26 weeks. Triglycerides decreased by 50 mg/dL in the treatment group. More treated participants withdrew because of adverse events, although overall adverse-event frequency did not differ significantly (PMID 18057338). Falutz 2010 pooled two phase 3 trials. The placebo-adjusted VAT effect was minus 15.4 percent at week 26. Continued treatment maintained a 17.5 percent reduction from original baseline at week 52. These percentages use different comparisons and should not be presented as interchangeable placebo-adjusted effects. Abdominal subcutaneous fat did not change significantly, and VAT returned toward baseline after withdrawal (PMID 20554713). Stanley 2014 randomized 50 participants. At six months, the VAT treatment effect was minus 42 cm2. The net liver lipid-to-water percentage effect was minus 2.9 percentage points. Fasting glucose showed an early placebo-adjusted increase of 7 mg/dL, without a significant between-group difference at six months (PMID 25038357). Stanley 2019 enrolled 61 adults with HIV and fatty liver disease. At 12 months, the hepatic fat treatment effect was minus 4.1 percentage points, corresponding to a 37 percent relative reduction. Liver fat fell below 5 percent in 35 percent of treated participants versus 4 percent receiving placebo. Histology findings remain preliminary (PMID 31611038). Makimura 2012 studied 60 abdominally obese adults without HIV who had reduced GH secretion. The VAT treatment effect was minus 35 cm2 over 12 months, with improvements in selected cardiovascular risk markers. This selected population does not represent all adults with obesity (PMID 23015655). Baker 2012 randomized 152 older adults, including participants with mild cognitive impairment. Executive-function results favored treatment after 20 weeks. Adverse events occurred in 68 percent versus 36 percent, and fasting insulin increased in the mild cognitive impairment subgroup (PMID 22869065). Clemmons 2017 studied 53 adults with type 2

Animal and mechanistic data. Ferdinandi 2007 reported GH and IGF-1 increases in pigs, rats, and dogs following repeat exposure. Doses up to 600 mcg/kg, administered IV or SC once daily, were reported across the nonclinical program (PMID 17214611). Toxicology studies lasted up to four months. Dogs developed reversible liver, kidney, hematologic, and organ-weight findings associated with sustained supraphysiological GH or IGF-1 exposure. These findings support biological activity and identify potential hazards; they do not define a human therapeutic margin. Jansen 2004 studied pulmonary delivery in dogs. Approximate single experimental doses were 375 mcg/kg by intratracheal dry powder insufflation and 38 mcg/kg SC (PMID 15113616). Estimated absolute pulmonary bioavailability was 13 percent. This experiment does not validate nasal sprays, oral preparations, or human inhalation. Animal doses cannot be transferred to humans by simple body-weight scaling.

diabetes for 12 weeks. Between-group differences in insulin response and final glycemic control were not significant. The study was too small and short to exclude diabetes-related harm (PMID 28617838). Adrian 2019 reported improved trunk muscle imaging measures in selected VAT responders. Excluding treatment nonresponders limits causal interpretation and generalizability (PMID 31237318). Two 2026 meta-analyses reported a lean-mass increase near 1.42 kg, which is not equivalent to contractile muscle gain (PMIDs 42538058 and 41545261). The discontinuation estimate in PMID 42538058 was imprecise and did not reach conventional statistical significance.

REGULATORY STATUS AND SPORT

STATUS

Tesamorelin received initial US approval in 2010 for excess abdominal fat in adults with HIV-associated lipodystrophy. It is not indicated for weight management, and long-term cardiovascular safety remains unestablished. Current formulation requirements are documented in the [Egrifta WR prescribing information](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022505s020lbl.pdf). The European application was withdrawn before authorization, as documented in the [EMA withdrawal record](https://www.ema.europa.eu/en/documents/press-release/ferrer-internacional-sa-withdraws-its-marketing-authorisation-application-egrifta-tesamorelin_en.pdf). Research-material labeling does not establish pharmaceutical quality or authorization for human treatment.

WADA

Prohibited at all times, both in and out of competition. The 2026 WADA Prohibited List explicitly names tesamorelin under S2.2.4, growth hormone releasing factors. A prescription alone is not a therapeutic use exemption. Use without an applicable exemption can constitute an anti-doping rule violation. Source: [2026 WADA Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf).

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

SC administration is the established human route in the cited trials. Approved labels specify abdominal administration. Intratracheal delivery appears only in the cited dog experiment (PMID 15113616). No validated oral or intranasal human regimen was identified. Poor expected peptide absorption is a pharmacological concern, not proof that every possible delivery technology is ineffective.

HALF-LIFE

Half-life is formulation-dependent. Label estimates in healthy subjects are approximately 8 minutes for Egrifta SV and 11 minutes for Egrifta WR. The population model in PMID 25358450 and dog estimates of 21 to 45 minutes in PMID 17214611 describe different datasets. Neither animal estimates nor a short human half-life establishes a rationale for additional daily administrations.

TIMING

The cognition trial specified administration 30 minutes before bedtime (PMID 22869065). That design does not establish bedtime as superior to morning administration. The approved labels specify daily administration without a universal clock time. Fasting and carbohydrate-avoidance schedules are commonly cited in non-clinical use; not validated in trials. Physiological effects of glucose on GH secretion do not establish a tested meal-timing protocol for tesamorelin.

CYCLE LENGTH

The cited studies include 12-week, 20-week, 26-week, and 12-month interventions, with longer extension phases in some programs. These durations reflect different study questions, not an established optimal cycle. The phase 3 withdrawal data demonstrate loss of VAT benefit after discontinuation (PMID 20554713). They do not establish the same rebound magnitude or timing for every individual. Eight- to 16-week physique cycles and intermittent schedules remain unvalidated.

TITRATION

There is no validated self-directed titration algorithm for physique goals. Labeled dosing is formulation-specific, as detailed above. Lower-dose research arms do not establish a universal starting dose or escalation sequence. IGF-1 changes, glucose status, adverse effects, and clinical benefit inform reassessment. An 8 percent VAT reduction defined responders in the exploratory muscle analysis (PMID 31237318); it is not a universal prescribing threshold. Waist measurements cannot reproduce a CT-defined response criterion.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Historical phase 3 formulation, HIV-associated excess abdominal fat	**2 mg SC once daily, as studied in PMIDs 18057338 and 20554713.**	SC	Once daily for 26 weeks, with a further 26-week extension in the pooled program.	Original-formulation randomized trials, PMIDs 18057338 and 20554713. This is a historical study dose, not a universal dose for current formulations. · PMID 20554713
Egrifta SV labeled treatment of excess abdominal fat in adults with HIV-associated lipodystrophy	**1.4 mg SC once daily, per the Egrifta SV prescribing information.**	SC, abdomen	Once daily	Egrifta SV prescribing information, dosage and administration section.
Egrifta WR labeled treatment of excess abdominal fat in adults with HIV-associated lipodystrophy	**1.28 mg SC once daily, per the Egrifta WR prescribing information.**	SC, abdomen	Once daily	Egrifta WR prescribing information, revised March 2025. Weekly vial preparation does not mean weekly administration.
Selected abdominally obese adults without HIV and with reduced GH secretion	**2 mg SC once daily, as studied in PMID 23015655.**	SC	Once daily for 12 months	Randomized placebo-controlled trial in 60 participants, PMID 23015655. · PMID 23015655
Older adults with normal cognition or mild cognitive impairment	**1 mg SC once daily, as studied in PMID 22869065.**	SC	Once daily, 30 minutes before bedtime, for 20 weeks	Randomized placebo-controlled trial, PMID 22869065. This was not the only human study investigating a lower dose. · PMID 22869065
Adults with type 2 diabetes, short-term metabolic study	**1 mg or 2 mg SC once daily in separate randomized groups, as studied in PMID 28617838.**	SC	Once daily for 12 weeks	Randomized placebo-controlled trial in 53 participants, PMID 28617838. Neither regimen is an approved diabetes treatment. · PMID 28617838
HIV-associated fatty liver disease	**2 mg SC once daily, as studied in PMID 31611038.**	SC	Once daily during a 12-month randomized phase, followed by a six-month open-label phase.	Randomized multicenter trial, PMID 31611038. Liver disease remains outside the approved indication. · PMID 31611038
Animal pharmacology and toxicology	**Up to 600 mcg/kg IV or SC once daily across the nonclinical program, PMID 17214611.**	IV or SC, depending on the experiment	Daily repeat administration; toxicology studies extended up to four months.	Nonclinical study program, PMID 17214611. The abstract does not assign every maximum dose to each species and duration. · PMID 17214611
Unvalidated physique protocols	**1 mg to 2 mg SC once daily, commonly cited in non-clinical use; not validated in trials.**	SC	Once daily in commonly cited nonclinical protocols, often described as eight to 16 weeks.	Commonly cited in non-clinical use; not validated in trials. PMID 42395176 discusses self-administration practices, not evidence establishing this schedule. · PMID 42395176

STACKING

+ Ipamorelin	Hypothesis only. GHRH and ghrelin-receptor agonism provide different inputs to GH secretion. No tesamorelin-ipamorelin combination trial was verified here. Larger GH	**– CJC-1295**	Overlapping GHRH-receptor stimulation without established combination benefit. Hormonal exposure and attribution of adverse effects become less predictable.

	responses would not establish better body composition or lower risk. Additive endocrine exposure could increase edema, dysglycemia, or excessive IGF-1.
+ GHRP-2	Hypothesis only. A second GH-release pathway could alter hormonal responses, but clinical benefit from this specific combination is unestablished. Cortisol and prolactin effects are additional concerns with GHRP-2. Findings from other GHRH-GHRP experiments cannot establish tesamorelin combination dosing, efficacy, or tolerability.
+ Semaglutide	Hypothesis only. The compounds affect body composition through different mechanisms. No combination trial establishing additive benefit was verified here. Glucose lowering cannot be assumed to cancel tesamorelin-related metabolic risk. Reported lean-mass changes do not establish protection against muscle loss during weight reduction.
– Sermorelin	Overlapping GHRH-receptor activity without verified clinical benefit from combining them. Differences in structure and exposure do not support a simple weaker-versus-stronger equivalence. Additional stimulation complicates interpretation of IGF-1 changes and adverse effects.
– IGF-1 LR3	Adds an unapproved IGF-1 analog to treatment that already raises endogenous IGF-1. Human combination efficacy and safety are unestablished. Glucose effects may be unpredictable, and mitogenic concerns remain unresolved. Endogenous feedback does not provide a proven safeguard.

SAFETY

COMMON EFFECTS

Reported effects include local injection reactions, arthralgia, myalgia, peripheral edema, paresthesia, and headache. The cognition trial reported more adverse events with treatment (PMID 22869065). The JAMA trial found an early glucose increase that was not sustained as a significant group difference at six months (PMID 25038357). This does not exclude individual glucose deterioration. Meta-analysis identified an imprecise increase in discontinuations, rather than a conclusively doubled risk (PMID 42538058).

SERIOUS SIGNALS

Clinically important signals include excessive IGF-1, diabetes, significant fluid retention, carpal tunnel symptoms, and hypersensitivity. Original-label trials reported diabetes-range HbA1c in 5 percent of treated participants versus 1 percent receiving placebo. Neoplasm warnings reflect GH and IGF-1 biology and uncertainty, not proof that treatment necessarily causes cancer. Source: [original Egrifta prescribing information](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022505s000lbl.pdf). Animal organ findings should not be described as established human toxicities (PMID 17214611).

CONTRAINDICATIONS

Label contraindications include disrupted hypothalamic-pituitary function, active malignancy, pregnancy, and hypersensitivity to tesamorelin or formulation excipients. Prior malignancy, diabetes or retinopathy, and acute critical illness require specific clinical assessment. Pediatric efficacy and safety are unestablished. Excipient lists differ by formulation; mannitol alone is not a complete allergy screen.

STOP RULES

Label-based reasons for discontinuation or reassessment include suspected hypersensitivity, recurrent malignancy, pregnancy, persistent IGF-1 above 3 standard deviation scores, and unfavorable glucose changes without clear benefit. Severe allergic symptoms warrant urgent medical assessment. Persistent edema, neuropathic symptoms, or absent benefit also warrant review. Decisions depend on severity and clinical context.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

Egrifta SV contains 2 mg per single-dose vial, per its prescribing information. Egrifta WR contains 11.6 mg per single-patient-use vial, per its prescribing information. These are vial strengths, not administered doses. The formulations are not substitutable. Unapproved vial strengths do not establish equivalent concentration, potency, bioavailability, or stability.

SOLVENT

Egrifta SV labeling specifies supplied Sterile Water for Injection and immediate use after preparation. Egrifta WR labeling specifies supplied Bacteriostatic Water for Injection. Preservative presence alone does not validate prolonged storage of another formulation. The relevant preparation source for SV is the [Egrifta SV prescribing information](https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=3d783378-b02d-4f19-99dd-0fc91a042224).

STORAGE

Egrifta SV labeling specifies room-temperature storage of the unmixed product and immediate use after reconstitution, with remaining solution discarded. Egrifta WR labeling specifies 20 to 25 C before and after preparation, protection from light, no freezing, and disposal seven days after mixing. No generic two- to four-week refrigerated shelf life is established for unapproved tesamorelin solutions. Clear appearance cannot establish sterility, potency, or freedom from degradation.

```
Label-based calculation only. Egrifta SV labeling specifies a 2 mg vial prepared with 0.5 mL diluent, producing 4 mg/mL. Its labeled dose of 1.4 mg SC once daily corresponds to 1.4 mg divided by 4 mg/mL, or 0.35 mL. Egrifta WR labeling states a final concentration of 8 mg/mL after preparation with 1.3 mL diluent. Its labeled dose of 1.28 mg SC once daily corresponds to 0.16 mL. These calculations describe approved presentations. They do not validate preparation of research material. The labeled final concentration takes precedence over a calculation using nominal vial strength alone.
```

BUYING NOTES

A research certificate of analysis does not establish pharmaceutical equivalence or fitness for human administration. Identity, chromatographic purity, peptide content, sterility, endotoxin contamination, stability, and chain of custody are separate questions. A high HPLC area percentage does not verify vial mass or exclude biologically important contaminants.

An interpretable analytical report identifies the tested batch, sampling and test dates, methods, laboratory, and underlying results. A matching molecular mass supports identity but cannot alone confirm the complete sequence or exclude all related impurities. A report for another batch provides no batch-specific evidence. Independent testing also depends on whether the tested sample represents the supplied material.

There is no universal HPLC threshold that transforms research material into an approved injectable medicine. Bacteriostatic diluent does not sterilize contaminated contents. Stability requires formulation-specific evidence, so claims about premixed material cannot be assessed from peptide size or appearance alone. The narrative review discusses these uncertainties in unregulated supply chains without validating their products (PMID 42395176).

COMMON MISTAKES

- Treating visceral fat reduction as equivalent to general weight loss. The strongest evidence concerns a specific HIV-associated fat distribution disorder, and BMI often changed little.
- Claiming complete preservation of all nonvisceral fat. Abdominal subcutaneous fat generally did not change significantly, but one meta-analysis found a small limb-fat reduction (PMID 41545261).
- Assuming benefits persist after discontinuation. The phase 3 extension showed VAT returning toward baseline after treatment withdrawal (PMID 20554713).
- Equating endogenous GH release with guaranteed physiological IGF-1. Feedback remains relevant, but excessive IGF-1 can still occur.
- Interpreting stable average glucose as absence of diabetes risk. Small metabolic trials and pooled averages do not exclude clinically important events in susceptible individuals.
- Converting a short half-life into a more frequent schedule. The cited clinical regimens used daily administration, and formulation-specific exposure matters.
- Interchanging vial strength, historical study dose, and current labeled dose. These describe different quantities and presentations.
- Calling a lean-mass increase proven muscle hypertrophy. Lean mass includes water and nonmuscle tissue, while responder-selected imaging analyses do not establish strength gains.

- Treating the cognition substudy as independent replication of the parent trial. Participants overlapped, and neither study established dementia prevention (PMIDs 22869065 and 23689947).
- Assuming a prescription resolves anti-doping restrictions. Tesamorelin remains prohibited at all times unless an applicable therapeutic use exemption permits its use.

REFERENCES

1. Falutz J et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV.. *The New England journal of medicine*, 2007. PMID 18057338 DOI 10.1056/NEJMoa072375 (Pivotal randomized trial, visceral fat and lipid outcomes, IGF-1 response, and adverse-event withdrawals. Historical dose: 2 mg SC once daily for 26 weeks, PMID 18057338.)
2. Falutz J et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data.. *The Journal of clinical endocrinology and metabolism*, 2010. PMID 20554713 DOI 10.1210/jc.2010-0490 (Pooled phase 3 population, VAT treatment effects, continued-treatment durability, withdrawal findings, and subcutaneous fat outcomes.)
3. Stanley TL et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial.. *JAMA*, 2014. PMID 25038357 DOI 10.1001/jama.2014.8334 (Six-month VAT and liver-fat outcomes, including the early fasting-glucose increase and later group comparisons.)
4. Stanley TL et al. Effects of tesamorelin on non-alcoholic fatty liver disease in HIV: a randomised, double-blind, multicentre trial.. *The lancet. HIV*, 2019. PMID 31611038 DOI 10.1016/S2352-3018(19)30338-8 (HIV-associated fatty liver trial, hepatic fat outcomes, histology assessment, and randomized plus open-label study phases.)
5. Makimura H et al. Metabolic effects of a growth hormone-releasing factor in obese subjects with reduced growth hormone secretion: a randomized controlled trial.. *The Journal of clinical endocrinology and metabolism*, 2012. PMID 23015655 DOI 10.1210/jc.2012-2794 (Selected adults without HIV, VAT and cardiovascular risk-marker outcomes. Study dose: 2 mg SC once daily for 12 months, PMID 23015655.)
6. Baker LD et al. Effects of growth hormone–releasing hormone on cognitive function in adults with mild cognitive impairment and healthy older adults: results of a controlled trial.. *Archives of neurology*, 2012. PMID 22869065 DOI 10.1001/archneurol.2012.1970 (Cognitive, endocrine, body-composition, and adverse-event findings. Study dose: 1 mg SC once daily, 30 minutes before bedtime, for 20 weeks, PMID 22869065.)
7. Ferdinandi ES et al. Non-clinical pharmacology and safety evaluation of TH9507, a human growth hormone-releasing factor analogue.. *Basic & clinical pharmacology & toxicology*, 2007. PMID 17214611 DOI 10.1111/j.1742-7843.2007.00008.x (Structural modification, degradation resistance, animal GH and IGF-1 responses, toxicology, and dog elimination estimates.)
8. González-Sales M et al. Population pharmacokinetic analysis of tesamorelin in HIV-infected patients and healthy subjects.. *Clinical pharmacokinetics*, 2015. PMID 25358450 DOI 10.1007/s40262-014-0202-x (Population pharmacokinetic model, clearance, distribution volume, and covariate limitations.)
9. Fourman LT et al. Effects of tesamorelin on hepatic transcriptomic signatures in HIV-associated NAFLD.. *JCI insight*, 2020. PMID 32701508 DOI 10.1172/jci.insight.140134 (Exploratory paired-biopsy gene-expression findings from the HIV-associated fatty liver trial.)
10. Friedman SD et al. Growth hormone-releasing hormone effects on brain γ-aminobutyric acid levels in mild cognitive impairment and healthy aging.. *JAMA neurology*, 2013. PMID 23689947 DOI 10.1001/jamaneurol.2013.1425 (Thirty-participant neurochemical substudy, overlapping parent-trial participants, and absence of significant neurochemical-cognitive associations.)
11. Clemmons DR et al. Safety and metabolic effects of tesamorelin, a growth hormone-releasing factor analogue, in patients with type 2 diabetes: A randomized, placebo-controlled trial.. *PloS one*, 2017. PMID 28617838 DOI 10.1371/journal.pone.0179538 (Twelve-week diabetes study and lower-dose research arm. Study doses: 1 mg or 2 mg SC once daily in separate groups, PMID 28617838.)
12. Adrian S et al. The Growth Hormone Releasing Hormone Analogue, Tesamorelin, Decreases Muscle Fat and Increases Muscle Area in Adults with HIV.. *The Journal of frailty & aging*, 2019. PMID 31237318 DOI 10.14283/jfa.2018.45 (Exploratory trunk-muscle imaging analysis restricted to tesamorelin VAT responders; does not establish training performance or strength benefit.)
13. Ditta AM et al. Efficacy and Safety of Tesamorelin in People Living With HIV (PLWH) With Lipodystrophy: A Systematic Review and Meta-Analysis.. *Journal of the International Association of Providers of AIDS Care*, 2026. PMID 42538058 DOI 10.1177/23259582261475549 (Four-trial synthesis, body-composition outcomes, lean-mass estimate, and statistically imprecise discontinuation estimate.)
14. Badran AS et al. Body composition, hepatic fat, metabolic, and safety outcomes of Tesamorelin, a GHRH analogue, in HIV-associated lipodystrophy: A meta-analysis of randomized controlled trials.. *Obesity research & clinical practice*, 2026. PMID 41545261 DOI 10.1016/j.orcp.2026.01.002 (Five-trial synthesis, VAT and hepatic-fat outcomes, lean-mass increase, small limb-fat reduction, and nonsignificant subcutaneous-fat and BMI changes.)
15. Jansen M et al. Pulmonary delivery of TH9507, a growth hormone releasing factor analogue, in the dog.. *International journal of pharmaceutics*, 2004. PMID 15113616 DOI 10.1016/j.ijpharm.2004.02.012 (Experimental pulmonary delivery, relative and absolute bioavailability, and dog route-specific pharmacokinetics.)
16. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI

10.3389/fendo.2026.1822475 (Narrative assessment of self-administration practices, uncertain physique claims, endocrine risks, stacking, and unregulated product composition.)

IGF-1 LR3

Long R3 IGF-1

IGF-1 analog with reduced binding-protein affinity | Module 2 · Recomposition | Goals: Hypertrophy | Route: SC | WADA prohibited

---

An experimental IGF-1 analog with reduced binding-protein affinity. Animal activity is established; human muscle-building efficacy, dosing, and pharmacokinetics remain unestablished.

WHAT IT IS

IGF-1 LR3, also called Long R3 IGF-1 or Long Arg3 IGF-I, is an engineered analog of insulin-like growth factor 1. Native IGF-1 contains 70 amino acids. LR3 replaces glutamate with arginine at position 3 and adds a 13-residue N-terminal extension. The extension contains the first 11 residues of methionyl porcine growth hormone followed by Val-Asn. Francis and colleagues describe this construct in PMID 1378742. The resulting protein contains 83 amino acids. The modifications reduce its affinity for IGF-binding proteins, which regulate IGF availability, distribution, and clearance. They do not simply create a stronger version of native IGF-1 at every receptor or in every tissue. In the original cell experiments, enhanced biological potency depended substantially on the binding-protein environment. In cells without detectable secreted binding proteins, LR3 was less potent than native IGF-1. This distinction explains why a potency claim from cell culture cannot establish a clinical advantage. LR3 is used experimentally to investigate IGF signaling while reducing interference from binding proteins. Its research applications include cell proliferation, protein metabolism, tissue distribution, and disease models. These applications establish biological activity, not an approved therapeutic use or a human administration standard. The PubMed searches performed for this review did not identify a published human administration trial establishing LR3 efficacy, dose-response, or pharmacokinetics. Human-derived cells and human proteins appear in many search results, but experiments involving those materials are not human clinical trials. Published analytical work also documents LR3-related material in an injection vial, which establishes product availability rather than clinical validation.

MECHANISM

IGF-1 LR3 activates the type 1 IGF receptor, a receptor tyrosine kinase involved in growth, survival, and metabolism. Receptor activation engages intracellular pathways that include PI3K, Akt, and mTOR. In experimental muscle systems, these pathways regulate protein synthesis and the expression of genes associated with protein breakdown. Receptor activation is not specific to skeletal muscle, and pathway engagement does not establish a useful training outcome. Latres and colleagues examined native IGF-1 signaling rather than LR3 specifically. Their study found that both Akt/FOXO and Akt/mTOR signaling contributed to IGF-1-induced transcriptional changes. IGF-1 suppressed dexamethasone-associated expression of the atrophy-related ubiquitin ligases MuRF1 and MAFbx. The mTOR-dependent component was distinct from the FOXO component. These findings support the general anabolic and anti-catabolic mechanism discussed here, but they do not demonstrate LR3-induced hypertrophy in humans. The correct print publication year is 2005, although the article appeared electronically in 2004, PMID 15550386. The binding-protein interaction is central to understanding LR3. King and colleagues characterized the shorter Arg3-substituted analog and found poor binding to bovine IGFBP-2. Its binding to the type 1 receptor was slightly weaker than native IGF-1 in their assay. They attributed increased biological potency primarily to reduced binding-protein interaction, PMID 1311930. That study provides part of the engineering rationale, rather than characterization of every property of the full LR3 construct. Francis and colleagues subsequently studied the extended Long Arg3 molecule. It stimulated protein and DNA synthesis and inhibited protein breakdown in rat myoblast cultures. Its potency exceeded native IGF-1 in cell systems that secreted binding proteins. In chicken embryo fibroblasts without detectable secreted binding proteins, LR3 was less potent than native IGF-1. The same paper examined activity in a hepatoma system where IGFs acted through insulin receptors, PMID 1378742. These observations support context-dependent potency rather than universally stronger receptor activation. Reduced binding also changes disposition. In a radiotracer study, most circulating

LR3 was detected as free peptide, and it cleared faster than native IGF-1. Tissue distribution differed between the molecules and between pregnant and nonpregnant rats, PMID 7693845. Binding proteins therefore cannot be treated solely as obstacles to activity. They also contribute to the circulating reservoir and influence delivery to tissues. Reduced binding may increase availability in one compartment while reducing persistence or delivery in another. IGF signaling has insulin-like metabolic effects, making low blood glucose a plausible LR3 hazard. The evidence reviewed does not justify that exclusive explanation or a claim that every IGF preparation has an identical dose-limiting effect. LR3 lowered circulating glucose in tumour-bearing rats, while native recombinant IGF-1 has documented hypoglycemia in patients. These are related findings, with different molecules, populations, and levels of certainty. The training interpretation remains unproven. In one rat comparison, LR3 had greater potency for body weight, visceral organ weights, and feed efficiency. It was only approximately equipotent with native IGF-1 for reversing carcass muscle loss, PMID 8708565. Whole-body growth, nitrogen retention, muscle protein synthesis, and functional hypertrophy are different endpoints. None establishes preferential growth of a selected human muscle. The literature reviewed does not validate targeted muscle growth through injection location. Systemic distribution is documented, but local tissue exposure cannot be dismissed solely from the molecule's design.

EVIDENCE · GRADE C

Grade C for proposed muscle-building or performance use. Direct evidence includes cell experiments and animal studies, without identified clinical evidence establishing benefit in trained adults. The animal literature extends beyond short rat experiments from the 1990s. A later mouse study involved prolonged intranasal exposure, but it also does not validate a human training protocol. Mechanistic findings alone are grade D; direct animal findings support the overall grade C classification. Evidence for approved native recombinant IGF-1 belongs to that molecule and indication, and does not upgrade LR3.

Human data. No published human administration trial establishing LR3 efficacy, dose-response, or pharmacokinetics was identified in the PubMed searches performed for this review. Searches included compound-name variants, human and clinical terms, and clinical-trial or human indexing. Results included human-derived cell experiments, animal studies, analytical reports, and reviews. This is a search-based conclusion, not proof that no unpublished exposure or unindexed report exists. Native recombinant human IGF-1, mecasermin, provides relevant but indirect clinical context. Kemp's review describes increased growth velocity in children with severe IGF-1 deficiency or growth hormone insensitivity. It also discusses hypoglycemia and the influence of binding-protein concentrations on circulating half-life, PMID 19627167. Under this product's scale, an approved drug can qualify as grade A for its approved indication. That classification does not establish efficacy for healthy adults, bodybuilding, or an altered IGF-1 analog. Several differences prevent direct transfer. LR3 has a different amino-acid sequence and markedly different binding-protein interactions. The pediatric deficiency population has a different physiological baseline from adults with normal endogenous IGF-1. Treatment goals, exposure, formulation, and clinical monitoring also differ. Even a favorable result with native IGF-1 cannot supply a conversion factor for LR3 dosing. A published analytical report identified a His-tagged Long-R3-IGF-I protein in an injection vial, PMID 20675162. This was a chemical identification study, not a clinical case series establishing administered

Animal and mechanistic data. In streptozotocin-diabetic rats, LR3 and another low-binding-protein analog increased growth and nitrogen retention. They were approximately 2.5 to 3 times more potent than native IGF-1 for restoring growth. Increased muscle protein synthesis did not coincide with correction of all insulin-dependent abnormalities. Glucosuria and urinary N-tau-methylhistidine excretion were not reduced by the IGFs, PMID 7683875. The highest numerical dose highlighted in that abstract belongs to native IGF-1, so it is not presented as an LR3 dose here. In normal and dexamethasone-catabolic rats, a seven-day experiment compared subcutaneous continuous infusion with once- or twice-daily injection. Continuous infusion produced greater efficacy, particularly for anti-catabolic outcomes. LR3 retained greater potency for several growth measures after injection, despite faster clearance. However, it was only approximately equipotent with native IGF-1 for reversing carcass muscle loss, PMID 8708565. This supports a delivery-dependent animal effect, not a preferred human administration schedule. In rats bearing mammary adenocarcinomas, osmotic-pump infusion of IGFs reduced food intake, insulin, and circulating glucose. Host muscle protein accretion did not improve, and tumour growth increased, particularly with LR3. The same tumour cells did not show growth stimulation in the accompanying culture experiment, PMID 8053901. The discrepancy illustrates why isolated cell assays cannot exclude organism-level tumour effects. These were animals with established tumours; the study does not quantify cancer initiation or cancer incidence in humans. A

dose, efficacy, or adverse-event rates. It supports concern about molecular identity in available material. It does not show that all products contain the same alteration or permit an estimate of the frequency of such problems. There are no established LR3 reference ranges, treatment targets, or validated monitoring algorithms in the clinical evidence reviewed. A laboratory result concerning endogenous IGF-1 would not by itself establish LR3 exposure or tissue activity. Any interpretation would depend on the assay and its demonstrated ability to recognize the analog.

separate renal-ischaemia study found improved anabolic measures without improved renal recovery. LR3 worsened early renal functional outcomes and was associated with greater tubular epithelial calcification, PMID 8138750. This is a disease-model signal, not proof of a corresponding effect at an unknown human exposure. It nevertheless prevents describing LR3 as broadly organ-protective. Later work studied intranasal LR3 over seven months in male mice, including an Alzheimer's disease model. Some body-composition and cortical amyloid findings changed, but behavioral and memory outcomes were not preserved, PMID 39610283. This study was published in print in 2025. It does not establish cognitive benefit, long-term human tolerability, or efficacy in resistance-trained adults.

REGULATORY STATUS AND SPORT

STATUS

No FDA or EMA medicinal authorization for IGF-1 LR3 was identified in the sources reviewed. An approved native IGF-1 medicine does not authorize the structurally modified LR3 analog. A research-use designation also does not establish suitability for clinical administration. The United States Increlex label covers specified pediatric growth-failure indications involving severe primary IGF-1 deficiency or growth hormone gene deletion with neutralizing antibodies. The European indication is severe primary IGF-1 deficiency in children and adolescents. These are distinct regulatory statements concerning mecasermin. Sources: [United States prescribing information] (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d5b2b0e1-c523-468d-9a0b-4ae4e4a8dbce) and [European product information] (https://www.ema.europa.eu/en/documents/product-information/increlex-epar-product-information_en.pdf). Those conclusions require jurisdiction-specific authority and details about the material, intended use, and supply arrangement. The original blanket statements about every jurisdiction and every compounding situation exceeded the verification available. Laboratory availability, a chemical identifier, and a certificate of analysis are different from medicinal approval. None supplies an approved LR3 indication, clinical formulation, or human dosing standard.

WADA

Prohibited at all times, in competition and out of competition. The 2026 WADA Prohibited List explicitly includes IGF-1 and its analogues under S2.3, Growth Factors and Growth Factor Modulators. LR3 falls within that named analog category. Source: [2026 WADA Prohibited List] (https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). The classification concerns the substance, not whether a seller describes it as research material. A personal purpose such as recovery, physique change, or rehabilitation does not change its listed status. The historical review by Nicholls and Holt discusses IGF-1 in the context of hormone misuse in sport, PMID 27347885. It is background literature rather than the authority for the current list. No therapeutic authorization or exemption for LR3 is established here.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Subcutaneous continuous infusion through osmotic pumps and subcutaneous once- or twice-daily injection were compared in the rat study reported in PMID 8708565. Subcutaneous osmotic-pump administration also appears in the renal-ischaemia study, PMID 8138750. Intravenous radiotracer boluses were used to investigate clearance and distribution in rats, PMID 7693845. Intranasal administration was studied in mice, PMID 39610283. These routes address different experimental questions and cannot be treated as interchangeable. A tracer experiment does not establish therapeutic administration, and a mouse intranasal experiment does not demonstrate human intranasal bioavailability. Likewise, an osmotic pump creates an exposure pattern that differs from an intermittent injection. No human LR3 route has established clinical efficacy or dosing in the literature reviewed. The vial format alone does not establish an appropriate route.

HALF-LIFE

A numerical human plasma half-life for LR3 was not established by the literature reviewed. The often-repeated 20 to 30 hour figure should therefore not be presented as a measured human parameter. Molecular engineering alone cannot establish or definitively exclude a particular terminal half-life. Direct measurements, formulation, route, assay, and the sampled compartment matter. The relevant measured finding is faster plasma clearance than native IGF-1 in rats. Bastian and colleagues administered radiolabeled peptides intravenously and compared pregnant with

nonpregnant animals. Native IGF-1 disposition changed substantially with the binding-protein environment, while LR3 was predominantly detected as free peptide, PMID 7693845. Tomas and colleagues also describe more rapid LR3 clearance in their administration-comparison study, PMID 8708565. These findings undermine the assumption that reduced binding necessarily prolongs circulating exposure. Binding proteins can restrict immediate receptor access while also protecting a circulating reservoir. Removing that interaction can increase availability and clearance simultaneously. Neither effect supplies a human duration of action. Kemp's review describes shorter mecasermin half-life in patients with low IGFBP-3 and acid-labile subunit concentrations, PMID 19627167. That is useful physiological context, not an LR3 pharmacokinetic estimate. Plasma half-life, tissue residence, receptor signaling duration, and persistence of a biological response are separate measurements. None should be substituted for another when interpreting a proposed schedule.

TIMING

No human LR3 study identified an optimal relationship to training, meals, sleep, or time of day. The rat administration-comparison study found greater efficacy with continuous infusion than with the injection schedules tested, PMID 8708565. That finding establishes schedule dependence in that model. It does not establish a preferred human timing strategy or justify reproducing pump exposure outside research. Meal-associated administration belongs to the mecasermin clinical framework because of its hypoglycemic effects, PMID 19627167. It cannot establish that a meal neutralizes LR3 risk. Exercise, food intake, and additional glucose-active substances could affect the consequences of exposure, but their interaction with LR3 has not been clinically characterized. Timing claims should therefore remain separate from validated pharmacokinetics.

CYCLE LENGTH

Four- to six-week blocks are commonly cited in non-clinical use; not validated in trials. No human LR3 evidence reviewed establishes an effective cycle, recovery interval, or washout period. The proposed explanation involving predictable receptor downregulation is also unvalidated for these schedules. The cited growth and tumour experiments lasted approximately one week, PMIDs 8708565 and 8053901. The later intranasal mouse study lasted seven months, PMID 39610283. Neither duration identifies a human treatment window. A longer experiment also does not establish comprehensive long-term safety, particularly when its species, route, disease model, and endpoints differ. Duration needs to be interpreted alongside exposure and outcome. A short study can reveal an acute hazard without defining cumulative risk. A long disease-model study can miss outcomes that were not measured. There is no evidentiary basis here for calling a particular human cycle protective.

TITRATION

No validated human LR3 titration schedule was identified. The mecasermin label describes supervised adjustment for a different molecule, with glucose-related precautions. Its numerical schedule appears only in the labeled comparator entry above. A lower starting amount does not establish a validated LR3 escalation strategy. Neither normal glucose on one occasion nor absence of symptoms establishes acceptable exposure for other tissues. The reviewed animal studies cannot identify a human threshold for hypoglycemia, tumour promotion, fluid changes, or renal effects. Likewise, circulating endogenous IGF-1 is not a validated LR3 dose target. Interpreting such a measurement would require assay-specific information and clinical validation. The absence of an established titration method is a substantive evidence gap, rather than a reason to borrow one from another growth-axis compound.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved human comparator only: native recombinant IGF-1, mecasermin, for specified pediatric growth-failure indications. This is a different molecule and population from LR3 use in trained adults.	**The United States Increlex label reports 0.04 to 0.08 mg/kg per dose subcutaneously twice daily initially. After at least one week of tolerability, label increments are 0.04 mg/kg per dose, up to 0.12 mg/kg per dose subcutaneously twice daily.**	Subcutaneous, according to the United States Increlex prescribing information.	Twice daily, close to a meal or snack, according to the United States Increlex prescribing information.	United States Increlex prescribing information, sections 2.1 and 2.2. This label does not provide an LR3 starting dose, conversion ratio, or titration schedule.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Normal growing rats and dexamethasone-catabolic rats, studied for seven days. The experiment compared native IGF-1 with LR3 using different delivery patterns.	**PMID 8708565 reports 320 mcg/day in normal rats and 400 mcg/day in catabolic rats, delivered subcutaneously by continuous infusion or divided into once- or twice-daily injections.**	Subcutaneous osmotic-pump infusion or subcutaneous injection, PMID 8708565.	Continuous infusion, once-daily injection, or twice-daily injection for seven days, PMID 8708565.	Tomas FM and colleagues, The Journal of endocrinology, 1996, PMID 8708565. These are total daily rodent amounts, not amounts per injection or human-equivalent doses. · PMID 8708565
Rats with experimentally induced renal ischaemia. LR3 was evaluated for anabolic effects and recovery of renal function.	**PMID 8138750 reports LR3 at 1.5 mg/kg/day by continuous subcutaneous osmotic-pump infusion in the seven-day experiment and the separate three-day post-ischaemia experiment.**	Continuous subcutaneous osmotic-pump infusion, PMID 8138750.	Continuous delivery for seven days, or for three days after ischaemia in the separate acute experiment, PMID 8138750.	Martin AA and colleagues, The Journal of endocrinology, 1994, PMID 8138750. LR3 worsened early renal functional outcomes in this model. This is an experimental exposure, not a clinical dose. · PMID 8138750
Amounts circulated in non-clinical training discussions. Included as unvalidated claims, without an established population, dose-response relationship, or verified frequency of use.	**20 to 50 mcg/day subcutaneously once daily, and 50 to 100 mcg/day subcutaneously once daily: commonly cited in non-clinical use; not validated in trials.**	Subcutaneous, as described in non-clinical use; not established by human LR3 trials.	Once daily in the quoted non-clinical descriptions; not validated in trials.	commonly cited in non-clinical use; not validated in trials. The origins and prevalence of these ranges were not independently established. They are not recommendations or evidence-based exposure limits. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

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

– CJC-1295

No validated LR3 combination benefit is established in the evidence reviewed. Stimulating endogenous growth-axis activity while adding an IGF analog creates overlapping biological effects without a characterized exposure-response relationship. Possible metabolic and tissue-growth consequences remain hypotheses for this pair. Different points of action do not establish complementary clinical benefit.

– Ipamorelin

No clinically validated LR3 pairing is established here. Claims about selectivity or a cleaner hormone profile do not resolve the uncertainty introduced by concurrent IGF signaling. Combined exposure also complicates attribution of symptoms and laboratory changes. This is a precaution concerning an unstudied combination, not a documented

	contraindication based on interaction trials.
– Follistatin-344	Manipulating activin or myostatin biology alongside IGF signaling is a mechanistic proposal, not demonstrated human synergy. Distinct pathways can interact unpredictably, and separate anabolic mechanisms do not establish additive benefit, tissue specificity, or acceptable combined risk.
– BPC-157	The reviewed evidence establishes neither benefit nor compatibility for this pairing. An absence of a known shared receptor cannot establish an absence of interaction. Claims that BPC-157 protects the gut or connective tissue during LR3 exposure are not supported by combination data presented here. No protective effect is established.
– Semaglutide	A direct LR3 interaction study was not identified in the reviewed evidence. Reduced intake or gastrointestinal intolerance could plausibly complicate an exposure capable of lowering glucose. This is a risk inference, not proof that the pair causes severe hypoglycemia.
– Tirzepatide	Combined effects with LR3 have not been clinically characterized in the evidence reviewed. Changes in intake and glucose regulation create uncertainty, particularly during poor oral intake. No quantitative interaction estimate or comparison with semaglutide is justified here. This precaution does not establish that every exposed person will experience hypoglycemia.
– PEG-MGF	No validated benefit from pairing PEG-MGF with LR3 is established here. IGF-1 splice biology, proposed E-domain peptides, and modified experimental products are not interchangeable. Uncertain identity, mechanism, and exposure prevent a defensible claim of either redundancy or synergy.

SAFETY

COMMON EFFECTS

The frequency of adverse effects in humans exposed to LR3 is unknown. There is no clinical LR3 adverse-event table from which to identify common effects reliably. Hypoglycemia is a biologically

plausible concern, supported indirectly by native IGF-1 experience and directly by lowered glucose in tumour-bearing rats, PMIDs 19627167 and 8053901. Mecasermin clinical experience includes hypoglycemia, headache, injection-site changes, and lymphoid tissue enlargement. These are comparator-drug observations, not measured LR3 rates. Symptoms such as sweating, tremor, palpitations, hunger, or confusion can be consistent with hypoglycemia, but symptoms alone do not establish its cause. Product-related reactions form a separate uncertainty. A mislabeled protein, unexpected tag, contaminant, or unsuitable formulation can create risks that do not follow from the intended LR3 sequence. The analytical finding in PMID 20675162 illustrates an identity problem without estimating its prevalence.

SERIOUS SIGNALS

Direct LR3 animal signals include increased growth of an established tumour and failure to improve host muscle protein accretion, PMID 8053901. Another study found worse early renal recovery after ischaemia, PMID 8138750. These findings justify concern while leaving the magnitude and relevance of human risk unresolved. Mecasermin labeling documents severe hypoglycemia, anaphylaxis, intracranial hypertension, and complications of lymphoid enlargement. These provide indirect clinical warning signals, not proof of identical LR3 incidence. Source: [European mecasermin product information](https://www.ema.europa.eu/en/documents/product-information/increlex-epar-product-information_en.pdf). The tumour-bearing rat experiment does not prove that LR3 initiates cancer in healthy humans. Equally, absence of tumour-cell proliferation in one culture assay did not exclude accelerated tumour growth in the animal. The relevant distinction is between growth of an existing malignancy, development of a new malignancy, and the risk magnitude in a particular population. No human LR3 data reviewed establish a duration or exposure below which these concerns disappear. A short symptom-free period does not answer questions about cumulative tissue effects or formulation-related hazards.

CONTRAINDICATIONS

LR3 has no approved prescribing information defining formal contraindications. The following are precautionary concerns, based on related clinical evidence, direct animal findings, and uncharacterized human exposure. Active or suspected malignancy and a history of malignancy warrant particular concern because LR3 accelerated established tumour growth in rats, PMID 8053901. Renal disease or recent renal injury also warrants concern given the renal-ischaemia findings, PMID 8138750. Concurrent insulin or other glucose-lowering treatment raises potential interaction concerns, rather than establishing a studied LR3 contraindication. Pregnancy, breastfeeding, childhood, and adolescence lack an established LR3 benefit-risk basis. A prior severe reaction to the actual preparation or one of its components is an additional concern. A history of allergy to any recombinant protein is not automatically equivalent to allergy to every recombinant protein. Mecasermin is used for pediatric growth failure, while its label excludes growth promotion after epiphyseal closure. That distinction provides no pediatric or adult indication for LR3.

STOP RULES

After suspected exposure, confusion, seizure, loss of consciousness, collapse, or breathing difficulty warrants emergency assessment. Hives with facial or tongue swelling can indicate a serious allergic reaction. These are emergency signals regardless of whether LR3 is ultimately confirmed as the cause. Persistent severe headache, new visual disturbance, or repeated vomiting warrants prompt medical assessment. New sleep-related breathing pauses, marked swelling, or unexplained deterioration in kidney function also warrants evaluation. A new mass or unexplained weight loss requires investigation, without assuming that exposure caused cancer. An increasingly painful, red, hot, or swollen administration site, particularly with fever, requires assessment for infection or another local complication. These observations do not validate continued exposure when symptoms are absent. Clinical evaluation depends on the symptoms, timing, actual material, and concurrent substances.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

There is no approved LR3 vial strength, formulation, or clinical presentation. Package amounts vary, and the number printed on a container does not independently establish its contents. For unit interpretation only, a label stating 1 mg nominal peptide content represents 1000 mcg. This is a mass conversion, not a dose or evidence that the labeled amount is present. Total dry powder mass, net peptide content, chromatographic purity, and biological activity are different quantities. Excipients and residual moisture can contribute to powder mass. A purity percentage does not directly establish recoverable peptide mass or potency. The analytical report in PMID 20675162 also shows why the molecular identity must be distinguished from the general product name.

SOLVENT

No validated clinical reconstitution solvent for LR3 was established by the sources reviewed. A laboratory method may specify a particular solvent, pH, concentration, container, or carrier protein for a defined experiment. Those conditions do not automatically describe a formulation suitable for human administration. Bacteriostatic water is not a method for sterilizing contaminated powder. A preservative also does not establish protein stability, compatibility, or a validated period of repeated access. Conversely, an acidic solvent used for laboratory solubility does not become suitable for

administration because the protein dissolves in it. The original universal solvent advice has therefore been removed. A research formulation requires its own documented preparation and stability method. Solubility, visible clarity, sterility, endotoxin content, and retained biological activity require separate evidence. None can be inferred reliably from the others.

STORAGE

No universal storage temperature or post-reconstitution shelf life for clinically administered LR3 was established. Laboratory stability depends on formulation, concentration, container, processing, and the conditions tested. A recommendation for one research preparation cannot be transferred automatically to another preparation with a similar name. Chemical degradation, aggregation, loss of biological activity, and microbial contamination are different failure modes. Refrigeration or the presence of a preservative does not establish control of all four. A generic multidose-container convention is also not peptide-specific stability evidence. So have unsupported universal freezing and refrigeration instructions. A preparation's documented storage specification needs to identify the tested formulation, conditions, duration, and acceptance criteria. Cloudiness or particles can identify an obvious problem, but a clear solution can still have incorrect content, contamination, or reduced activity. Visual inspection therefore cannot establish suitability or extend an undocumented storage period.

```
Illustrative concentration arithmetic only, without an administration procedure: 1 mg equals 1000
mcg. If an analytical preparation contains a verified 1000 mcg in a final volume of 2 mL, its
calculated concentration is 500 mcg/mL. The final volume is the total solution volume, which is not
always identical to the volume of solvent added. This example does not establish an LR3 dose,
compatible diluent, route, or stability period. It also assumes that the stated mass is accurate
and fully recovered in solution. Loss to containers, incomplete recovery, degradation, or incorrect
identity would not be detected by the arithmetic. A volume marking describes volume, whereas mcg
describes peptide mass. Neither becomes an IU of LR3 through conversion. Changing dilution can
alter the size of a measured volume, but it cannot correct uncertain peptide identity, potency,
sterility, or clinical exposure. Greater dilution is therefore not inherently better. It can also
change adsorption, stability, and analytical recovery, depending on the preparation. These
questions require formulation-specific evidence rather than a universal rule.
```

BUYING NOTES

Quality documentation can answer specific analytical questions, but it cannot create a clinical indication or establish human tolerability. A research certificate of analysis may document selected tests on a submitted sample. Its meaning depends on the actual sample, method, laboratory, date, and acceptance criteria. A document for a product family is weaker evidence than a traceable report linked to the relevant lot. Identity testing should distinguish the intended LR3 sequence from native IGF-1, fragments, tagged constructs, and other proteins. Intact mass can help, but mass alone may not establish the complete sequence, correct disulfide arrangement, or functional activity. Orthogonal evidence such as peptide mapping and a relevant activity assay addresses different parts of that question. A concrete published example illustrates the limitation. Kohler and colleagues identified a His-tagged Long-R3-IGF-I protein in an injection vial using immunoaffinity and mass-spectrometric methods, PMID 20675162. The tag changed the actual molecule. This finding supports careful identity interpretation, but it does not establish how often mislabeled material occurs or characterize every preparation. Chromatographic purity and net peptide content answer different questions. A high area percentage for one peak is not necessarily the percentage of the container's total mass that is active peptide. Moisture, residual solvents, salts, excipients, aggregates, and analytical response characteristics can affect interpretation. A universal purity cutoff does not establish fitness for human administration. Sterility and bacterial endotoxin testing are separate from identity and purity testing. A research COA may include either test, both, or neither. Their presence, methods, limits, and relationship to the final filled container must be explicit. Lyophilization alone does not establish sterility, and a test on bulk material does not automatically characterize every later filled container. Independent testing can improve confidence in the attributes actually measured. It cannot eliminate sampling limitations, establish an untested storage period, or substitute for clinical development. Price, powder appearance, dissolution behavior, and a research-use label are not reliable substitutes for analytical evidence. No supplier recommendation or purchasing instruction is provided.

COMMON MISTAKES

- Presenting a 20 to 30 hour human half-life as established. No supporting human pharmacokinetic study was identified. Rat studies show faster LR3 plasma clearance than native IGF-1, PMIDs 7693845 and

8708565. That finding supports rejecting an unsupported numerical claim, but it does not independently calculate a human half-life.

- Equating stronger cell activity with preferential muscle growth. The original experiments showed that binding-protein conditions changed the relative potency of LR3 and native IGF-1, PMID 1378742. A rat growth study found greater effects on several whole-body measures without a corresponding advantage for reversal of carcass muscle loss, PMID 8708565.
- Claiming that all LR3 animal evidence comes from week-long rat experiments. The historical studies remain relevant, but later research includes seven months of intranasal treatment in mice, PMID 39610283. That study did not preserve behavioral or memory outcomes in the disease model and does not validate human longevity or cognitive use.
- Mislabeling a native IGF-1 comparator amount as an LR3 dose. The highest amount highlighted in the diabetic-rat abstract belongs to native IGF-1, PMID 7683875. Dose extraction requires identifying the molecule, experimental group, route, frequency, and duration before copying the number into an LR3 entry.
- Turning a rodent total daily amount into a human schedule. The same amount delivered continuously and intermittently produced different effects in rats, PMID 8708565. Body-weight arithmetic alone does not account for species differences, exposure profiles, binding proteins, disease state, or the endpoint being measured.
- Treating injection location as a validated way to select muscle growth. The literature reviewed does not establish this practice in humans. Systemic distribution is documented in rats, PMID 7693845. Neither circulation nor a plausible local concentration gradient demonstrates a useful, selective hypertrophy outcome.
- Assuming food or a glucose reading resolves the risk. Native IGF-1 experience establishes a meaningful hypoglycemia concern, PMID 19627167. It does not establish an LR3 timing protocol or eliminate other tissue effects. Absence of symptoms and an isolated normal measurement cannot define a validated exposure range.
- Promoting mechanistic pairings as proven synergies. Distinct pathways do not establish additive benefit, and a missing interaction study does not establish compatibility. The listed combinations lack validated human LR3 benefit in the evidence reviewed. Claims of protection, reduced adverse effects, or superior tissue targeting require direct evidence.
- Treating mecasermin approval as approval of LR3. The approved medicine contains native recombinant human IGF-1 and addresses specified pediatric growth disorders. LR3 differs structurally and in binding-protein interactions. The comparator's efficacy, dose limits, adverse-event frequencies, and growth-plate rules cannot be transferred unchanged.
- Treating a COA or high purity percentage as proof of an appropriate clinical preparation. Identity, content, activity, sterility, endotoxin, and stability are separate attributes. A documented His-tagged LR3-related vial shows that molecular identity itself can differ from expectations, PMID 20675162. One analytical result cannot establish every attribute.
- Assuming a dilution calculation validates preparation or storage. Correct arithmetic can describe a hypothetical concentration while the actual contents remain uncertain. Preservative-containing water does not sterilize powder or establish a peptide-specific shelf life. The original syringe conversions and universal storage window exceeded the evidence.
- Reading the tumour signal as either irrelevant or proof of inevitable human cancer. LR3 accelerated an established tumour in rats without improving host muscle protein accretion, PMID 8053901. This is a relevant hazard signal. It does not quantify human cancer incidence, establish cancer initiation, or identify a risk-free exposure threshold.
- Overlooking organ-specific adverse findings because an anabolic marker improved. In rats with renal ischaemia, LR3 improved some anabolic measures while worsening early renal outcomes, PMID 8138750. Changes in nitrogen retention or body weight do not establish organ protection, functional recovery, or a favorable overall outcome.
- Assuming research-use labeling changes anti-doping status. The 2026 WADA list includes IGF-1 analogues under S2.3 and prohibits them at all times. A laboratory designation, personal recovery goal, or claim about detectability does not change the named substance category. No testing-evasion information is provided.

REFERENCES

1. King R et al. Production and characterization of recombinant insulin-like growth factor-I (IGF-I) and potent analogues of IGF-I, with Gly or Arg substituted for Glu3, following their expression in Escherichia coli as fusion proteins.. *Journal of molecular endocrinology*, 1992. PMID 1311930 DOI 10.1677/jme.0.0080029 (Characterizes Gly3 and Arg3 IGF-I analogues. Reduced IGFBP-2 binding, rather than stronger receptor binding, was proposed to explain enhanced biological potency. This is supporting engineering evidence, not a human LR3 trial.)

2. Francis GL et al. Novel recombinant fusion protein analogues of insulin-like growth factor (IGF)-I indicate the relative importance of IGF-binding protein and receptor binding for enhanced biological potency.. *Journal of molecular endocrinology*, 1992. PMID 1378742 DOI 10.1677/jme.0.0080213 (Describes the extended Long Arg3 construct and compares biological activity across cell systems. Supports context-dependent potency and lower relative activity in fibroblasts without detectable secreted IGF-binding proteins.)

3. Latres E et al. Insulin-like growth factor-1 (IGF-1) inversely regulates atrophy-induced genes via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway.. *The Journal of biological chemistry*, 2005. PMID 15550386 DOI 10.1074/jbc.M407517200 (Supports native IGF-1 signaling through Akt/FOXO and Akt/mTOR in regulation of atrophy-related genes. This is mechanistic context rather than direct evidence of LR3 efficacy in humans.)

4. Tomas FM et al. Insulin-like growth factor-I and more potent variants restore growth of diabetic rats without inducing all characteristic insulin effects.. *The Biochemical journal*, 1993. PMID 7683875 DOI 10.1042/bj2910781 (Supports increased growth and nitrogen balance in diabetic rats, with greater growth potency for low-binding-protein variants. Also documents failure to reproduce all characteristic insulin effects. The highlighted maximum comparator dose is native IGF-I.)

5. Tomas FM et al. Superior potency of infused IGF-I analogues which bind poorly to IGF-binding proteins is maintained when administered by injection.. *The Journal of endocrinology*, 1996. PMID 8708565 DOI 10.1677/joe.0.1500077 (Reports 320 mcg/day and 400 mcg/day in normal and catabolic rats, respectively, administered subcutaneously by continuous infusion or once- or twice-daily injection for seven days. Supports schedule-dependent efficacy and limited superiority for reversal of carcass muscle loss.)

6. Tomas FM et al. Effects of insulin and insulin-like growth factors on protein and energy metabolism in tumour-bearing rats.. *The Biochemical journal*, 1994. PMID 8053901 DOI 10.1042/bj3010769 (Documents increased tumour growth, reduced food intake and circulating glucose, and lack of improved host muscle protein accretion with IGF exposure, particularly LR3, in tumour-bearing rats. Does not establish human cancer incidence.)

7. Kemp SF et al. Insulin-like growth factor-I deficiency in children with growth hormone insensitivity: current and future treatment options.. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 2009. PMID 19627167 DOI 10.2165/00063030-200923030-00002 (Provides indirect human context concerning mecasermin, pediatric growth outcomes, hypoglycemia, and binding-protein effects on circulating half-life. It does not establish LR3 clinical efficacy, dosing, or pharmacokinetics.)

8. Nicholls AR et al. Growth Hormone and Insulin-Like Growth Factor-1.. *Frontiers of hormone research*, 2016. PMID 27347885 DOI 10.1159/000445173 (Provides historical context on growth-axis substances and performance-related misuse. Current prohibited status is established separately from the 2026 WADA list, rather than inferred from this review.)

9. Bastian SE et al. Plasma clearance and tissue distribution of labelled insulin-like growth factor-I (IGF-I) and an analogue LR3IGF-I in pregnant rats.. *The Journal of endocrinology*, 1993. PMID 7693845 DOI 10.1677/joe.0.1380327 (Direct radiotracer evidence of faster LR3 plasma clearance, predominantly free circulating analog, and tissue-distribution differences in pregnant and nonpregnant rats. Does not provide a human plasma half-life.)

10. Martin AA et al. Effects of insulin-like growth factor-I peptides in rats with acute renal failure.. *The Journal of endocrinology*, 1994. PMID 8138750 DOI 10.1677/joe.0.1400023 (Reports LR3 at 1.5 mg/kg/day by continuous subcutaneous osmotic-pump infusion in renal-ischaemia experiments. Supports worse early renal functional outcomes despite improvement in some anabolic measures.)

11. Kohler M et al. Detection of His-tagged Long-R³-IGF-I in a black market product.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2010. PMID 20675162 DOI 10.1016/j.ghir.2010.07.001 (Documents identification of a His-tagged Long-R3-IGF-I protein in an injection vial. Supports a concrete molecular-identity concern, without establishing clinical effects or the prevalence of product-quality failures.)

12. Engel MG et al. Intranasal long R3 insulin-like growth factor-1 treatment promotes amyloid plaque remodeling in cerebral cortex but fails to preserve cognitive function in male 5XFAD mice.. *Journal of Alzheimer's disease : JAD*, 2025. PMID 39610283 DOI 10.1177/13872877241299056 (Documents seven months of intranasal treatment in male mice, with some body-composition and amyloid findings but no preservation of behavioral or memory outcomes.)

PEG-MGF

Pegylated mechano growth factor, IGF-1Ec

IGF-1 splice variant, pegylated | Module 2 · Recomposition | Goals: Hypertrophy, Recovery | Route: SC

WADA prohibited

An experimental PEG-conjugated MGF E peptide with no identified human administration trials, uncertain pharmacokinetics, and disputed muscle-growth mechanisms.

WHAT IT IS

PEG-MGF usually refers to a synthetic 24 amino acid fragment from the distinctive C-terminal region of an IGF-1 E domain, conjugated to polyethylene glycol. MGF means mechano growth factor. The name has also been used for an IGF-1 transcript, its precursor protein, and several synthetic peptide constructs. Those meanings are not interchangeable. In humans, the relevant transcript is generally called IGF-1Ec. The corresponding rodent splice variant is commonly called IGF-1Eb. These precursors contain the mature IGF-1 sequence and differing E domains. The isolated synthetic C-terminal fragment does not contain mature IGF-1. Research on the full precursor therefore cannot automatically establish the activity of the short fragment. PEG attachment is intended to change a molecule's distribution, degradation, or elimination. Its effects depend on the peptide sequence, attachment site, PEG size, and formulation. It can also change biological activity. A longer circulating lifetime and retained activity cannot be assumed for an unspecified PEG-MGF preparation. Three evidence questions need separate answers: whether the transcript responds to exercise, whether a synthetic E peptide has biological effects, and whether PEG-MGF benefits people. Human biopsy studies support the first. Mixed cell and animal findings address the second. The label PEG-MGF does not provide a complete molecular specification. Meaningful comparison with a publication requires the exact peptide sequence, chemical modifications, PEG characteristics, and measured content. A shared name alone does not establish that two preparations are equivalent.

MECHANISM

Alternative splicing of IGF-1 produces precursor proteins with different E domains while retaining the mature IGF-1 sequence. The distinctive human IGF-1Ec sequence includes a 49 base pair insertion that changes the reading frame. The corresponding rodent insertion differs. The synthetic MGF peptide represents the final 24 amino acids of the distinctive E-domain region, rather than the complete E domain or precursor. Kandalla 2011, PMID 21354439, describes this structural context.

Human exercise research establishes a temporal expression pattern. Philippou 2009, PMID 19567392, studied ten healthy male volunteers after exercise-induced muscle damage. Muscle biopsies showed rapid, transient MGF transcript upregulation, followed by more sustained increases in other IGF-1 transcripts. The investigators also reported protein-expression changes. These measurements do not establish the concentration or biological activity of a freely circulating 24 amino acid peptide.

Some experiments support biological activity of synthetic E peptides. In the same Philippou study, an IGF-1 receptor-neutralizing antibody did not block the synthetic peptide's proliferative effect in C2C12 cells. Akt phosphorylation was not detected. Those observations suggested signaling that differed from mature IGF-1 under those experimental conditions. They do not establish a unique receptor or prove receptor independence in every tissue.

Kandalla 2011, PMID 21354439, reported increased proliferative lifespan and delayed senescence in muscle progenitor cultures from neonatal and young adult donors. Those lifespan effects were absent in cultures from older donors. The study also reported effects on fusion and hypertrophy. It does not support a blanket statement that the peptide consistently prevents muscle-cell fusion.

Replication has been inconsistent. Fornaro 2014, PMID 24253050, describes experiments conducted at two pharmaceutical companies. MGF peptides did not reproduce the reported proliferation, differentiation, or ERK-signaling effects across the tested systems. Mature IGF-1 and the full precursor produced responses in

comparison experiments. This challenges specific MGF E-peptide claims. It was not a clinical trial or a definitive test of every possible PEG-MGF construct.

The endogenous peptide question also remains distinct from synthetic peptide activity. Matheny 2010, PMID 20130113, reported that an analogous free peptide had not been isolated from the biological sources reviewed. That is a dated assessment of endogenous processing evidence. It does not mean the transcript is fictitious, or that a synthetic peptide cannot have pharmacological activity.

Later mechanistic work complicates the claim that no interacting protein has ever been identified. Podratz 2020, PMID 32511954, identified nucleolin as an MGF-binding partner in neuronal experiments. Nucleolin antibodies prevented the reported protective effect in culture. This does not establish a validated PEG-MGF receptor in human skeletal muscle, but it makes an absolute absence-of-target statement inaccurate.

The defensible mechanism is therefore conditional. Exercise-responsive transcript biology is documented. Synthetic E peptides have shown context-dependent effects, including positive animal findings and negative replication experiments. PEG-MGF-specific target engagement, tissue exposure, dose-response relationships, and clinical effects remain uncharacterized in the human literature identified here.

EVIDENCE · GRADE D

Grade D applies to PEG-MGF-specific claims about muscle growth, recovery, and performance. No human administration trial or controlled animal efficacy study of a clearly specified PEG-MGF conjugate was identified in this search. The evidence supporting its proposed use is indirect, mechanistic, or anecdotal.

Related MGF E peptides do have published animal data. Those experiments support grade C for the particular constructs and outcomes studied, not an automatic upgrade for PEG-MGF. The distinction concerns molecular identity as well as species. A peptide delivered from a PEG-based scaffold is also different from a peptide chemically conjugated to PEG.

The negative replication study is relevant but does not establish universal inactivity. Conversely, positive cell or animal findings do not establish hypertrophy or recovery benefits in healthy adults. The available literature supports uncertainty about translation, rather than either guaranteed benefit or proven absence of all biological activity.

Human data. Philippou 2009, PMID 19567392, measured IGF-1 isoform expression in exercised human muscle. Participants did not receive PEG-MGF. The reported transcript and protein-expression changes describe endogenous responses to damage, not the efficacy of an administered research compound. Kandalla 2011, PMID 21354439, used human muscle progenitor cells in culture. Increased proliferative lifespan and delayed senescence depended on donor age. Human-derived cells do not constitute a human treatment trial, and their responses do not establish improvements in strength or recovery. The PubMed search identified no published human administration study of PEG-MGF or the isolated synthetic MGF E peptide. Dominikowski 2026, PMID 42395176, reviews the uneven evidence surrounding performance-oriented GH and IGF-1 axis peptides. It emphasizes uncertain composition, dosing, and combinations in self-administration reports. A narrative review does not supply missing clinical outcomes or establish adverse-event rates for PEG-MGF. Kletzl 2017, PMID 28110155, studied a different PEGylated recombinant IGF-1 molecule in 62 healthy volunteers. Its pharmacokinetic findings illustrate that a defined PEG conjugate can be studied systematically. Neither its

Animal and mechanistic data. Animal evidence exists for related synthetic E peptides and must not be omitted. Mills 2007, PMID 17845560, reported improved engraftment of human myogenic precursor cells in mice following delivery of an MGF E peptide. This was a transplantation model, not a trial of PEG-MGF for hypertrophy in healthy people. Shioura 2014, PMID 25606570, reported that a stabilized synthetic MGF E-domain analog improved selected cardiovascular measurements after myocardial infarction in mice. Effects depended on the disease setting and treatment period. The study does not establish the efficacy or pharmacokinetics of an unspecified PEG-MGF conjugate. Peña 2015, PMID 25678113, delivered E peptide using PEG-based polymeric microstructures in a mouse myocardial-infarction model. The study reported functional benefits. PEG was part of the delivery material, which is not evidence that the peptide itself was PEGylated. These studies prevent describing all MGF peptide evidence as exclusively in vitro. They still leave PEG-MGF-specific efficacy, systemic toxicity, reproductive effects, and long-term outcomes unresolved. Mouse cells tested outside the animal in Fornaro 2014, PMID 24253050, remain in vitro evidence, even though their source was an animal.

exposure measurements nor its short-term tolerability findings establish the behavior of a PEGylated E-domain fragment.

REGULATORY STATUS AND SPORT

STATUS

PEG-MGF is an experimental research compound. No approved therapeutic PEG-MGF product or prescribing label was identified in the sources reviewed. Accordingly, there is no established approved indication, clinical dosing schedule, or product-specific patient information to reproduce here. A research-use label does not establish suitability for human administration. A certificate of analysis likewise does not establish approval, clinical effectiveness, or pharmaceutical manufacturing compliance. Compounding status and import rules require separate, current jurisdiction-specific review. The available evidence does not justify categorical claims about every country's laws or every possible supplier. The name also creates a regulatory and scientific identification problem. A full-length IGF-1Ec-related protein, a synthetic E-domain fragment, and a PEG-conjugated fragment are different materials. Thevis 2014, PMID 25466910, characterized a modified full-length MGF-related protein. That paper cannot establish the composition of every preparation labeled PEG-MGF. Product identity must be resolved before evidence about a particular molecule can be applied.

WADA

Prohibited at all times under S2.3, Growth Factors and Growth Factor Modulators, of the 2026 WADA Prohibited List. The subsection explicitly names mechano growth factors. PEG modification does not provide an exemption from the class prohibition. Source: [WADA 2026 Prohibited List](https://www.wada-ama.org/sites/default/files/2025-09/2026list_en_final_clean_september_2025.pdf). Prohibition applies during competition and outside competition. Historical analytical work, including Thevis 2014, PMID 25466910, supports that MGF-related materials have been relevant to doping controls. A published assay for one construct does not establish identical detection behavior for every PEG-MGF preparation. No detection windows or testing-avoidance claims are provided.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

Subcutaneous and intramuscular administration are described in non-clinical accounts of PEG-MGF use. Neither route has a validated human absorption, bioavailability, or efficacy profile for this compound. Reports of administration near a trained muscle do not establish selective delivery or a local growth effect. Animal E-peptide studies used construct-specific delivery methods. Mills 2007, PMID 17845560, describes intramuscular or systemic delivery in mice. Peña 2015, PMID 25678113, used local cardiac delivery from polymeric microstructures. Neither establishes interchangeability with routine subcutaneous administration of PEG-MGF. Oral, intranasal, and topical bioavailability have not been established in the sources reviewed. The absence of such evidence is more precise than a categorical claim that every possible formulation is inactive by those routes.

HALF-LIFE

Unknown for a clearly specified PEG-MGF preparation in humans. No validated human or animal pharmacokinetic estimate for the marketed PEG-MGF category was identified. Claims of prolonged exposure remain a formulation hypothesis unless supported by measurements of the actual conjugate. Kletzl 2017, PMID 28110155, reported a 140 to 200 hour half-life for a different PEGylated recombinant IGF-1 molecule. That value does not belong to PEG-MGF. The peptide sequence, PEG attachment, molecular size, target interactions, and analytical method differ. A measured signal also requires interpretation. An assay may detect intact active material, a fragment, or related immunoreactivity. Persistence of a laboratory signal does not necessarily equal persistence of biological activity. A defensible PEG-MGF half-life claim would identify the molecular construct, species, administration route, assay specificity, and sampled time course.

TIMING

Post-training administration is described in non-clinical use, but no clinical study establishes an effective PEG-MGF timing window. The rationale borrows from the endogenous expression pattern in Philippou 2009, PMID 19567392. That study measured tissue responses after exercise-induced damage rather than the effects of an administered peptide. Transcript production, precursor processing, peptide distribution, and target engagement occur at different biological levels. A transient rise in messenger RNA cannot identify when an external PEG conjugate should be present. It also cannot determine whether external exposure would reinforce, disrupt, or leave the endogenous response unchanged. Published disease-model experiments with related E peptides address their own treatment windows. They do not validate post-workout timing for healthy adults. Training-day and non-training-day schedules remain untested conventions.

CYCLE LENGTH

No evidence-based cycle length or washout interval exists for PEG-MGF. Courses lasting 4 to 6 weeks, sometimes followed by a similar break, are commonly cited in non-clinical use; not validated in trials. This describes a circulating convention and is not a recommended schedule. A

training block is not a pharmacokinetic study. Without a characterized conjugate and repeated-exposure measurements, its accumulation and persistence cannot be calculated reliably. A break of a particular duration also cannot be assumed to reverse biological effects, prevent immune responses, or remove longer-term risk. Animal study durations with other E-peptide constructs do not supply a validated human cycle. Their species, disease model, delivery method, and endpoints differ from performance-oriented use.

TITRATION

No validated titration method, therapeutic window, or treatment target exists. Serum IGF-1 has not been established as a marker of PEG-MGF exposure or response. The synthetic fragment differs from mature IGF-1, and cross-reactivity with a clinical assay would require separate validation. Changing the amount until soreness, recovery, or body weight changes does not establish a dose-response relationship. Those outcomes also respond to training load, food intake, sleep, fluid balance, and other substances. Lack of an immediate symptom cannot establish tolerability over repeated exposure. A clinical assessment of suspected adverse effects may include laboratory testing chosen for the presentation. That is different from a validated protocol for adjusting PEG-MGF. No target concentration, escalation step, or dose-adjustment rule can be derived from the studies cited here.

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
PEG-MGF dosing descriptions from non-clinical use. These are reported conventions, not established starting doses or an effective therapeutic range.	**100 to 200 mcg per administration, commonly cited in non-clinical use; not validated in trials.**	Subcutaneous; some non-clinical accounts describe intramuscular administration.	Two to three administrations per week in non-clinical accounts; this frequency is not validated in trials.	commonly cited in non-clinical use; not validated in trials. No verified study establishes efficacy, tolerability, dose equivalence between routes, or a reliable relationship between labeled and delivered content. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.
A higher PEG-MGF range also appears in non-clinical descriptions. Its presence does not establish a dose-response relationship or justify escalation.	**200 to 400 mcg per administration, commonly cited in non-clinical use; not validated in trials.**	Subcutaneous or intramuscular in non-clinical descriptions; comparative bioavailability is unknown.	Two to three administrations per week in circulating non-clinical descriptions; no validated frequency exists.	commonly cited in non-clinical use; not validated in trials. This range is retained as a description of reported use, not as evidence that higher exposure improves outcomes. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.
Laboratory exposure to MGF peptides in a negative replication study. This was not a PEG-MGF administration study or a human body dose.	**Up to 0.5 mcg/mL in culture medium, equivalent to the 500 ng/mL reported by Fornaro 2014, PMID 24253050.**	In vitro addition to culture medium in myoblast experiments.	Exposure during experimental assays; the abstract does not establish one universal exposure duration or replenishment schedule.	Fornaro 2014, PMID 24253050. The investigators reported no increase in proliferation at concentrations up to this level. Other assays also failed to reproduce proposed differentiation or signaling effects. These concentrations cannot be converted directly into an injected dose. · PMID 24253050

STACKING

+ CJC-1295

Proposed pairing only; no demonstrated synergy. Non-clinical descriptions combine GH-axis stimulation with a presumed local E-peptide effect. No PEG-MGF combination trial was identified. Evidence that one component changes GH or

– IGF-1 LR3

No validated combination exists. IGF-1 LR3 and an isolated MGF E fragment should not be treated as interchangeable or as a proven complementary pair. Adding an IGF-1 analog introduces separate metabolic and growth-signaling concerns.

	IGF-1 cannot establish the contribution of the other. CJC-1295 constructs also differ, so a shared name does not guarantee equivalent pharmacology. The broader evidence limitations are discussed in Dominikowski 2026, PMID 42395176.
+ Ipamorelin	Proposed pairing only; no demonstrated synergy. GH-release physiology is used to justify combining ipamorelin with PEG-MGF, but the combination has not been clinically characterized. Claims about selectivity of a secretagogue do not establish combination tolerability. A change in weight, recovery, or laboratory measurements cannot be assigned to PEG-MGF when exposures and training variables change together.
+ BPC-157	Proposed recovery pairing with no identified combination evidence. A shared marketing goal does not establish complementary mechanisms or additive benefit. Neither a positive animal result for one compound nor an uncontrolled experience with both measures the interaction. This pairing has no validated dose relationship, treatment duration, or adverse-event profile. No synergy claim is supported.
+ TB-500	Proposed tissue-repair pairing with no identified combination trial. Evidence involving thymosin-related molecules and evidence involving MGF E peptides concern different constructs and experimental settings. Combining their mechanistic narratives does not establish improved healing. Molecular identity, co-exposure, and outcome attribution remain unresolved. No additive or synergistic effect can be quantified from the sources reviewed.
	PEG-MGF's contribution to those risks is unknown. The combination does not have a quantified human mitogenic exposure or an established monitoring strategy.
– Hexarelin	No validated interaction study exists. Hexarelin adds GH-axis pharmacology to an already uncharacterized exposure. Dominikowski 2026, PMID 42395176, discusses endocrine and metabolic concerns across this broader peptide category. Those class observations are not a measured PEG-MGF interaction rate. Multiple simultaneous exposures complicate interpretation of symptoms and laboratory changes without establishing an added benefit.

SAFETY

COMMON EFFECTS

The frequency and character of PEG-MGF adverse effects are unknown. No prospective human administration study was identified from which common, uncommon, or dose-dependent effects could be estimated. Anecdotal reports cannot reliably separate the intended peptide from contamination, incorrect identity, or other substances used concurrently. Dominikowski 2026, PMID 42395176, discusses fluid retention, musculoskeletal symptoms, injection-site reactions, and endocrine or metabolic disturbances across GH and IGF-1 axis peptides. Those findings must remain class-level context. They do not show that isolated PEG-MGF causes each listed effect. Kletzl 2017, PMID 28110155, reported injection-site erythema with a different PEGylated IGF-1

molecule. That observation does not supply a PEG-MGF adverse-event profile. General administration-related irritation is plausible, but it should not be presented as a measured incidence or an expected harmless reaction.

SERIOUS SIGNALS

Potential serious problems include severe allergic reactions, contaminated-material infections, and unexpected pharmacological effects from incorrectly identified contents. These are plausible hazards of uncharacterized parenteral material, not quantified outcomes from PEG-MGF trials. Mitogenic effects require careful wording. Growth and survival signaling in related experimental systems creates a concern about effects on existing abnormal tissue. Whether a specific PEG-MGF conjugate promotes tumors in humans is unknown. The class discussion in Dominikowski 2026, PMID 42395176, describes biological plausibility rather than a demonstrated PEG-MGF cancer risk. Hypoglycemia is a concern with some IGF-1-active exposures, but its incidence with PEG-MGF has not been established. It cannot be ruled out for material with uncertain identity or additional substances. PEG-related hypersensitivity or immune responses are also potential formulation concerns whose frequency has not been characterized here. Absence of reported events cannot establish long-term tolerability. Reproductive toxicity, carcinogenicity, organ toxicity, and repeated-exposure immunogenicity remain important unanswered questions for the actual conjugate.

CONTRAINDICATIONS

There is no approved PEG-MGF label with formally established contraindications. Precautionary exclusions must therefore be distinguished from contraindications proven in PEG-MGF trials. Pregnancy, breastfeeding, and use in children lack supporting reproductive or developmental safety evidence. Known hypersensitivity to PEG or another formulation component raises an additional concern. Active malignancy, an unexplained mass, or a previous cancer history requires individualized clinical assessment because growth-signaling effects are unresolved. Diabetes, recurrent hypoglycemia, proliferative retinopathy, acromegaly, or an untreated pituitary disorder complicate interpretation of growth-axis or metabolic symptoms. These conditions are reasons for particular clinical caution, not validated PEG-MGF-specific interaction findings. Unverified identity, sterility, or content prevents a reliable assessment regardless of medical history. Anti-doping prohibition is a separate eligibility issue, not a medical contraindication. Its classification belongs in the WADA field.

STOP RULES

Following exposure, breathing difficulty, throat or facial swelling, collapse, seizure, or severe confusion warrants emergency care and no further exposure. These signs can indicate anaphylaxis, severe metabolic disturbance, or another acute illness. Expanding redness, increasing pain, warmth, drainage, or fever after an injection warrants prompt assessment for infection. Recurrent sweating, tremor, confusion, or faintness also requires assessment, particularly when additional glucose-active substances may be involved. New visual changes, marked swelling, persistent numbness, or an unexplained lump require clinical evaluation. These findings do not establish that PEG-MGF caused the problem, but they should not be normalized as evidence of tissue repair. An exposure history should include the product label, claimed contents, timing, route, and all concurrent substances. Available packaging and laboratory documentation may help clinicians assess an uncertain exposure. Symptom improvement alone does not validate restarting or changing the amount.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No approved standard vial presentation exists. Labels describing 2 mg or 5 mg containers appear in non-clinical descriptions; these are claimed container contents, not validated doses or proof of available peptide. The actual specification may differ between preparations carrying the same name. For a conjugated molecule, mass can refer to the complete peptide-PEG conjugate, peptide-equivalent content, or an inadequately defined nominal amount. Excipients, counterions, water content, and analytical assumptions can also affect interpretation. It is inaccurate to assume that every stated mass means gross vial weight, or that it always means isolated peptide mass. A usable analytical specification identifies what the mass represents and how it was measured. Without that information, a concentration calculation is only arithmetic applied to an unverified label. It cannot establish the amount of intact active material.

SOLVENT

No clinically validated PEG-MGF diluent, reconstitution procedure, or compatibility specification was identified. Bacteriostatic water and sterile water appear in non-clinical descriptions, but their use does not demonstrate stability or suitability for a particular conjugate. A preservative can limit growth of some organisms under specified conditions. It does not sterilize contaminated powder, eliminate endotoxin, or establish compatibility with the peptide. Likewise, a sterile diluent does not make the resulting preparation a validated sterile medicine. Solubility, adsorption to surfaces, aggregation, pH tolerance, and preservative compatibility require formulation-specific measurements. Laboratory handling conditions depend on the characterized material and the experiment. No solvent choice or mixing method here should be read as a procedure for preparing an unapproved compound for human administration.

STORAGE

No validated PEG-MGF storage temperature, post-reconstitution shelf life, freeze-thaw tolerance, or beyond-use interval was identified. Chemical stability, biological activity, and microbiological quality are separate questions. A solution may retain its appearance while losing activity or becoming contaminated. Refrigeration and a preservative do not independently establish an acceptable storage interval. The absence of cloudiness or visible particles does not establish sterility. Conversely, general peptide-handling conventions cannot prove that every PEG-MGF construct must never be frozen or shaken. Those effects depend on the conjugate, solvent, concentration, container, and handling conditions. A defensible storage claim requires testing of the actual formulation under the stated conditions. For laboratory material, documented stability limits must come from a qualified, formulation-specific specification. Visible particles, discoloration, or container damage indicate a quality problem, but visual inspection cannot validate a preparation that appears unchanged.

Hypothetical concentration arithmetic only, with no administration route or frequency assigned. If an analytically confirmed 2 mg of a specified material were contained in a final volume of 2 mL, the concentration would be 1 mg/mL. The same concentration is 1000 mcg/mL. These numbers are mathematical inputs, not study doses, labeled PEG-MGF instructions, or a proposed treatment. A final volume is the total solution volume after preparation. It is not necessarily identical to the volume of liquid initially added. The distinction matters whenever exact concentration is required. It also assumes complete dissolution, uniform distribution, and no material loss during preparation. If the same confirmed 2 mg were contained in a final volume of 1 mL, the calculated concentration would be 2 mg/mL. That is 2000 mcg/mL. This second hypothetical example illustrates that concentration changes when volume changes; it does not establish a preferred dilution. The calculation also depends on the stated mass basis. A result expressed as conjugate mass per mL is not automatically peptide-equivalent mass per mL. Neither can be converted into a biological activity unit without a validated activity assay. Syringe-barrel markings are volume graduations and should not be confused with IU of peptide activity. No established PEG-MGF potency standard connects such markings to an effective amount.

BUYING NOTES

A research-use label and a high purity percentage answer different questions from clinical suitability. Neither establishes approved status, reliable content, sterility, endotoxin control, or a demonstrated benefit. An analytical certificate can help characterize a sample, but its scope and limitations matter.

Thevis 2014, PMID 25466910, characterized material presented as full-length MGF and found a modified IGF-1Ec-related sequence. The product lacked a terminal lysine and contained an R109H substitution. This illustrates identity ambiguity in an MGF-related preparation. It does not prove that all PEG-MGF material has those alterations or that every supplier uses the same construct.

Mongongu 2021, PMID 33587816, reported oxidized forms and quality concerns in preparations of other IGF-1 analogs. That is supporting context about related unregulated material, not a direct survey of PEG-MGF purity. Its analytical findings do not establish clinical effectiveness or a pharmacokinetic profile for PEG-MGF.

An informative certificate identifies the tested batch, sampling date, analytical laboratory, methods, acceptance criteria, and measured results. Molecular identity generally requires suitable structural analysis, rather than a chromatographic purity number alone. A dominant chromatographic peak can represent the wrong molecule. Co-eluting impurities and substances outside the method's detection scope can also be missed.

PEG conjugation adds further specification requirements: peptide sequence, PEG molecular-weight distribution, attachment site, conjugation ratio, unconjugated peptide, and residual reagents. Mass spectrometry may contribute to identity confirmation, but heterogeneous PEG distributions can require additional methods. One instrument result does not automatically answer every structural question.

Content testing establishes how much specified material was measured. Purity testing estimates composition under the chosen method. Sterility and endotoxin testing address separate hazards. Batch matching and sample traceability determine whether the report applies to the material being discussed.

Even extensive analytical characterization would not supply missing human pharmacology or establish suitability for self-administration. It reduces some identity uncertainty while leaving clinical benefit, dosing, and longer-term safety unresolved.

COMMON MISTAKES

- Treating an exercise-responsive transcript as proof that administering PEG-MGF improves hypertrophy. Expression studies and intervention trials answer different questions, and the latter were not identified for PEG-MGF.
- Using MGF to mean the transcript, full precursor, isolated E peptide, and PEG conjugate interchangeably. Each requires its own molecular specification and evidence assessment.
- Describing the Fornaro replication as proof that PEG-MGF cannot work in any setting. It challenged particular E-peptide effects in specified cell systems, not every construct or clinical outcome.
- Claiming there are no animal studies of MGF peptides. Related E peptides have animal findings, but those findings do not establish efficacy of a PEG-MGF conjugate.
- Confusing peptide release from a PEG-based polymer scaffold with chemical PEG attachment to the peptide. The Peña delivery study, PMID 25678113, supports the former.
- Borrowing the 140 to 200 hour half-life from a different PEGylated IGF-1 molecule, PMID 28110155. That measurement cannot establish PEG-MGF exposure or scheduling.
- Treating post-training timing, cycle length, or a circulating dose range as established practice. These descriptions have no validated PEG-MGF clinical dose-response basis.
- Reading a purity percentage as proof of identity, content, sterility, and endotoxin control. These require distinct measurements and a report traceable to the relevant sample.
- Assuming a preservative or refrigeration validates a multiweek storage interval. No formulation-specific PEG-MGF stability or microbiological interval was identified.
- Attributing progress to a peptide while training, food intake, sleep, and other exposures change simultaneously. Such observations cannot establish PEG-MGF efficacy or combination synergy.

REFERENCES

1. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Narrative review of GH and IGF-1 axis performance peptides, evidence limitations, self-administration patterns, uncertain composition and combinations, and class-level adverse effects. It does not establish PEG-MGF-specific event rates.)
2. Fornaro M et al. Mechano-growth factor peptide, the COOH terminus of unprocessed insulin-like growth factor 1, has no apparent effect on myoblasts or primary muscle stem cells.. *American journal of physiology. Endocrinology and metabolism*, 2014. PMID 24253050 DOI 10.1152/ajpendo.00408.2013 (Negative replication of proposed MGF E-peptide proliferation, differentiation, and signaling effects in cell systems. Supports the reported laboratory concentration and contested mechanism, not universal PEG-MGF inactivity.)
3. Matheny RW Jr et al. Minireview: Mechano-growth factor: a putative product of IGF-I gene expression involved in tissue repair and regeneration.. *Endocrinology*, 2010. PMID 20130113 DOI 10.1210/en.2009-1217 (Distinguishes IGF-I transcripts, precursor proteins, and synthetic MGF peptides. Reports the absence of an isolated analogous endogenous free peptide in the biological sources reviewed at that time.)
4. Kandalla PK et al. Mechano Growth Factor E peptide (MGF-E), derived from an isoform of IGF-1, activates human muscle progenitor cells and induces an increase in their fusion potential at different ages.. *Mechanisms of ageing and development*, 2011. PMID 21354439 DOI 10.1016/j.mad.2011.02.007 (Human muscle-cell culture findings involving age-dependent proliferative lifespan and senescence, plus fusion and hypertrophy effects. Also describes the human and rodent splice-sequence distinction.)
5. Philippou A et al. Expression of IGF-1 isoforms after exercise-induced muscle damage in humans: characterization of the MGF E peptide actions in vitro.. *In vivo (Athens, Greece)*, 2009. PMID 19567392 (Human muscle-biopsy expression changes after exercise-induced damage and separate synthetic E-peptide signaling experiments in cultured cells. It contains no PEG-MGF administration trial.)
6. Thevis M et al. Mass spectrometric characterization of a biotechnologically produced full-length mechano growth factor (MGF) relevant for doping controls.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2014. PMID 25466910 DOI 10.1016/j.ghir.2014.10.004 (Characterization of a modified full-length MGF-related protein, including terminal lysine loss and an R109H substitution. Supports construct-specific identity concerns and historical relevance to doping controls.)
7. Kletzl H et al. First-in-man study with a novel PEGylated recombinant human insulin-like growth factor-I.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2017. PMID 28110155 DOI 10.1016/j.ghir.2017.01.001 (Human pharmacokinetic and tolerability findings for a different PEGylated recombinant IGF-1 molecule. Its half-life and injection-site findings cannot be transferred to PEG-MGF.)
8. Mongongu C et al. Detection of LongR(3) -IGF-I, Des(1-3)-IGF-I, and R(3) -IGF-I using immunopurification and high resolution mass spectrometry for antidoping purposes.. *Drug testing and analysis*, 2021. PMID 33587816 DOI 10.1002/dta.3016 (Analytical

characterization and oxidized forms in preparations of other IGF-I analogs. Retained only for related-material quality context, not PEG-MGF dosing, clearance, or detection windows.)

9. Mills P et al. A synthetic mechano growth factor E Peptide enhances myogenic precursor cell transplantation success.. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2007. PMID 17845560 DOI 10.1111/j.1600-6143.2007.01927.x (Positive synthetic E-peptide findings involving human myogenic precursor transplantation into mice. Establishes related animal evidence without establishing PEG-MGF efficacy in people.)
10. Shioura K et al. Administration of a Synthetic Peptide Derived from the E-domain Region of Mechano-Growth Factor Delays Decompensation Following Myocardial Infarction.. *International journal of cardiovascular research*, 2014. PMID 25606570 DOI 10.4172/2324-8602.1000169 (Cardiovascular findings following a stabilized synthetic MGF E-domain analog in a mouse myocardial-infarction model. It does not establish results for an unspecified PEG-MGF conjugate.)
11. Peña JR et al. Localized delivery of mechano-growth factor E-domain peptide via polymeric microstructures improves cardiac function following myocardial infarction.. *Biomaterials*, 2015. PMID 25678113 DOI 10.1016/j.biomaterials.2014.12.050 (Mouse cardiac findings using E-peptide delivery from PEG-based polymeric microstructures. Supports distinguishing a PEG-containing delivery scaffold from a PEG-conjugated peptide.)
12. Podratz JL et al. Mechano growth factor interacts with nucleolin to protect against cisplatin-induced neurotoxicity.. *Experimental neurology*, 2020. PMID 32511954 DOI 10.1016/j.expneurol.2020.113376 (Identifies nucleolin as an MGF-binding partner in neuronal experiments.)

Follistatin-344 (FST-344)

FST-344

Activin and myostatin binding protein | Module 2 · Recomposition | Goals: Hypertrophy | Route: SC (research) | WADA prohibited

An activin and myostatin binding protein with preliminary human gene therapy findings, mixed animal protein data, and no established injectable protein regimen for trained adults.

WHAT IT IS

Follistatin is an endogenous protein that binds several members of the TGF-beta superfamily, including activins and myostatin. These signaling molecules influence muscle growth, reproductive physiology, and other tissue functions. Binding them can reduce their availability to receptors. However, inhibiting a regulator of muscle growth does not establish that a particular preparation improves strength or physique. Follistatin is a folded, disulfide-rich protein rather than a short synthetic peptide. Its sequence, processing, aggregation state, and biological activity matter when interpreting research material. A name on a container does not establish equivalence to the material used in a publication. The number 344 describes a precursor isoform. Alternative splicing produces precursors containing 344 or 317 amino acids. Removal of a 29 amino acid signal peptide yields FST315 or FST288, respectively. FST315 is generally associated with circulation, whereas FST288 binds cell surfaces more strongly. The longer isoform has an acidic extension that influences accessibility of the heparin-binding region and tissue association (PMIDs 25322757 and 19273500). The human gene therapy studies used the FS344 coding sequence to produce secreted follistatin from transduced muscle. Selection of this isoform was intended to limit unwanted effects compared with more strongly tissue-bound forms. It does not establish molecular selectivity for muscle or exclude effects on reproductive and metabolic signaling. The central distinction is the intervention. An AAV vector delivers genetic instructions, allowing cells to produce protein over an extended period. Recombinant protein administration delivers an externally manufactured protein with its own absorption, distribution, and clearance. Vector genomes cannot be converted into mcg of injected protein. Results from gene transfer therefore do not establish a regimen for material labeled Follistatin-344.

MECHANISM

Follistatin acts through ligand binding rather than direct receptor blockade. Structural work summarized in the activin review describes two follistatin molecules surrounding a ligand dimer. This arrangement obstructs receptor-binding surfaces and reduces ligand availability. Binding affinity and tissue effects depend on the ligand, follistatin isoform, and local environment (PMID 19273500).

Activins and myostatin signal through combinations of type II and type I receptors. These include ActRIIA, ActRIIB, and downstream activin receptor-like kinases. Receptor preferences differ between ligands, so a single identical receptor sequence should not be assigned to every member of this family. A central downstream pathway involves phosphorylation of Smad2 and Smad3, followed by transcriptional regulation with Smad4.

In skeletal muscle, these signals can restrain growth and influence differentiation, protein turnover, and fibrosis. Follistatin-mediated ligand sequestration can reduce these restraints. Interactions with Akt and mTOR signaling help explain increased protein synthesis in experimental systems. However, pathway diagrams do not specify how much protein reaches human muscle after subcutaneous administration. They also do not establish the duration of receptor-level effects or the balance between muscle and non-muscle exposure (PMIDs 27695802 and 33802348).

Follistatin is broader than a selective myostatin inhibitor. Activin binding contributes to its biological effects, including effects that cannot be explained by myostatin inhibition alone. This breadth helps explain substantial hypertrophy in some animal models, but it also creates uncertainty outside muscle. Activin participates in pituitary FSH regulation, ovarian biology, pancreatic function, immune signaling, and tissue repair. These roles

provide reasons to investigate systemic effects, not proof that every exposed person develops a particular adverse event (PMID 19273500).

Muscle growth also depends on disease context and functional innervation. In severe spinal muscular atrophy mice, follistatin overexpression produced little additional muscle mass and no improvement in motor function or survival. Ligand inhibition could not overcome the principal disease process in that model. This finding limits claims that removing myostatin signaling reliably produces useful strength (PMID 19477958).

Endogenous follistatin changes with exercise. Hansen and colleagues reported a roughly sevenfold plasma increase, peaking three hours into recovery after three hours of cycling. They found no measurable net release from the exercising limb. Complementary mouse experiments supported the liver as a likely source (PMID 21068158).

That experiment did not compare recombinant protein with gene therapy or measure long-term hypertrophy from those interventions. It therefore cannot prove that transient protein exposure is ineffective. Its narrower implication is that circulating follistatin is physiologically variable. An isolated serum concentration is not an established measure of muscle target engagement or a validated dosing target.

EVIDENCE · GRADE C

Grade C applies to the claim that recombinant Follistatin-344 protein improves muscle size or performance in trained adults. Animal evidence exists, but the human gene therapy studies evaluate a different intervention. No published trial identified in this review establishes efficacy, pharmacokinetics, or a dosing regimen for unmodified recombinant FST344 or FST315 administered to healthy trained adults. The small human AAV-FS344 studies constitute preliminary grade B evidence for those specific investigational interventions in muscle disease. They cannot transfer that grade to a protein preparation or a bodybuilding schedule. The broader follistatin mechanism has experimental support, but product identity, exposure, population, and clinical outcome remain separate questions. A rat study administered recombinant FS288 protein and reported mixed effects on muscle size and force. That study strengthens the evidence inventory without validating the non-clinical subcutaneous schedule described below (PMID 35747585). The myostatin literature also documents repeated difficulty translating increased muscle mass into meaningful functional benefit. This is a limitation of clinical translation, not evidence that every intervention in the pathway is ineffective. The cited review describes the field through its 2021 publication date and should not be treated as a current worldwide regulatory inventory (PMID 33802348).

Human data. The Becker muscular dystrophy study enrolled six participants in two ascending-dose cohorts. Four showed increases of 29 to 125 m on the six-minute walk test. The abstract described the other two as showing no improvement. The full text reports a 9 m increase in one and a 14 m decrease in the other, interpreted as no meaningful benefit. The lower-dose cohort had one year of reported follow-up; the higher-dose cohort had six months. Biopsies showed changes including reduced fibrosis and muscle fiber hypertrophy. These were uncontrolled observations, not proof of improved performance in healthy muscle (PMID 25322757). The inclusion body myositis study also treated six participants. Median annualized walking performance increased by 56.0 m per year, compared with a decline of 25.8 m per year in eight matched untreated subjects. The reported comparison had $p = 0.01$. Four treated participants improved by 58 to 153 m, while two improved by 5 to 23 m. Annualized change is a derived outcome and should not be presented as an identical one-year response for every participant (PMID 28279643). Both studies were small and lacked randomized placebo-controlled treatment assignment. The second used

Animal and mechanistic data. The nonhuman primate study reported increased quadriceps size and strength after intramuscular AAV1-FS344 gene delivery. The authors also reported no detected abnormalities in the organ assessments performed. Those observations apply to the animals, exposure, assays, and follow-up studied. They do not establish comprehensive human safety or validate repeated recombinant protein administration (PMID 20368179). PubMed now links that primate article to an August 2026 erratum. Its metadata was verified during this review, but the correction text could not be retrieved. The original findings are retained as reported findings with this unresolved qualification. The correction's consequences for individual figures or conclusions are not assumed (PMID 42555759). Rodent studies summarized in the myostatin literature show substantial hypertrophy after follistatin overexpression. Results depend on disease model and intervention. In severe spinal muscular atrophy mice, transgenic follistatin produced little muscle growth and no motor or survival benefit. This is evidence against universal efficacy, rather than evidence that all follistatin interventions fail (PMIDs

an untreated comparison group, which does not remove expectation effects, selection differences, or differences in supportive care. Both involved muscle disease rather than trained healthy adults. The studies also used protocol-based clinical monitoring and peri-treatment immunosuppression. A structured exercise program was explicitly introduced in the inclusion body myositis study. Greater exercise participation was associated with larger improvements, but exercise adherence was not randomized. The Becker report did not document the same prescribed exercise intervention. These publications support further investigation of gene delivery in selected muscle diseases. They do not establish that recombinant Follistatin-344 protein produces the same exposure, histological effects, or functional outcomes.

27695802 and 19477958). Direct recombinant protein research also exists. Feger and colleagues studied FS288 in rats after temporary muscle denervation and reinnervation. A subcutaneously implanted pump and catheter system delivered protein locally. Results included increased satellite cell counts after denervation, but mixed muscle weight and force outcomes. Some groups had smaller muscles or reduced force. A surgically implanted local infusion system is not equivalent to intermittent subcutaneous injection of FST315 or an unspecified FST344 preparation (PMID 35747585).

REGULATORY STATUS AND SPORT

STATUS

No approved follistatin treatment or prescribing label was identified in this review. The cited AAV-FS344 studies were investigational clinical studies, not marketing authorizations. Their existence does not establish authorization for recombinant protein preparations. In a 2020 enforcement letter, FDA identified follistatin among substances used in compounded products that did not qualify for the cited section 503A exemptions. That document supports a specific United States regulatory finding. It does not establish the current legal status of every formulation, research activity, or jurisdiction. [FDA enforcement letter, April 1, 2020](https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/tailor-made-compounding-llc-594743-04012020). A laboratory reagent designation does not constitute approval for administration to people. Regulatory authorization, lawful research supply, and product quality are separate questions.

WADA

Prohibited at all times under S4.3 of the 2026 WADA Prohibited List, Agents Preventing Activin Receptor IIB Activation. Follistatin is explicitly listed as a myostatin-binding protein. Gene transfer with potential to enhance sport performance is separately prohibited under M3.1. [WADA Prohibited List](https://www.wada-ama.org/en/prohibited-list). These prohibitions apply in and out of competition. A research designation or absence of an approved indication does not create an exemption.

RESEARCH USE · REPORTED, NOT RECOMMENDED

ROUTES

The cited human AAV studies used direct bilateral intramuscular administration into quadriceps muscles during a single treatment session. A treatment session involved multiple injection sites, so describing the intervention as one injection is misleading. The Becker study used imaging-guided administration across selected quadriceps muscles (PMID 25322757). Local vector administration does not guarantee that the expressed protein remains local. The FS344 construct produces a secreted isoform, and circulating or remote effects are biologically possible. Route of vector delivery and distribution of the resulting protein are different properties. Animal recombinant protein research includes local delivery through a catheter connected to a subcutaneously implanted pump. The pump's location does not make its exposure equivalent to an ordinary subcutaneous bolus (PMID 35747585). No human route was identified as validated for the unmodified recombinant protein preparations discussed here. Oral and intranasal bioavailability were also not established in the reviewed evidence.

HALF-LIFE

A clinically usable human elimination half-life was not identified for unmodified recombinant FST344 or FST315 administered by the non-clinical subcutaneous route. Values assigned to endogenous follistatin, another isoform, an engineered derivative, or another species cannot be transferred without supporting pharmacokinetic data. The exercise study measured a changing endogenous concentration. Production, secretion, distribution, binding, and clearance can all contribute to that curve. It was not an injected-protein pharmacokinetic study and cannot establish an elimination half-life. Protein size alone also does not determine persistence (PMID 21068158). Gene therapy requires a different description. Vector persistence, transgene expression, secreted protein turnover, and the duration of a biological effect are separate quantities. The primate study reported durable effects after gene transfer, but those findings do not supply a half-life for a

recombinant protein preparation. Its linked 2026 erratum remains a qualification to interpretation (PMIDs 20368179 and 42555759).

TIMING

No validated timing relative to resistance training, meals, or sleep was identified for recombinant Follistatin-344 protein. The endogenous exercise response does not supply a treatment schedule or establish an optimal administration window. The inclusion body myositis study incorporated exercise and reported greater improvement among participants who exercised more. That association cannot isolate the contribution of exercise, gene transfer, or differences between participants. It also cannot establish that protein administration immediately before or after exercise changes outcomes (PMID 28279643). The appropriate interpretation is that exercise was part of the studied clinical context. The reported findings do not justify importing training-day timing rules into a recombinant protein protocol.

CYCLE LENGTH

The human AAV studies used a single treatment session, followed by clinical observation. In the Becker report, follow-up differed between cohorts, with approximately six months or one year reported. Observation length is not a validated treatment cycle or the time when transgene expression necessarily ends (PMID 25322757). For recombinant protein, courses of 10 to 30 days are commonly cited in non-clinical use; not validated in trials. No identified human study establishes an optimal course, washout interval, cumulative exposure limit, or repeated-course outcome for that practice. Gene transfer can produce persistent expression without a routine way to terminate it on demand. Immune responses to the vector can complicate repeat administration. Those concerns are specific to gene delivery and should not be presented as a universal prohibition on every future vector-based treatment.

TITRATION

No validated individual titration schedule was identified for recombinant Follistatin-344 protein. The Becker study escalated the vector dose between separate cohorts. That design evaluated preliminary tolerability and possible benefit; it did not establish how an individual should adjust exposure over time (PMID 25322757). Each cohort contained three participants, follow-up durations differed, and functional responses varied. More prominent histological changes at the higher dose therefore do not establish a reliable dose-response curve. Serum follistatin is not an established titration target for this use. Exercise-related variability complicates interpretation, but variability alone does not make every measurement useless. A validated assay, sampling framework, exposure-response relationship, and clinically relevant target would be needed before a concentration could guide dosing (PMID 21068158).

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Approved drug label	**No approved follistatin prescribing label or label dose was identified.**	Not applicable.	Not applicable.	Regulatory review. Investigational vector doses are not approved protein doses.
Human Becker muscular dystrophy trial, lower-dose cohort, three participants	**3 x 10^11 vg/kg per leg of AAV1.CMV.FS344, delivered intramuscularly to both quadriceps during one treatment session, PMID 25322757.**	Bilateral intramuscular quadriceps administration across multiple sites.	One treatment session.	Published phase 1/2a study, PMID 25322757. Two participants increased six-minute walking distance by 58 and 125 m. The third had no meaningful improvement. The publication reports one year of follow-up for this cohort. · PMID 25322757
Human Becker muscular dystrophy trial, higher-dose cohort, three participants	**6 x 10^11 vg/kg per leg of AAV1.CMV.FS344, delivered intramuscularly to both quadriceps during one treatment session, PMID 25322757.**	Bilateral intramuscular quadriceps administration across multiple sites.	One treatment session.	Published phase 1/2a study, PMID 25322757. Two participants increased six-minute walking distance by 108 and 29 m. The third had no meaningful improvement. The publication reports six months of follow-up for this cohort. · PMID 25322757

CONTEXT	DOSE	ROUTE	FREQUENCY	PROVENANCE
Human sporadic inclusion body myositis trial, six participants	**6 x 10^11 vg/kg of rAAV1.CMV.huFS344, reported in the abstract for intramuscular delivery to quadriceps muscles of both legs during one treatment session, PMID 28279643.**	Bilateral intramuscular quadriceps administration.	One treatment session, with a participant exercise program.	Published study, PMID 28279643. The exponent is 11, not an unresolved rendering problem. The abstract does not explicitly attach per leg to this dose statement, so that qualifier is not inferred from the Becker study. · PMID 28279643
Animal recombinant FS288 protein study after muscle denervation and reinnervation	**The study used protein loaded into an implanted pump for continuous local delivery. No equivalent intermittent subcutaneous human dose can be derived from this experiment, PMID 35747585.**	Local catheter delivery from a subcutaneously implanted osmotic pump.	Continuous infusion during the experimental treatment period.	Primary rat study, PMID 35747585. Protein isoform, delivery system, target tissue, and disease model differ from non-clinical use of material labeled Follistatin-344. · PMID 35747585
Reported non-clinical use of recombinant protein labeled Follistatin-344	**100 mcg subcutaneously once daily for 10 to 30 days, commonly cited in non-clinical use; not validated in trials.**	Subcutaneous, reported non-clinical practice.	Once daily for 10 to 30 days, commonly cited in non-clinical use; not validated in trials.	commonly cited in non-clinical use; not validated in trials. No identified study establishes efficacy, systemic exposure, or safety for this exact preparation and schedule. This is not a recommended regimen. Vendor and forum usage, not evidence: listed so you can recognize it, not follow it; no trial has validated this regimen and it is not a recommendation.

STACKING

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

– IGF-1 LR3

No verified human combination study establishes benefit, tolerability, or dosing with follistatin. Different signaling pathways do not demonstrate additive clinical effects.

– Ipamorelin

No verified combination evidence supports adding this compound to recombinant follistatin. A proposed difference in mechanism does not establish complementary efficacy or acceptable combined exposure. Concurrent interventions would also complicate interpretation of changes in performance, fluid balance, or symptoms.

– CJC-1295

No verified human combination evidence was identified. Stimulation of a separate growth-related pathway is a mechanistic hypothesis, not an established synergy. Neither a combination dose nor a monitoring strategy can be derived from the cited follistatin gene therapy studies.

– BPC-157

Exercise participation in a gene therapy trial does not establish a need for another experimental

	compound. There is no verified basis here for claiming prevention of tendon injury or improved recovery.
– Semaglutide	No established interaction with follistatin was demonstrated in the reviewed references. Changes in energy intake and body composition could complicate attribution of muscle outcomes. That is a study-design concern, not evidence of a direct goal conflict or a reason to alter prescribed treatment.
– Retatrutide	No verified follistatin combination study was identified. Simultaneous changes in weight, appetite, training, and experimental exposures would make outcomes harder to interpret.
– FOXO4-DRI	No verified evidence establishes the benefit or safety of this combination. Combining experimental interventions introduces additional uncertainty and complicates adverse-event attribution. Mechanistic novelty does not supply a clinical rationale, and the absence of combination evidence does not quantify the magnitude of risk.

SAFETY

COMMON EFFECTS

A frequency-ranked adverse-effect profile has not been established for non-clinical recombinant Follistatin-344 protein use. The Becker study reported no adverse effects in six participants under its monitored gene therapy protocol. That small observation cannot exclude uncommon, delayed, or exposure-dependent problems. It also does not establish tolerability for repeated protein administration (PMID 25322757). Potential administration-related problems include local pain, inflammation, infection, and allergic or other immune reactions. These are general risks of parenteral protein products, not measured follistatin-specific incidence estimates. Product impurities, aggregates, residual manufacturing material, and microbial contamination can change those risks. The primate paper reported no detected abnormalities in its organ assessments. This is limited preclinical information, and the linked 2026 erratum requires review before treating particular original findings as definitive. Neither that report nor the small human studies establishes a comprehensive safety profile (PMIDs 20368179 and 42555759).

SERIOUS SIGNALS

Broad activin sequestration creates plausible concerns outside muscle. Reproductive hormone regulation, gonadal function, glucose regulation, immune signaling, and tissue repair are relevant areas for investigation. These concerns arise from activin biology. They are not a confirmed list of adverse reactions caused by the non-clinical protein schedule (PMID 19273500). Cancer-related effects require particular caution in interpretation. TGF-beta superfamily signaling can have context-dependent roles in tumor biology. The reviewed studies do not establish that recombinant follistatin causes cancer, protects against cancer, or has acceptable exposure in people with malignancy. A mechanistic association cannot determine an individual risk estimate. Reduced force or smaller muscles occurred in some groups receiving recombinant FS288 in the rat study. These findings show that biological effects can differ by tissue condition and treatment design. They do not establish corresponding human incidence or predict what an unspecified commercial preparation would do (PMID 35747585). For AAV gene delivery, persistent expression and vector-directed immunity are separate concerns. Expression is not routinely adjustable after administration, and immune responses can constrain subsequent treatment options. Long-term risk remains incompletely characterized in the small follistatin clinical literature. Bleeding syndromes observed with other pathway interventions should not be assigned to follistatin without compound-

specific evidence. Similarly, failure to improve function is an efficacy limitation unless accompanied by documented harm.

CONTRAINDICATIONS

There is no approved prescribing label establishing a formal contraindication list for this use. Pregnancy, breastfeeding, attempts to conceive, and pediatric exposure lack an established benefit-risk basis. Reproductive uncertainty is particularly relevant because activin participates in gonadal and pituitary regulation (PMID 19273500). Active or previous malignancy, significant endocrine disease, impaired glucose regulation, and previous serious reactions to biological products raise additional clinical concerns. These are precautionary considerations and evidence gaps, not confirmed label contraindications. AAV trial eligibility and exclusions also cannot be copied directly to a recombinant protein product. Known hypersensitivity to a formulation component would be a specific concern for that formulation. Missing identity, sterility, or stability documentation is a product-quality failure rather than a patient contraindication. Participation in regulated sport is governed separately by the WADA prohibition.

STOP RULES

Breathing difficulty, wheezing, facial or tongue swelling, collapse, or rapidly progressive systemic symptoms require emergency evaluation. Fever with spreading redness, warmth, severe pain, or drainage at an administration site requires prompt assessment for infection. New persistent swelling, unexplained bleeding, a new mass, marked changes in reproductive function, or symptoms of abnormal glucose regulation warrant clinical review. These are general reasons for evaluation, not established follistatin-specific toxicity markers. Further experimental exposure would not resolve their cause. No validated home monitoring threshold establishes that continued exposure is acceptable. Normal routine blood tests cannot exclude all immune, endocrine, or tissue effects. With gene transfer, stopping administration does not terminate protein expression already established.

RECONSTITUTION AND STORAGE

TYPICAL VIAL

No standardized clinical vial presentation exists for recombinant Follistatin-344. A stated protein mass is a content claim, not proof of identity, concentration, activity, sterility, or suitability for administration. Relevant product definitions include the actual amino acid sequence, mature isoform, expression system, formulation, and assay used to measure content. A precursor-based name alone does not specify these properties. The human AAV studies used investigational vector preparations rather than interchangeable lyophilized protein vials.

SOLVENT

No generally validated clinical diluent was identified for the unspecified recombinant protein preparations discussed here. Preservative compatibility, buffer composition, pH, ionic strength, and protein concentration can affect stability and activity. Bacteriostatic water does not sterilize a contaminated product or establish a multidose shelf life. A reagent's laboratory dissolution instructions also do not establish suitability for administration to people. Formulation-specific evidence would be required before assigning a solvent, handling method, or usable concentration range. Protein aggregation can be influenced by agitation and interfaces, but those general principles do not validate a specific preparation procedure. The original step-by-step administration-oriented instructions have therefore been replaced with the limits of the available formulation evidence.

STORAGE

No universal storage temperature or post-reconstitution shelf life can be assigned to unspecified material labeled Follistatin-344. Appropriate conditions depend on the actual isoform, formulation, concentration, container, and validated stability data. Temperature excursions and freeze-thaw cycles can affect proteins, but an excursion does not by itself quantify potency loss. Conversely, clear appearance does not establish stability, sterility, or biological activity. Visible particles or discoloration indicate a quality concern without identifying its exact cause. A credible stability claim requires defined conditions, time points, and suitable analytical or functional assays. A certificate issued at manufacture does not establish the condition of material after storage or transport. Shipping requirements should follow demonstrated formulation stability rather than an assumption that every protein must arrive with cold packs.

Concentration arithmetic only: a hypothetical laboratory sample containing 1 mg of protein in a final solution volume of 2 mL has a nominal concentration of 0.5 mg/mL, equivalent to 500 mcg/mL. These quantities describe an illustrative solution, not a documented clinical formulation or an administration dose.

The denominator is final solution volume. It is not automatically identical to the volume of liquid added, particularly when exact formulation volumes matter. The calculation also assumes that the stated mass is correct, that all material dissolves, and that the protein remains uniformly distributed.

Changing the final volume changes nominal concentration. It does not establish biological potency

or make an unverified protein preparation equivalent to study material. Measured protein content can differ from active protein content because of degradation, aggregation, or inactive species.

No administration volume or syringe setting is supplied here. Neither concentration arithmetic nor a vial label resolves the absence of a validated human protein dose, compatible formulation, or stability interval.

BUYING NOTES

The central quality question is whether the tested material matches the claimed molecular entity. Follistatin isoforms differ in sequence and tissue association. Expression systems and manufacturing processes can also alter processing, folding, glycosylation, and impurities. These properties affect the interpretation of a reagent, but price alone cannot establish authenticity or identify the cause of a quality failure. It also treated bacterial expression, low price, and warm delivery as proof of failure. Those conclusions require product-specific evidence. A preparation can differ from endogenous protein without its identity being fraudulent, while still being unsuitable for the claimed application. A useful certificate of analysis identifies the tested batch and the laboratory, methods, dates, specifications, and results. The batch identifier must connect the report to the material being described. A generic example certificate does not establish the properties of a particular batch. Independent testing can strengthen confidence when the tested sample and chain of custody are documented, but independence alone does not make an unsuitable assay informative. Identity may require peptide mapping, intact mass analysis, or other sequence-sensitive methods. Purity methods address different impurities and have different limitations. Electrophoretic purity does not establish receptor-binding activity. A high chromatographic purity percentage does not establish total protein content, correct folding, or absence of aggregates. Functional binding or cell-based assays answer questions that a purity percentage cannot. Microbiological quality is another separate issue. Endotoxin results do not demonstrate sterility, and sterility results do not establish an acceptable endotoxin burden. Residual host-cell proteins, nucleic acids, processing reagents, and particulate material may also matter. A research certificate is not equivalent to a complete pharmaceutical release assessment. The label Follistatin-344 requires clarification because it commonly refers to a precursor sequence. Nevertheless, a manufactured reagent could contain an engineered precursor, a mature isoform, a tagged construct, or another specified sequence. The number alone neither proves impossibility nor identifies the contents. The claim must be checked against sequence and analytical documentation. Finally, evidence of chemical identity does not establish clinical efficacy, dosing, regulatory authorization, or long-term safety. Even a correctly characterized laboratory reagent would not close the gap between recombinant protein administration and the published AAV gene therapy studies.

COMMON MISTAKES

- Transferring gene therapy results to recombinant protein. The human studies administered an AAV vector that changed protein production in muscle. An externally manufactured protein has a different exposure profile. Neither vector genomes nor clinical outcomes can be converted into a protein schedule without additional evidence.
- Treating an endogenous exercise response as a treatment experiment. The Hansen study documented changing circulating follistatin and supported a likely hepatic contribution. It did not compare injected protein with gene therapy or test long-term hypertrophy. It therefore establishes neither effectiveness nor ineffectiveness of recombinant protein administration (PMID 21068158).
- Reading the clinical participants as trained lifters. The cited human trials involved degenerating muscle, functional impairment, and clinical monitoring. Fibrosis, innervation, muscle reserve, and disease progression influence treatment response. Findings in those settings do not establish performance benefits in healthy adults.
- Claiming that both human trials prescribed the same exercise program. A structured program was introduced in the inclusion body myositis study. Exercise adherence was associated with outcome but was not randomized. That association cannot separate the effects of exercise, gene transfer, supportive treatment, and participant differences (PMID 28279643).
- Assuming that protein studies do not exist. Recombinant FS288 was studied in rats using local catheter delivery from implanted pumps. Outcomes were mixed, including increased satellite cell counts alongside unfavorable muscle outcomes in some groups. The study is relevant evidence but does not validate intermittent subcutaneous FST344 use (PMID 35747585).

- Assuming more muscle necessarily produces more useful function. Severe spinal muscular atrophy mice did not gain motor or survival benefit from follistatin overexpression. The wider clinical literature also documents difficulty translating muscle growth into functional improvement. Disease context and outcome selection remain essential (PMIDs 19477958 and 33802348).
- Assigning a human protein half-life from an exercise graph or another follistatin-related molecule. Endogenous concentration changes reflect secretion as well as clearance. An isoform, engineered construct, species, or administration route requires its own pharmacokinetic interpretation. A plausible numerical estimate is not a measured clinical parameter.
- Treating concentration arithmetic as validation of administration. Correct unit conversion does not verify the actual protein mass, activity, sterility, solvent compatibility, or clinical dose. A calculated concentration remains nominal when the preparation and its stability have not been established.
- Treating proposed combinations as demonstrated synergies or contraindications. Different mechanisms do not establish additive benefit. Concurrent weight loss does not prove a direct drug interaction. The revised combination entries describe evidence gaps and attribution problems rather than advising changes to prescribed treatment.
- Using the wrong anti-doping category or equating a research designation with permission. The 2026 list explicitly places follistatin under S4.3, and performance-enhancing gene transfer is separately covered by M3.1. Both apply outside competition as well as during competition.

REFERENCES

1. Mendell JR et al. A phase 1/2a follistatin gene therapy trial for becker muscular dystrophy.. *Molecular therapy : the journal of the American Society of Gene Therapy*, 2015. PMID 25322757 DOI 10.1038/mt.2014.200 (Primary uncontrolled human AAV-FS344 study in six participants with Becker muscular dystrophy. Reports intramuscular quadriceps vector administration, cohort-specific doses and follow-up, walking outcomes, biopsy findings, and clinical monitoring. Also describes precursor processing. Does not validate recombinant protein administration.)
2. Mendell JR et al. Follistatin Gene Therapy for Sporadic Inclusion Body Myositis Improves Functional Outcomes.. *Molecular therapy : the journal of the American Society of Gene Therapy*, 2017. PMID 28279643 DOI 10.1016/j.ymthe.2017.02.015 (Small human AAV-FS344 study with six treated participants and eight matched untreated comparators. Reports annualized walking outcomes, histological findings, vector dose, an exercise program, and associations between exercise participation and improvement. Does not isolate a protein treatment effect.)
3. Kota J et al. Follistatin gene delivery enhances muscle growth and strength in nonhuman primates.. *Science translational medicine*, 2009. PMID 20368179 DOI 10.1126/scitranslmed.3000112 (Reports muscle size and strength findings and organ assessments after intramuscular AAV1-FS344 gene delivery in cynomolgus macaques. Interpretation is qualified by a linked 2026 erratum whose contents were not retrieved. Does not establish recombinant protein dosing or comprehensive human safety.)
4. Sumner CJ et al. Inhibition of myostatin does not ameliorate disease features of severe spinal muscular atrophy mice.. *Human molecular genetics*, 2009. PMID 19477958 DOI 10.1093/hmg/ddp253 (Negative disease-model evidence. Transgenic follistatin overexpression produced little additional muscle mass and no motor or survival benefit in severe spinal muscular atrophy mice. Supports limits on claims of universal functional benefit.)
5. Chen PR et al. INVITED REVIEW: Inhibitors of myostatin as methods of enhancing muscle growth and development.. *Journal of animal science*, 2016. PMID 27695802 DOI 10.2527/jas.2016-0532 (Review of myostatin inhibition, follistatin-related mechanisms, and experimental muscle growth. Provides preclinical context, not current regulatory status or a validated human recombinant protein regimen.)
6. Nielsen TL et al. Antimyostatin Treatment in Health and Disease: The Story of Great Expectations and Limited Success.. *Cells*, 2021. PMID 33802348 DOI 10.3390/cells10030533 (Review of clinical translation limitations in myostatin-directed treatment through 2021. Supports distinguishing muscle mass outcomes from functional benefit and avoiding transfer of animal findings to untested clinical applications.)
7. Hansen J et al. Exercise induces a marked increase in plasma follistatin: evidence that follistatin is a contraction-induced hepatokine.. *Endocrinology*, 2011. PMID 21068158 DOI 10.1210/en.2010-0868 (Human exercise physiology with complementary mouse experiments. Reports increased circulating follistatin after prolonged cycling, no detectable net release from the exercising limb, and evidence supporting a likely hepatic source. Does not measure injected-protein elimination or comparative treatment efficacy.)
8. Xia Y et al. The biology of activin: recent advances in structure, regulation and function.. *The Journal of endocrinology*, 2009. PMID 19273500 DOI 10.1677/JOE-08-0549 (Activin biology, structural regulation by binding proteins, and reproductive, metabolic, and immune functions. Supports mechanistic discussion and precautionary concerns, not a confirmed adverse-event incidence or formal follistatin contraindication list.)
9. Feger MA et al. Follistatin Protein Enhances Satellite Cell Counts in Reinnervated Muscle.. *Journal of brachial plexus and peripheral nerve injury*, 2022. PMID 35747585 DOI 10.1055/s-0042-1748535 (Primary rat study of recombinant FS288 protein delivered locally using an implanted pump and catheter system after denervation and reinnervation. Reports increased satellite cell counts after denervation and mixed muscle size and force findings.)

10. et al. Erratum for the Research Article "Follistatin gene delivery enhances muscle growth and strength in nonhuman primates".. *Science translational medicine*, 2026. PMID 42555759 DOI 10.1126/scitranslmed.aek4223 (Confirms a published correction linked to PMID 20368179. PubMed esummary lists no authors. The correction text was not retrieved, so its effect on individual results remains unresolved.)

Reference index

267 records cited in this module. Every PMID resolves at pubmed.ncbi.nlm.nih.gov/PMID.

1. et al. Erratum for the Research Article "Follistatin gene delivery enhances muscle growth and strength in nonhuman primates".. *Science translational medicine*, 2026. PMID 42555759 DOI 10.1126/scitranslmed.aek4223 (Confirms a published correction linked to PMID 20368179. PubMed esummary lists no authors. The correction text was not retrieved, so its effect on individual results remains unresolved.)
2. Adrian S et al. The Growth Hormone Releasing Hormone Analogue, Tesamorelin, Decreases Muscle Fat and Increases Muscle Area in Adults with HIV.. *The Journal of frailty & aging*, 2019. PMID 31237318 DOI 10.14283/jfa.2018.45 (Exploratory trunk-muscle imaging analysis restricted to tesamorelin VAT responders; does not establish training performance or strength benefit.)
3. Agbo E et al. Modulation of PTEN by hexarelin attenuates coronary artery ligation-induced heart failure in rats.. *Turkish journal of medical sciences*, 2019. PMID 31091855 DOI 10.3906/sag-1812-49 (Rat coronary-ligation heart failure research involving PTEN modulation. Does not establish efficacy or safety in human heart failure.)
4. Agbo E et al. Hexarelin protects cardiac H9C2 cells from angiotensin II-induced hypertrophy via the regulation of autophagy.. *Die Pharmazie*, 2019. PMID 31526442 DOI 10.1691/ph.2019.9324 (Cultured cardiac-cell research on autophagy and hypertrophy. Classified as mechanistic cell evidence, not an animal or human outcome trial.)
5. Ahmed M et al. Efficacy and Safety of Cagrilintide and Cagrisema Versus Semaglutide as Anti-Obesity Medications: A Systematic Review, Meta-Analysis and Meta-Regression.. *Diabetes, obesity & metabolism*, 2026. PMID 41834765 DOI 10.1111/dom.70667 (Pooled weight comparisons, nausea and administration-site events, a serious-adverse-event association for monotherapy, and LDL cholesterol differences. The abstract does not establish causation for the serious-event imbalance.)
6. Alawadhi AA et al. LEAN mass Preservation with Resistance Exercise and Protein during semaglutide and tirzepatide therapy (LEAN-PREP study): a protocol for a randomised controlled trial.. *BMJ open*, 2026. PMID 42020128 DOI 10.1136/bmjopen-2026-116911 (Planned resistance-exercise and protein trial. This publication reports a protocol, not efficacy results.)
7. Alba M et al. Once-daily administration of CJC-1295, a long-acting growth hormone-releasing hormone (GHRH) analog, normalizes growth in the GHRH knockout mouse.. *American journal of physiology. Endocrinology and metabolism*, 2006. PMID 16822960 DOI 10.1152/ajpendo.00201.2006 (Per-animal dose, experimental intervals, growth and body composition findings, and pituitary changes in GHRH-knockout mice. FDA's review of this study clarifies the change from subcutaneous to intraperitoneal administration. Does not establish enhancement or tumor risk in humans.)
8. Alhalabi H et al. In vitro metabolic profiling of weight-loss-inducing amylin receptor agonists in the context of preventive doping research.. *Journal of pharmaceutical and biomedical analysis*, 2026. PMID 41702251 DOI 10.1016/j.jpba.2026.117418 (Background statement reporting semaglutide monitoring since 2024; does not establish liraglutide monitoring or prohibition.)
9. Andersen NB et al. The growth hormone secretagogue ipamorelin counteracts glucocorticoid-induced decrease in bone formation of adult rats.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2001. PMID 11735244 DOI 10.1054/ghir.2001.0239 (Three-month subcutaneous rat regimen, muscle tetanic tension and periosteal bone formation in a glucocorticoid model.)
10. Antonijevic IA et al. Sexually dimorphic effects of GHRH on sleep-endocrine activity in patients with depression and normal controls - part I: the sleep eeg.. *Sleep research online : SRO*, 2000. PMID 11382894 (Different non-REM sleep responses in men and women. Does not establish efficacy for SC sermorelin.)
11. Argente J et al. Growth hormone-releasing peptides: clinical and basic aspects.. *Hormone research*, 1996. PMID 8950613 DOI 10.1159/000185015 (GHRP-2 interaction with GHRH 1-29 NH2 and separately identified GHRP-6 experiments involving rat hypothalamic gene expression.)
12. Aroda VR et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes.. *Diabetes care*, 2019. PMID 31186300 DOI 10.2337/dc19-0749 (Original oral trial doses, glycemic outcomes and identification of reported weight differences as placebo-adjusted estimates.)
13. Aronne LJ et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity.. *The New England journal of medicine*, 2025. PMID 40353578 DOI 10.1056/NEJMoa2416394 (SURMOUNT-5 maximum-tolerated-dose comparison, administration schedule and weight outcomes.)
14. Aronne LJ et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial.. *JAMA*, 2024. PMID 38078870 DOI 10.1001/jama.2023.24945 (Randomized continuation versus withdrawal and weight change measured from week 36.)
15. Arvat E et al. Effects of GHRP-2 and hexarelin, two synthetic GH-releasing peptides, on GH, prolactin, ACTH and cortisol levels in man. Comparison with the effects of GHRH, TRH and hCRH.. *Peptides*, 1997. PMID 9285939 DOI 10.1016/s0196-9781(97)00016-8 (Acute endocrine comparisons using single IV administrations of 1 or 2 mcg/kg, reported in PMID 9285939.)
16. Arvat E et al. Tyr-Ala-Hexarelin, a synthetic octapeptide, possesses the same endocrine activities of Hexarelin and GHRP-2 in humans.. *Journal of endocrinological investigation*, 1999. PMID 10195374 DOI 10.1007/BF03350386 (Acute endocrine comparison describing a single 2 mcg/kg IV GHRP-2 dose as maximally effective in that context, reported in PMID 10195374.)

17. Arvat E et al. Arginine and growth hormone-releasing hormone restore the blunted growth hormone-releasing activity of hexarelin in elderly subjects.. *The Journal of clinical endocrinology and metabolism*, 1994. PMID 7962341 DOI 10.1210/jcem.79.5.7962341 (Age-related differences in hexarelin responses and potentiation by GHRH or arginine under specific acute experimental conditions. Supports population-dependent endocrine responses.)

18. Arvat E et al. Modulation of growth hormone-releasing activity of hexarelin in man.. *Neuroendocrinology*, 1995. PMID 7731498 DOI 10.1159/000126827 (Human interactions with GHRH, somatostatin and neuroactive interventions. Somatostatin blunted the hexarelin response under the studied conditions.)

19. Badran AS et al. Body composition, hepatic fat, metabolic, and safety outcomes of Tesamorelin, a GHRH analogue, in HIV-associated lipodystrophy: A meta-analysis of randomized controlled trials.. *Obesity research & clinical practice*, 2026. PMID 41545261 DOI 10.1016/j.orcp.2026.01.002 (Five-trial synthesis, VAT and hepatic-fat outcomes, lean-mass increase, small limb-fat reduction, and nonsignificant subcutaneous-fat and BMI changes.)

20. Bajaj HS et al. Efficacy and safety of retatrutide, a GIP, GLP-1, and glucagon receptor agonist, in people with type 2 diabetes and inadequate glycaemic control with diet and exercise (TRANSCEND-T2D-1): a double-blind, randomised, phase 3 trial.. *Lancet (London, England)*, 2026. PMID 42250575 DOI 10.1016/S0140-6736(26)00967-0 (Phase 3 diabetes population, maintenance targets, 40-week treatment-regimen estimand results and adverse-event discontinuations.)

21. Baker LD et al. Effects of growth hormone–releasing hormone on cognitive function in adults with mild cognitive impairment and healthy older adults: results of a controlled trial.. *Archives of neurology*, 2012. PMID 22869065 DOI 10.1001/archneurol.2012.1970 (Cognitive, endocrine, body-composition, and adverse-event findings. Study dose: 1 mg SC once daily, 30 minutes before bedtime, for 20 weeks, PMID 22869065.)

22. Bastian SE et al. Plasma clearance and tissue distribution of labelled insulin-like growth factor-I (IGF-I) and an analogue LR3IGF-I in pregnant rats.. *The Journal of endocrinology*, 1993. PMID 7693845 DOI 10.1677/joe.0.1380327 (Direct radiotracer evidence of faster LR3 plasma clearance, predominantly free circulating analog, and tissue-distribution differences in pregnant and nonpregnant rats. Does not provide a human plasma half-life.)

23. Batsis JA et al. Effect of Incretin-Based and Nonpharmacologic Weight Loss on Body Composition : A Systematic Review.. *Annals of internal medicine*, 2026. PMID 41996180 DOI 10.7326/ANNALS-25-00478 (Heterogeneous body-composition outcomes across 35 studies and limitations of treating different muscle-related indices as equivalent.)

24. Beck DE et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients.. *International journal of colorectal disease*, 2014. PMID 25331030 DOI 10.1007/s00384-014-2030-8 (Randomized postoperative ileus trial, intravenous regimen, enrollment and analysis populations, overall adverse-event rates and nonsignificant efficacy comparisons.)

25. Bjerre Knudsen L et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation.. *Endocrinology*, 2010. PMID 20203154 DOI 10.1210/en.2009-1272 (Class-level thyroid C-cell pharmacology and species differences, with explicit limits on semaglutide-specific and human-risk inference.)

26. Blundell J et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity.. *Diabetes, obesity & metabolism*, 2017. PMID 28266779 DOI 10.1111/dom.12932 (Small human crossover study of appetite, measured meal intake, body weight and resting metabolic rate adjusted for lean mass.)

27. Bodart V et al. CD36 mediates the cardiovascular action of growth hormone-releasing peptides in the heart.. *Circulation research*, 2002. PMID 11988484 DOI 10.1161/01.res.0000016164.02525.b4 (Identification of CD36 as a cardiac hexarelin-binding protein and CD36-dependent increases in coronary perfusion pressure in isolated hearts. This is a preclinical vascular finding.)

28. Bowers CY et al. History to the discovery of ghrelin.. *Methods in enzymology*, 2012. PMID 22975043 DOI 10.1016/B978-0-12-381272-8.00001-5 (Historical development of growth hormone releasing peptides before the discovery of ghrelin.)

29. Bowers CY et al. Sustained elevation of pulsatile growth hormone (GH) secretion and insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3), and IGFBP-5 concentrations during 30-day continuous subcutaneous infusion of GH-releasing peptide-2 in older men and women.. *The Journal of clinical endocrinology and metabolism*, 2004. PMID 15126555 DOI 10.1210/jc.2003-031799 (Thirty-day hormone responses, normal screening tests and separate GHRH combination experiments. Continuous SC exposure was 1 mcg/kg per hour for 30 days, reported in PMID 15126555.)

30. Bowers CY et al. Growth hormone/insulin-like growth factor-1 response to acute and chronic growth hormone-releasing peptide-2, growth hormone-releasing hormone 1-44NH2 and in combination in older men and women with decreased growth hormone secretion.. *Endocrine*, 2001. PMID 11322505 DOI 10.1385/ENDO:14:1:079 (Acute and repeated-exposure experiments in older adults, including a single 10 mcg/kg SC bolus reported in PMID 11322505.)

31. Bowers CY et al. Growth hormone (GH)-releasing peptide stimulates GH release in normal men and acts synergistically with GH-releasing hormone.. *The Journal of clinical endocrinology and metabolism*, 1990. PMID 2108187 DOI 10.1210/jcem-70-4-975 (Acute intravenous endocrine dose response in 18 men, synergy with GHRH-(1-44)-NH2, and prolactin and cortisol responses. Does not establish muscle gain or chronic combination efficacy.)

32. Bowers CY et al. The growth hormone-releasing activity of a synthetic hexapeptide in normal men and short statured children after oral administration.. *The Journal of clinical endocrinology and metabolism*, 1992. PMID 1730807 DOI 10.1210/jcem.74.2.1730807 (Oral endocrine activity, route-specific hormone timing, comparison with intravenous activity, and an older immunoreactive peptide half-life estimate. The relative activity estimate is not universal absolute bioavailability.)

33. Bowers CY et al. GH releasing peptides--structure and kinetics.. *The Journal of pediatric endocrinology*, 1993. PMID 8374685 DOI 10.1515/jpem.1993.6.1.21 (GHRP pharmacology. The explicitly described combination experiment involved GHRP-1 and GHRH(1-44)-NH2, not sermorelin plus GHRP-2.)

34. Branine N et al. Online-Sourced Retatrutide Complicating Impending Diabetic Ketoacidosis in a Patient With Type 1 Diabetes and Concurrent Shigella Gastroenteritis.. *Cureus*, 2026. PMID 42669023 DOI 10.7759/cureus.115260 (Confounded case involving an online-labelled product, gastrointestinal illness, ketonaemia, dehydration and acute kidney injury. Causation was not established.)

35. Brown C et al. Retatrutide: Obesity drug opens to "compassionate use" in US after speculation Trump took it.. *BMJ (Clinical research ed.)*, 2026. PMID 42567543 DOI 10.1136/bmj-2026-100530 (News report concerning US compassionate access. Not an efficacy trial or marketing authorization.)

36. Brywe KG et al. Growth hormone-releasing peptide hexarelin reduces neonatal brain injury and alters Akt/glycogen synthase kinase-3beta phosphorylation.. *Endocrinology*, 2005. PMID 16081643 DOI 10.1210/en.2005-0389 (Neonatal rat brain-injury research and associated signaling findings. Provides animal evidence for that injury model, not adult cognitive benefit.)

37. Buse JB et al. Cagrilintide-semaglutide (CagriSema) versus semaglutide or cagrilintide in people with type 2 diabetes (REIMAGINE 2): a double-blind, randomised, controlled, phase 3 study.. *The lancet. Diabetes & endocrinology*, 2026. PMID 42251859 DOI 10.1016/S2213-8587(26)00125-7 (REIMAGINE 2, 2713 participants and a 152-person cagrilintide arm. Combination targets were 2.4 mg each or 1.0 mg each subcutaneously once weekly, PMID 42251859.)

38. Cabrales A et al. Pharmacokinetic study of Growth Hormone-Releasing Peptide 6 (GHRP-6) in nine male healthy volunteers.. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 2013. PMID 23099431 DOI 10.1016/j.ejps.2012.10.006 (Single intravenous pharmacokinetic study, peptide sequence and molecular weight, distribution and elimination half-life estimates. Publication year follows PubMed pubdate, with online publication in 2012.)

39. Cao J et al. Structural and dynamic features of cagrilintide binding to calcitonin and amylin receptors.. *Nature communications*, 2025. PMID 40204768 DOI 10.1038/s41467-025-58680-y (Structural characterization of cagrilintide at AMY1R, AMY2R, AMY3R and calcitonin receptors, including receptor-complex dynamics.)

40. Carvas AO et al. Cagrilintide lowers bodyweight through brain amylin receptors 1 and 3.. *EBioMedicine*, 2025. PMID 40609154 DOI 10.1016/j.ebiom.2025.105836 (RAMP1/3 knockout experiments and brainstem activation findings. The reported mouse experiment used cagrilintide 3 nmol/kg subcutaneously once daily for three weeks, PMID 40609154.)

41. Cella SG et al. Sixteen weeks of hexarelin therapy in aged dogs: effects on the somatotropic axis, muscle morphology, and bone metabolism.. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 1996. PMID 8914494 DOI 10.1093/gerona/51a.6.b439 (Aged-dog treatment and interruption periods, changing endocrine responsiveness and improvement in selected muscle indices in three of six animals. Does not validate human cycling.)

42. Chen PR et al. INVITED REVIEW: Inhibitors of myostatin as methods of enhancing muscle growth and development.. *Journal of animal science*, 2016. PMID 27695802 DOI 10.2527/jas.2016-0532 (Review of myostatin inhibition, follistatin-related mechanisms, and experimental muscle growth. Provides preclinical context, not current regulatory status or a validated human recombinant protein regimen.)

43. Chihara K et al. A simple diagnostic test using GH-releasing peptide-2 in adult GH deficiency.. *European journal of endocrinology*, 2007. PMID 17609397 DOI 10.1530/EJE-07-0066 (Diagnostic validation, assay-dependent interpretation and a single 100 mcg IV bolus after overnight fasting, as reported in PMID 17609397.)

44. Cibrián D et al. Use of growth-hormone-releasing peptide-6 (GHRP-6) for the prevention of multiple organ failure.. *Clinical science (London, England : 1979)*, 2006. PMID 16417467 DOI 10.1042/CS20050374 (Cell experiments and rat ischemia-reperfusion injury findings, including intraperitoneal pretreatment and reductions in selected injury markers. Does not establish human organ protection.)

45. Clemmons DR et al. Safety and metabolic effects of tesamorelin, a growth hormone-releasing factor analogue, in patients with type 2 diabetes: A randomized, placebo-controlled trial.. *PloS one*, 2017. PMID 28617838 DOI 10.1371/journal.pone.0179538 (Twelve-week diabetes study and lower-dose research arm. Study doses: 1 mg or 2 mg SC once daily in separate groups, PMID 28617838.)

46. Corpas E et al. Growth hormone (GH)-releasing hormone-(1-29) twice daily reverses the decreased GH and insulin-like growth factor-I levels in old men.. *The Journal of clinical endocrinology and metabolism*, 1992. PMID 1379256 DOI 10.1210/jcem.75.2.1379256 (Small adult crossover study of GH and IGF-I responses. Does not demonstrate improved body composition.)

47. Coskun T et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept.. *Molecular metabolism*, 2018. PMID 30473097 DOI 10.1016/j.molmet.2018.09.009 (Receptor pharmacology, mouse experiments, phase 1 regimens, tolerability, pharmacokinetics and investigational formulation methods.)

48. Coskun T et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept.. *Cell metabolism*, 2022. PMID 35985340 DOI 10.1016/j.cmet.2022.07.013 (Receptor activity, mouse intake and energy-expenditure mechanisms, and single-dose human observations through day 43.)

49. Coskun T et al. Effects of retatrutide on body composition in people with type 2 diabetes: a substudy of a phase 2, double-blind, parallel-group, placebo-controlled, randomised trial.. *The lancet. Diabetes & endocrinology*, 2025. PMID 40609566 DOI 10.1016/S2213-8587(25)00092-0 (DXA fat-mass reductions and the proportion of lean-mass loss relative to total weight loss. Does not establish strength preservation.)

50. Cox HD et al. Detection and in vitro metabolism of AOD9604.. *Drug testing and analysis*, 2015. PMID 25208511 DOI 10.1002/dta.1715 (Compound identity, analytical characterization and in vitro metabolism. Publication year follows PubMed's journal publication date rather than its earlier electronic publication date.)

51. D'Ascanio AM et al. Cagrilintide: A Long-Acting Amylin Analog for the Treatment of Obesity.. *Cardiology in review*, 2024. PMID 36883831 DOI 10.1097/CRD.0000000000000513 (Review of amylin-related satiation mechanisms and combination rationale. The PubMed issue publication year is 2024, following online publication in 2023.)

52. Davies MJ et al. Cagrilintide-Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes.. *The New England journal of medicine*, 2025. PMID 40544432 DOI 10.1056/NEJMoa2502082 (REDEFINE 2, 1206 participants, 68-week treatment-policy weight outcomes and gastrointestinal adverse events in adults with type 2 diabetes.)

53. De Gennaro-Colonna V et al. Endocrine, metabolic and cardioprotective effects of hexarelin in obese Zucker rats.. *The Journal of endocrinology*, 2000. PMID 10974647 DOI 10.1677/joe.0.1660529 (Rat subcutaneous exposure, cardiac findings, failure to improve somatotropic function in obese animals and increased glucose and insulin in the obese group.)

54. Demers A et al. Hexarelin Signaling to PPARgamma in Metabolic Diseases.. *PPAR research*, 2008. PMID 18288286 DOI 10.1155/2008/364784 (Mechanistic review of hexarelin-related metabolic signaling and PPARgamma. Supports proposed pathways, not established adult recomposition outcomes.)

55. Ditta AM et al. Efficacy and Safety of Tesamorelin in People Living With HIV (PLWH) With Lipodystrophy: A Systematic Review and Meta-Analysis.. *Journal of the International Association of Providers of AIDS Care*, 2026. PMID 42538058 DOI 10.1177/23259582261475549 (Four-trial synthesis, body-composition outcomes, lean-mass estimate, and statistically imprecise discontinuation estimate.)

56. Dominikowski A et al. The emerging landscape of performance-enhancing peptides modulating GH-IGF1 axis: bridging the gap between clinical evidence and patient self-administration.. *Frontiers in endocrinology*, 2026. PMID 42395176 DOI 10.3389/fendo.2026.1822475 (Secondary overview of unsuccessful obesity development and non-clinical practices. Reports 1 mg orally daily for 12 weeks and forum-derived subcutaneous daily totals. Its intravenous unit omission and current Category 2 claim were not adopted.)

57. Drucker DJ et al. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity.. *Diabetes care*, 2024. PMID 38843460 DOI 10.2337/dci24-0003 (Class-level discussion of gastrointestinal motility, anaesthesia, pancreatic and biliary concerns, and interpretation of muscle-related outcomes.)

58. Dutta D et al. Efficacy and Safety of Cagrilintide Alone and in Combination with Semaglutide (Cagrisema) as Anti-Obesity Medications: A Systematic Review and Meta-Analysis.. *Indian journal of endocrinology and metabolism*, 2024. PMID 39676787 DOI 10.4103/ijem.ijem_45_24 (Earlier pooled efficacy and tolerability comparisons, including lower vomiting with cagrilintide monotherapy than with GLP-1 comparators. Included trials overlap with other cited evidence.)

59. Enebo LB et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial.. *Lancet (London, England)*, 2021. PMID 33894838 DOI 10.1016/S0140-6736(21)00845-X (Phase 1b combination study, half-life of 159 to 195 hours, peak concentration timing, dose-dependent exposure and semaglutide pharmacokinetics. Cagrilintide targets were 0.16 to 4.5 mg subcutaneously once weekly, PMID 33894838.)

60. Engel MG et al. Intranasal long R3 insulin-like growth factor-1 treatment promotes amyloid plaque remodeling in cerebral cortex but fails to preserve cognitive function in male 5XFAD mice.. *Journal of Alzheimer's disease : JAD*, 2025. PMID 39610283 DOI 10.1177/13872877241299056 (Documents seven months of intranasal treatment in male mice, with some body-composition and amyloid findings but no preservation of behavioral or memory outcomes.)

61. Falutz J et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV.. *The New England journal of medicine*, 2007. PMID 18057338 DOI 10.1056/NEJMoa072375 (Pivotal randomized trial, visceral fat and lipid outcomes, IGF-1 response, and adverse-event withdrawals. Historical dose: 2 mg SC once daily for 26 weeks, PMID 18057338.)

62. Falutz J et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data.. *The Journal of clinical endocrinology and metabolism*, 2010. PMID 20554713 DOI 10.1210/jc.2010-0490 (Pooled phase 3 population, VAT treatment effects, continued-treatment durability, withdrawal findings, and subcutaneous fat outcomes.)

63. Feger MA et al. Follistatin Protein Enhances Satellite Cell Counts in Reinnervated Muscle.. *Journal of brachial plexus and peripheral nerve injury*, 2022. PMID 35747585 DOI 10.1055/s-0042-1748535 (Primary rat study of recombinant FS288 protein delivered locally using an implanted pump and catheter system after denervation and reinnervation. Reports increased satellite cell counts after denervation and mixed muscle size and force findings.)

64. Ferdinandi ES et al. Non-clinical pharmacology and safety evaluation of TH9507, a human growth hormone-releasing factor analogue.. *Basic & clinical pharmacology & toxicology*, 2007. PMID 17214611 DOI 10.1111/j.1742-7843.2007.00008.x (Structural modification, degradation resistance, animal GH and IGF-1 responses, toxicology, and dog elimination estimates.)

65. Filigheddu N et al. Hexarelin protects H9c2 cardiomyocytes from doxorubicin-induced cell death.. *Endocrine*, 2001. PMID 11322493 DOI 10.1385/ENDO:14:1:113 (Cultured cardiomyocyte injury research. Does not establish prevention of chemotherapy-associated cardiotoxicity in patients.)

66. Fornaro M et al. Mechano-growth factor peptide, the COOH terminus of unprocessed insulin-like growth factor 1, has no apparent effect on myoblasts or primary muscle stem cells.. *American journal of physiology. Endocrinology and metabolism*, 2014. PMID 24253050 DOI 10.1152/ajpendo.00408.2013 (Negative replication of proposed MGF E-peptide proliferation, differentiation, and signaling effects in cell systems. Supports the reported laboratory concentration and contested mechanism, not universal PEG-MGF inactivity.)

67. Fourman LT et al. Effects of tesamorelin on hepatic transcriptomic signatures in HIV-associated NAFLD.. *JCI insight*, 2020. PMID 32701508 DOI 10.1172/jci.insight.140134 (Exploratory paired-biopsy gene-expression findings from the HIV-associated

fatty liver trial.)

68. Francis GL et al. Novel recombinant fusion protein analogues of insulin-like growth factor (IGF)-I indicate the relative importance of IGF-binding protein and receptor binding for enhanced biological potency.. *Journal of molecular endocrinology*, 1992. PMID 1378742 DOI 10.1677/jme.0.0080213 (Describes the extended Long Arg3 construct and compares biological activity across cell systems. Supports context-dependent potency and lower relative activity in fibroblasts without detectable secreted IGF-binding proteins.)
69. Frias JP et al. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial.. *Lancet (London, England)*, 2023. PMID 37364590 DOI 10.1016/S0140-6736(23)01163-7 (Controlled phase 2 combination exposures, 32-week weight outcomes and limits of extrapolation to independently prepared combinations.)
70. Frieboes RM et al. Growth hormone-releasing peptide-6 stimulates sleep, growth hormone, ACTH and cortisol release in normal man.. *Neuroendocrinology*, 1995. PMID 7617137 DOI 10.1159/000126883 (Human GHRP-6 sleep and hormone findings. Included as a clearly identified comparator, not evidence that ipamorelin improves sleep.)
71. Frieboes RM et al. Effects of growth hormone-releasing peptide-6 on the nocturnal secretion of GH, ACTH and cortisol and on the sleep EEG in man: role of routes of administration.. *Journal of neuroendocrinology*, 1999. PMID 10336729 DOI 10.1046/j.1365-2826.1999.00364.x (Different nocturnal endocrine and sleep responses across oral, intranasal and sublingual preparations. Demonstrates limitations of generalizing across routes and formulations.)
72. Frieboes RM et al. Hexarelin decreases slow-wave sleep and stimulates the secretion of GH, ACTH, cortisol and prolactin during sleep in healthy volunteers.. *Psychoneuroendocrinology*, 2004. PMID 15177700 DOI 10.1016/S0306-4530(03)00152-5 (Hexarelin-specific sleep and endocrine effects. Retained as qualified related-compound context, not evidence from a GHRP-6 combination trial.)
73. Friedman SD et al. Growth hormone-releasing hormone effects on brain γ-aminobutyric acid levels in mild cognitive impairment and healthy aging.. *JAMA neurology*, 2013. PMID 23689947 DOI 10.1001/jamaneurol.2013.1425 (Thirty-participant neurochemical substudy, overlapping parent-trial participants, and absence of significant neurochemical-cognitive associations.)
74. Frías JP et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes.. *The New England journal of medicine*, 2021. PMID 34170647 DOI 10.1056/NEJMoa2107519 (SURPASS-2 comparative glycemic and weight outcomes, study doses and gastrointestinal adverse events.)
75. Fujioka K et al. Early Weight Loss with Liraglutide 3.0 mg Predicts 1-Year Weight Loss and is Associated with Improvements in Clinical Markers.. *Obesity (Silver Spring, Md.)*, 2016. PMID 27804269 DOI 10.1002/oby.21629 (Predictive value of at least 4 percent weight loss at week 16 after initiation.)
76. Gabe MBN et al. Cagrilintide is not associated with clinically relevant QTc prolongation: A thorough QT study in healthy participants.. *Diabetes, obesity & metabolism*, 2024. PMID 39279639 DOI 10.1111/dom.15951 (Randomized QT study in 105 healthy participants. Cagrilintide was escalated to 4.5 mg subcutaneously once weekly, without clinically relevant QTc prolongation, PMID 39279639.)
77. Gabery S et al. Semaglutide lowers body weight in rodents via distributed neural pathways.. *JCI insight*, 2020. PMID 32213703 DOI 10.1172/jci.insight.133429 (Rodent neural access and activation, reduced food intake and experimental energy-expenditure findings.)
78. Gabery S et al. Characterization of 0839 - A tool compound for pre-clinical mode-of-action studies of amylin analogues such as cagrilintide.. *Life sciences*, 2025. PMID 40628316 DOI 10.1016/j.lfs.2025.123845 (Direct cagrilintide and related-tool-compound comparisons in rodents, species-dependent responses, fat-mass findings and semaglutide combination effects. The two compounds are not identical.)
79. Garvey WT et al. Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2025. PMID 40544433 DOI 10.1056/NEJMoa2502081 (REDEFINE 1 combination regimen, treatment-policy weight outcome and gastrointestinal event frequency.)
80. Gasperi M et al. Low dose hexarelin and growth hormone (GH)-releasing hormone as a diagnostic tool for the diagnosis of GH deficiency in adults: comparison with insulin-induced hypoglycemia test.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 10443652 DOI 10.1210/jcem.84.8.5904 (Adult diagnostic research comparing a hexarelin-GHRH challenge with insulin-induced hypoglycemia. Diagnostic performance is distinct from treatment efficacy.)
81. Ghigo E et al. Growth hormone-releasing peptides.. *European journal of endocrinology*, 1997. PMID 9186261 DOI 10.1530/eje.0.1360445 (Historical review of receptor distinction, proposed hypothalamic actions, routes, response modifiers and partial desensitization.)
82. Ghigo E et al. Growth hormone-releasing activity of growth hormone-releasing peptide-6 is maintained after short-term oral pretreatment with the hexapeptide in normal aging.. *European journal of endocrinology*, 1994. PMID 7952160 DOI 10.1530/eje.0.1310499 (Four days of repeated oral exposure in seven elderly women preserved growth hormone responsiveness without significantly increasing IGF-1.)
83. Ghigo E et al. Growth hormone-releasing activity of hexarelin, a new synthetic hexapeptide, after intravenous, subcutaneous, intranasal, and oral administration in man.. *The Journal of clinical endocrinology and metabolism*, 1994. PMID 8126144 DOI 10.1210/jcem.78.3.8126144 (Human four-route pharmacology, documented experimental exposures, dose-related responses and biological bioavailability estimated from growth hormone release. Does not establish direct systemic peptide bioavailability or universal route equivalence.)

84. Ghigo E et al. Effects of recombinant human insulin-like growth factor I administration on growth hormone (GH) secretion, both spontaneous and stimulated by GH-releasing hormone or hexarelin, a peptidyl GH secretagogue, in humans.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 9920097 DOI 10.1210/jcem.84.1.5386 (Recombinant human IGF-1 feedback on stimulated growth hormone in eight women under fed experimental conditions. The compound studied was not IGF-1 LR3.)

85. Gobburu JV et al. Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers.. *Pharmaceutical research*, 1999. PMID 10496658 DOI 10.1023/a:1018955126402 (Single-dose intravenous human dose-ranging study, pharmacokinetics and acute GH response. Does not establish subcutaneous dosing or performance outcomes.)

86. Gondo RG et al. Growth hormone-releasing peptide-2 stimulates GH secretion in GH-deficient patients with mutated GH-releasing hormone receptor.. *The Journal of clinical endocrinology and metabolism*, 2001. PMID 11443201 DOI 10.1210/jcem.86.7.7694 (Residual GH responsiveness in GHRH-receptor deficiency and limitations on interpreting dependence on intact GHRH signaling.)

87. González-Sales M et al. Population pharmacokinetic analysis of tesamorelin in HIV-infected patients and healthy subjects.. *Clinical pharmacokinetics*, 2015. PMID 25358450 DOI 10.1007/s40262-014-0202-x (Population pharmacokinetic model, clearance, distribution volume, and covariate limitations.)

88. Granhall C et al. Safety and Pharmacokinetics of Single and Multiple Ascending Doses of the Novel Oral Human GLP-1 Analogue, Oral Semaglutide, in Healthy Subjects and Subjects with Type 2 Diabetes.. *Clinical pharmacokinetics*, 2019. PMID 30565096 DOI 10.1007/s40262-018-0728-4 (Oral clinical pharmacokinetics and prolonged systemic exposure.)

89. Gu YM et al. Structural and mechanistic insights into dual activation of cagrilintide in amylin and calcitonin receptors.. *Acta pharmacologica Sinica*, 2026. PMID 40847076 DOI 10.1038/s41401-025-01635-2 (AMY1R and calcitonin receptor structures, Gs signaling and specific binding features. The PubMed issue publication year is 2026, following online publication in 2025.)

90. Guldner J et al. Reduced efficacy of growth hormone-releasing hormone in modulating sleep endocrine activity in the elderly.. *Neurobiology of aging*, 1997. PMID 9390775 DOI 10.1016/s0197-4580(97)00106-1 (Laboratory sleep responses to IV GHRH in seniors, with reduced efficacy compared with younger subjects.)

91. Gupta D et al. β1-adrenergic receptors mediate plasma acyl-ghrelin elevation and depressive-like behavior induced by chronic psychosocial stress.. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 2019. PMID 30758330 DOI 10.1038/s41386-019-0334-7 (Chronic GHRP-2 did not improve depressive-like behavior in the mouse social-defeat experiment.)

92. Habibullah MM et al. Human Growth Hormone Fragment 176-191 Peptide Enhances the Toxicity of Doxorubicin-Loaded Chitosan Nanoparticles Against MCF-7 Breast Cancer Cells.. *Drug design, development and therapy*, 2022. PMID 35783198 DOI 10.2147/DDDT.S367586 (Computational and cultured-cell study using material described as hGH fragment 176-191 in a nanoparticle formulation. Does not establish human anticancer efficacy, fat loss, or safety.)

93. Hansen J et al. Exercise induces a marked increase in plasma follistatin: evidence that follistatin is a contraction-induced hepatokine.. *Endocrinology*, 2011. PMID 21068158 DOI 10.1210/en.2010-0868 (Human exercise physiology with complementary mouse experiments. Reports increased circulating follistatin after prolonged cycling, no detectable net release from the exercising limb, and evidence supporting a likely hepatic source. Does not measure injected-protein elimination or comparative treatment efficacy.)

94. Haruta I et al. One-year intranasal application of growth hormone releasing peptide-2 improves body weight and hypoglycemia in a severely emaciated anorexia nervosa patient.. *Journal of cachexia, sarcopenia and muscle*, 2015. PMID 26401470 DOI 10.1002/jcsm.12028 (One-year adult intranasal case report with weight, appetite and reported strength improvements. Does not establish causality or efficacy in trained adults.)

95. Hayashi S et al. Intranasal administration of His-D-Trp-Ala-Trp-D-Phe-LysNH2 (growth hormone releasing peptide) increased plasma growth hormone and insulin-like growth factor-I levels in normal men.. *Endocrinologia japonica*, 1991. PMID 1915110 DOI 10.1507/endocrj1954.38.15 (Intranasal dose-related endocrine responses and increased IGF-1 after seven consecutive administrations in six men. Does not establish long-term treatment outcomes.)

96. He L et al. Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials.. *JAMA internal medicine*, 2022. PMID 35344001 DOI 10.1001/jamainternmed.2022.0338 (Class-level relative risks for gallbladder or biliary disease across 76 randomized trials.)

97. Heffernan M et al. The effects of human GH and its lipolytic fragment (AOD9604) on lipid metabolism following chronic treatment in obese mice and beta(3)-AR knock-out mice.. *Endocrinology*, 2001. PMID 11713213 DOI 10.1210/endo.142.12.8522 (Beta-3 receptor expression and knockout experiments. Supports indirect pathway involvement rather than demonstrated direct beta-3 receptor agonism.)

98. Heffernan MA et al. Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment.. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, 2001. PMID 11673763 DOI 10.1038/sj.ijo.0801740 (Direct AOD-9604 rodent metabolic experiments and in vitro GH receptor competition and proliferation assays. Does not establish human efficacy or comprehensive absence of growth-related risk.)

99. Heffernan MA et al. Effects of oral administration of a synthetic fragment of human growth hormone on lipid metabolism.. *American journal of physiology. Endocrinology and metabolism*, 2000. PMID 10950816 DOI 10.1152/ajpendo.2000.279.3.E501 (Related AOD9401 study in obese mice and isolated rodent and human adipose tissue. Supports attribution correction and the distinction between human tissue experiments and clinical trials.)

100. Henninge J et al. Identification of CJC-1295, a growth-hormone-releasing peptide, in an unknown pharmaceutical preparation.. *Drug testing and analysis*, 2010. PMID 21204297 DOI 10.1002/dta.233 (Analytical identification of a 29-amino-acid amidated peptide consistent with material marketed as CJC-1295, plus historical WADA S2 classification. Does not establish that this material was the albumin-binding clinical molecule or support universal detection claims.)

101. Hu R et al. Effects of GHRP-2 and Cysteamine Administration on Growth Performance, Somatotropic Axis Hormone and Muscle Protein Deposition in Yaks (Bos grunniens) with Growth Retardation.. *PloS one*, 2016. PMID 26894743 DOI 10.1371/journal.pone.0149461 (Direct animal skeletal-muscle findings, including increased fiber diameter and area in growth-retarded yaks.)

102. Huang J et al. The Growth Hormone Secretagogue Hexarelin Protects Rat Cardiomyocytes From in vivo Ischemia/Reperfusion Injury Through Interleukin-1 Signaling Pathway.. *International heart journal*, 2017. PMID 28321024 DOI 10.1536/ihj.16-241 (Rat ischemia-reperfusion research involving interleukin-1 signaling. Supports the existence of experimental cardiac mechanisms, not a clinical protocol.)

103. Ikushima I et al. A Randomized Trial Investigating the Pharmacokinetics, Pharmacodynamics, and Safety of Subcutaneous Semaglutide Once-Weekly in Healthy Male Japanese and Caucasian Subjects.. *Advances in therapy*, 2018. PMID 29536338 DOI 10.1007/s12325-018-0677-1 (Dedicated human subcutaneous pharmacokinetics and prolonged elimination half-life.)

104. Imbimbo BP et al. Growth hormone-releasing activity of hexarelin in humans. A dose-response study.. *European journal of clinical pharmacology*, 1994. PMID 7957536 DOI 10.1007/BF00191904 (Human double-blind rising-dose pharmacology, placebo placement, peak versus integrated growth hormone responses, modeled ED50 estimates and growth hormone response timing. The reported hormone half-life is not a measured hexarelin elimination half-life.)

105. Ionescu M et al. Pulsatile secretion of growth hormone (GH) persists during continuous stimulation by CJC-1295, a long-acting GH-releasing hormone analog.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 17018654 DOI 10.1210/jc.2006-1702 (Single-administration human study showing preserved GH pulsatility and increased trough GH and IGF-1. Supports the study doses and sampling interval. The lack of a significant dose-group difference does not establish a plateau. IGF-1 changes did not correlate with measured GH secretion parameters.)

106. Jaffe CA et al. Effects of a prolonged growth hormone (GH)-releasing peptide infusion on pulsatile GH secretion in normal men.. *The Journal of clinical endocrinology and metabolism*, 1993. PMID 7903313 DOI 10.1210/jcem.77.6.7903313 (A 34-hour infusion increased pulse amplitude and IGF-1 without changing pulse frequency. Response to an additional GHRP challenge decreased, qualifying claims about preserved responsiveness.)

107. Jansen M et al. Pulmonary delivery of TH9507, a growth hormone releasing factor analogue, in the dog.. *International journal of pharmaceutics*, 2004. PMID 15113616 DOI 10.1016/j.ijpharm.2004.02.012 (Experimental pulmonary delivery, relative and absolute bioavailability, and dog route-specific pharmacokinetics.)

108. Jastreboff AM et al. Tirzepatide Once Weekly for the Treatment of Obesity.. *The New England journal of medicine*, 2022. PMID 35658024 DOI 10.1056/NEJMoa2206038 (SURMOUNT-1 population, SC weekly doses, weight changes and adverse-event discontinuation.)

109. Jastreboff AM et al. Tirzepatide for Obesity Treatment and Diabetes Prevention.. *The New England journal of medicine*, 2025. PMID 39536238 DOI 10.1056/NEJMoa2410819 (SURMOUNT-1 extension through 176 treatment weeks in participants with obesity and prediabetes.)

110. Jastreboff AM et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial.. *The New England journal of medicine*, 2023. PMID 37366315 DOI 10.1056/NEJMoa2301972 (Obesity trial population, weekly subcutaneous doses, starting-dose groups, weight outcomes, gastrointestinal tolerability and heart rate changes.)

111. Jensen L et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species.. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 2017. PMID 28323117 DOI 10.1016/j.ejps.2017.03.020 (Proteolysis, fatty-acid side-chain metabolism and urinary and fecal elimination of drug-related material.)

112. Jessup SK et al. Blockade of endogenous growth hormone-releasing hormone receptors dissociates nocturnal growth hormone secretion and slow-wave sleep.. *European journal of endocrinology*, 2004. PMID 15538933 DOI 10.1530/eje.0.1510561 (GHRH antagonist experiment separating GH suppression from measured slow-wave sleep. Provides indirect context for evaluating sleep claims. It did not test CJC-1295 and cannot determine its sleep effects.)

113. Jetté L et al. Human growth hormone-releasing factor (hGRF)1-29-albumin bioconjugates activate the GRF receptor on the anterior pituitary in rats: identification of CJC-1295 as a long-lasting GRF analog.. *Endocrinology*, 2005. PMID 15817669 DOI 10.1210/en.2004-1286 (Molecular design, albumin attachment, in vitro stability, GH secretion assays and prolonged activity in normal rats. Distinguishes plasma detection beyond 72 hours from the separately demonstrated albumin-associated signal. This was not a deficiency-restoration experiment.)

114. Jiang B et al. Hexarelin attenuates abdominal aortic aneurysm formation by inhibiting SMC phenotype switch and inflammasome activation.. *Microvascular research*, 2022. PMID 34856183 DOI 10.1016/j.mvr.2021.104280 (Preclinical abdominal aortic aneurysm research involving smooth muscle phenotype and inflammasome pathways. The PubMed publication year is 2022 despite the 2021 DOI component.)

115. Johansen PB et al. Ipamorelin, a new growth-hormone-releasing peptide, induces longitudinal bone growth in rats.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 1999. PMID 10373343 DOI 10.1054/ghir.1999.9998 (Divided daily subcutaneous doses in female rats, longitudinal bone growth without increased total IGF-I and modestly reduced subsequent ipamorelin responsiveness.)

116. Johansen PB et al. Pharmacokinetic evaluation of ipamorelin and other peptidyl growth hormone secretagogues with emphasis on nasal absorption.. *Xenobiotica; the fate of foreign compounds in biological systems*, 1998. PMID 9879640 DOI 10.1080/004982598238976 (NNC 26-0161 alias and rat pharmacokinetics, including approximately 20 percent nasal bioavailability.)

117. Kandalla PK et al. Mechano Growth Factor E peptide (MGF-E), derived from an isoform of IGF-1, activates human muscle progenitor cells and induces an increase in their fusion potential at different ages.. *Mechanisms of ageing and development*, 2011. PMID 21354439 DOI 10.1016/j.mad.2011.02.007 (Human muscle-cell culture findings involving age-dependent proliferative lifespan and senescence, plus fusion and hypertrophy effects. Also describes the human and rodent splice-sequence distinction.)

118. Kemp SF et al. Insulin-like growth factor-I deficiency in children with growth hormone insensitivity: current and future treatment options.. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 2009. PMID 19627167 DOI 10.2165/00063030-200923030-00002 (Provides indirect human context concerning mecasermin, pediatric growth outcomes, hypoglycemia, and binding-protein effects on circulating half-life. It does not establish LR3 clinical efficacy, dosing, or pharmacokinetics.)

119. Kerkhofs M et al. Sleep-promoting effects of growth hormone-releasing hormone in normal men.. *The American journal of physiology*, 1993. PMID 8476038 DOI 10.1152/ajpendo.1993.264.4.E594 (Timing-dependent effects of IV GHRH on laboratory sleep. Does not validate SC sermorelin for sleep improvement.)

120. Khorram O et al. Effects of [norleucine27]growth hormone-releasing hormone (GHRH) (1-29)-NH2 administration on the immune system of aging men and women.. *The Journal of clinical endocrinology and metabolism*, 1997. PMID 9360512 DOI 10.1210/jcem.82.11.4363 (Endocrine and immune laboratory responses to a modified GHRH analog, explicitly distinguished from sermorelin.)

121. King R et al. Production and characterization of recombinant insulin-like growth factor-I (IGF-I) and potent analogues of IGF-I, with Gly or Arg substituted for Glu3, following their expression in Escherichia coli as fusion proteins.. *Journal of molecular endocrinology*, 1992. PMID 1311930 DOI 10.1677/jme.0.0080029 (Characterizes Gly3 and Arg3 IGF-I analogues. Reduced IGFBP-2 binding, rather than stronger receptor binding, was proposed to explain enhanced biological potency. This is supporting engineering evidence, not a human LR3 trial.)

122. Kinoshita Y et al. The arginine and GHRP-2 tests as alternatives to the insulin tolerance test for the diagnosis of adult GH deficiency in Japanese patients: a comparison.. *Endocrine journal*, 2013. PMID 23079545 DOI 10.1507/endocrj.ej12-0230 (Diagnostic comparison in 71 patients, with GHRP-2 sensitivity of 81.3 percent and specificity of 94.5 percent under the study's criteria.)

123. Kletzl H et al. First-in-man study with a novel PEGylated recombinant human insulin-like growth factor-I.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2017. PMID 28110155 DOI 10.1016/j.ghir.2017.01.001 (Human pharmacokinetic and tolerability findings for a different PEGylated recombinant IGF-1 molecule. Its half-life and injection-site findings cannot be transferred to PEG-MGF.)

124. Klinger B et al. Desensitization from long-term intranasal treatment with hexarelin does not interfere with the biological effects of this growth hormone-releasing peptide in short children.. *European journal of endocrinology*, 1996. PMID 8766941 DOI 10.1530/eje.0.1340716 (Seven-child prospective report covering 6 to 10 months of intranasal treatment. Growth velocity increased despite attenuated growth hormone challenge responses. Does not validate an adult performance regimen.)

125. Knop FK et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial.. *Lancet (London, England)*, 2023. PMID 37385278 DOI 10.1016/S0140-6736(23)01185-6 (OASIS 1 investigational daily oral regimen, trial population, 68-week outcomes and placebo-controlled design.)

126. Knudsen LB et al. The Discovery and Development of Liraglutide and Semaglutide.. *Frontiers in endocrinology*, 2019. PMID 31031702 DOI 10.3389/fendo.2019.00155 (Molecular modifications, albumin binding, DPP-4 resistance, receptor biology and development rationale.)

127. Kohler M et al. Detection of His-tagged Long-R³-IGF-I in a black market product.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2010. PMID 20675162 DOI 10.1016/j.ghir.2010.07.001 (Documents identification of a His-tagged Long-R3-IGF-I protein in an injection vial. Supports a concrete molecular-identity concern, without establishing clinical effects or the prevalence of product-quality failures.)

128. Korbonits M et al. The growth hormone secretagogue hexarelin stimulates the hypothalamo-pituitary-adrenal axis via arginine vasopressin.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 10404825 DOI 10.1210/jcem.84.7.5811 (Human ACTH, cortisol, growth hormone and prolactin responses, a small appetite increase, and CRH-desmopressin interaction findings consistent with a possible vasopressin contribution.)

129. Kota J et al. Follistatin gene delivery enhances muscle growth and strength in nonhuman primates.. *Science translational medicine*, 2009. PMID 20368179 DOI 10.1126/scitranslmed.3000112 (Reports muscle size and strength findings and organ assessments after intramuscular AAV1-FS344 gene delivery in cynomolgus macaques. Interpretation is qualified by a linked 2026 erratum whose contents were not retrieved. Does not establish recombinant protein dosing or comprehensive human safety.)

130. Krug O et al. Analysis of new growth promoting black market products.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2018. PMID 29864719 DOI 10.1016/j.ghir.2018.05.001 (Analytical identification of glycine-extended secretagogues, including Gly-Ipamorelin. Does not establish a general contamination or mislabeling prevalence.)

131. Kruse T et al. Development of Cagrilintide, a Long-Acting Amylin Analogue.. *Journal of medicinal chemistry*, 2021. PMID 34288673 DOI 10.1021/acs.jmedchem.1c00565 (Molecular development, stabilization and lipidation of a long-acting amylin analogue. Does not establish preparation or storage instructions for independently sourced material.)

132. Kwon DR et al. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model.. *Annals of clinical and laboratory science*, 2015. PMID 26275694 (Rabbit osteoarthritis experiment using 0.25 mg AOD-9604 per knee intra-articularly weekly during post-induction weeks 4 through 7. The combination arm included 6 mg hyaluronic acid per knee on that schedule.)

133. La Vignera S et al. Incretin-Based Therapies in Sports: Pharmacological Mechanisms, Performance-Enhancing Potential, and Anti-Doping Implications-A Narrative Review.. *International journal of molecular sciences*, 2026. PMID 42511463 DOI 10.3390/ijms27146116 (Narrative review of performance-related evidence and non-prohibited status. Monitoring status was checked separately against WADA documents.)

134. Laferrère B et al. Obese subjects respond to the stimulatory effect of the ghrelin agonist growth hormone-releasing peptide-2 on food intake.. *Obesity (Silver Spring, Md.)*, 2006. PMID 16861611 DOI 10.1038/oby.2006.121 (Randomized appetite experiment using continuous SC infusion at 0.1 or 1 mcg/kg per hour for 270 minutes per condition, reported in PMID 16861611.)

135. Laferrère B et al. Growth hormone releasing peptide-2 (GHRP-2), like ghrelin, increases food intake in healthy men.. *The Journal of clinical endocrinology and metabolism*, 2005. PMID 15699539 DOI 10.1210/jc.2004-1719 (Increased food intake in seven men during continuous SC infusion at 1 mcg/kg per hour for 270 minutes, reported in PMID 15699539.)

136. Lall S et al. Growth hormone (GH)-independent stimulation of adiposity by GH secretagogues.. *Biochemical and biophysical research communications*, 2001. PMID 11162489 DOI 10.1006/bbrc.2000.4065 (Mouse evidence of increased adiposity independent of normal GH production, with food-intake and leptin findings.)

137. Laron Z et al. Intranasal administration of the GHRP hexarelin accelerates growth in short children.. *Clinical endocrinology*, 1995. PMID 8548949 DOI 10.1111/j.1365-2265.1995.tb02929.x (Eight-child intranasal treatment study lasting up to 8 months, with reported increases in IGF-1 and linear growth velocity.)

138. Laron Z et al. Growth hormone releasing activity by intranasal administration of a synthetic hexapeptide (hexarelin).. *Clinical endocrinology*, 1994. PMID 7955465 DOI 10.1111/j.1365-2265.1994.tb02589.x (Intranasal and intravenous diagnostic testing in children with short stature and two growth hormone deficient adults. Provides route-specific hormone peak timing, not universal dose equivalence.)

139. Larsen AT et al. Does receptor balance matter? - Comparing the efficacies of the dual amylin and calcitonin receptor agonists cagrilintide and KBP-336 on metabolic parameters in preclinical models.. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, 2022. PMID 36242844 DOI 10.1016/j.biopha.2022.113842 (Preclinical receptor-balance experiments and weight and glucose outcomes in obese and diabetic rat models. Does not establish clinical benefits from calcitonin receptor activation alone.)

140. Latres E et al. Insulin-like growth factor-1 (IGF-1) inversely regulates atrophy-induced genes via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway.. *The Journal of biological chemistry*, 2005. PMID 15550386 DOI 10.1074/jbc.M407517200 (Supports native IGF-1 signaling through Akt/FOXO and Akt/mTOR in regulation of atrophy-related genes. This is mechanistic context rather than direct evidence of LR3 efficacy in humans.)

141. Lau DCW et al. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial.. *Lancet (London, England)*, 2021. PMID 34798060 DOI 10.1016/S0140-6736(21)01751-7 (Randomized monotherapy evidence, 706 participants across all groups, 26-week weight outcomes, gastrointestinal events and escalation. Reported cagrilintide targets were 0.3 to 4.5 mg subcutaneously once weekly, PMID 34798060.)

142. Lengyel AM et al. Novel mechanisms of growth hormone regulation: growth hormone-releasing peptides and ghrelin.. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas*, 2006. PMID 16906274 DOI 10.1590/s0100-879x2006000800002 (Discovery of the ghrelin receptor pathway, interaction with GHRH, hypothalamic participation and intracellular signaling. Supports mechanism, not a fitness dosing protocol.)

143. Li G et al. Growth hormone releasing peptide-2, a ghrelin agonist, attenuates lipopolysaccharide-induced acute lung injury in rats.. *The Tohoku journal of experimental medicine*, 2010. PMID 20805679 DOI 10.1620/tjem.222.7 (Rat lung injury and NF-kappaB findings after a single 100 mcg/kg SC pretreatment administration, reported in PMID 20805679.)

144. Lincoff AM et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes.. *The New England journal of medicine*, 2023. PMID 37952131 DOI 10.1056/NEJMoa2307563 (SELECT eligibility, cardiovascular event reduction, follow-up and permanent discontinuation because of adverse events.)

145. Liu X et al. Regulation of ghrelin gene expression in stomach and feeding response to a ghrelin analogue in two strains of rats.. *Peptides*, 2004. PMID 15572207 DOI 10.1016/j.peptides.2004.08.020 (GHRP-2 feeding responses differed with rat strain, feeding state and preferred diet.)

146. Locatelli V et al. Growth hormone-independent cardioprotective effects of hexarelin in the rat.. *Endocrinology*, 1999. PMID 10465272 DOI 10.1210/endo.140.9.6948 (Protection against experimental ischemia-reperfusion injury in hearts from hypophysectomized rats, supporting an effect independent of pituitary growth hormone release.)

147. Loche S et al. Acute administration of hexarelin stimulates GH secretion during day and night in normal men.. *Clinical endocrinology*, 1997. PMID 9156035 DOI 10.1046/j.1365-2265.1997.1240940.x (Morning-versus-sleep endocrine responses in eight men. Similar growth hormone peaks but greater integrated response during sleep, associated with slower hormone disappearance.)

148. Look M et al. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight.. *Diabetes, obesity & metabolism*, 2025. PMID 39996356 DOI 10.1111/dom.16275 (DXA substudy size, fat and lean-mass changes, and limitations of interpreting lean mass as muscle.)

149. Ludwig MQ et al. A cross-species atlas of the dorsal vagal complex reveals neural mediators of the effects of cagrilintide on energy balance.. *Nature metabolism*, 2026. PMID 42260119 DOI 10.1038/s42255-026-01539-3 (Cross-species brainstem cell mapping, acute and longer-term neuronal responses, and functional evidence involving Prlh in rats. Does not establish human dosing or fully independent neural circuits.)

150. Lundgren JR et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined.. *The New England journal of medicine*, 2021. PMID 33951361 DOI 10.1056/NEJMoa2028198 (Maintenance trial regimen, structured exercise, weight and body-fat outcomes, and limits of between-group comparisons.)

151. Ma J et al. Comparison of the effects of Liraglutide, Tirzepatide, and Retatrutide on diabetic kidney disease in db/db mice.. *Endocrine*, 2025. PMID 39212900 DOI 10.1007/s12020-024-03998-8 (Ten-week mouse kidney study and preclinical metabolic findings. The retrieved abstract does not state the dosing interval.)

152. Maccario M et al. Impact of two or three daily subcutaneous injections of hexarelin, a synthetic growth hormone (GH) secretagogue, on 24-h GH, prolactin, adrenocorticotropin and cortisol secretion in humans.. *European journal of endocrinology*, 2002. PMID 11888836 DOI 10.1530/eje.0.1460310 (Six-man, 24-hour study comparing two and three daily subcutaneous administrations. Both increased growth hormone secretion similarly without changing IGF-1 or integrated prolactin, ACTH and cortisol secretion.)

153. Maccario M et al. Metabolic modulation of the growth hormone-releasing activity of hexarelin in man.. *Metabolism: clinical and experimental*, 1995. PMID 7854159 DOI 10.1016/0026-0495(95)90300-3 (Oral glucose and lipid-heparin infusion reduced hexarelin-stimulated growth hormone in healthy men. These challenge experiments do not establish a meal-timing strategy for training outcomes.)

154. Maghnie M et al. The growth hormone response to hexarelin in patients with different hypothalamic-pituitary abnormalities.. *The Journal of clinical endocrinology and metabolism*, 1998. PMID 9814463 DOI 10.1210/jcem.83.11.5242 (Growth hormone responses in patients with imaging-characterized hypothalamic-pituitary abnormalities, supporting the importance of residual anatomical and vascular connections.)

155. Makimura H et al. Metabolic effects of a growth hormone-releasing factor in obese subjects with reduced growth hormone secretion: a randomized controlled trial.. *The Journal of clinical endocrinology and metabolism*, 2012. PMID 23015655 DOI 10.1210/jc.2012-2794 (Selected adults without HIV, VAT and cardiovascular risk-marker outcomes. Study dose: 2 mg SC once daily for 12 months, PMID 23015655.)

156. Mao Y et al. The cardiovascular action of hexarelin.. *Journal of geriatric cardiology : JGC*, 2014. PMID 25278975 DOI 10.11909/j.issn.1671-5411.2014.03.007 (Review of GHSR-related and CD36-related cardiovascular mechanisms. Provides context for the largely experimental cardiovascular literature without establishing clinical efficacy.)

157. Mao Y et al. Hexarelin treatment in male ghrelin knockout mice after myocardial infarction.. *Endocrinology*, 2013. PMID 23861368 DOI 10.1210/en.2013-1291 (Mouse myocardial infarction research involving ghrelin knockout animals. Defines a preclinical cardiovascular model rather than human efficacy evidence.)

158. Mao Y et al. One dose of oral hexarelin protects chronic cardiac function after myocardial infarction.. *Peptides*, 2014. PMID 24747279 DOI 10.1016/j.peptides.2014.04.004 (Preclinical investigation of oral hexarelin after myocardial infarction. Does not validate oral treatment for human cardiovascular disease.)

159. Marso SP et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.. *The New England journal of medicine*, 2016. PMID 27633186 DOI 10.1056/NEJMoa1607141 (SUSTAIN-6 subcutaneous once-weekly exposures, cardiovascular outcomes and diabetic retinopathy complication signal.)

160. Marso SP et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.. *The New England journal of medicine*, 2016. PMID 27295427 DOI 10.1056/NEJMoa1603827 (LEADER regimen, high-risk diabetes population, cardiovascular outcomes, follow-up duration, and pancreatitis findings.)

161. Martin AA et al. Effects of insulin-like growth factor-I peptides in rats with acute renal failure.. *The Journal of endocrinology*, 1994. PMID 8138750 DOI 10.1677/joe.0.1400023 (Reports LR3 at 1.5 mg/kg/day by continuous subcutaneous osmotic-pump infusion in renal-ischaemia experiments. Supports worse early renal functional outcomes despite improvement in some anabolic measures.)

162. Massoud AF et al. Hexarelin-induced growth hormone, cortisol, and prolactin release: a dose-response study.. *The Journal of clinical endocrinology and metabolism*, 1996. PMID 8954038 DOI 10.1210/jcem.81.12.8954038 (Acute growth hormone, prolactin and cortisol dose-response relationships. Documents the specific low-exposure intravenous GHRH(1-29)-NH2 combination, including prolactin elevation and no measured cortisol rise under that condition.)

163. Massoud AF et al. The effect of repeated administration of hexarelin, a growth hormone releasing peptide, and growth hormone releasing hormone on growth hormone responsivity.. *Clinical endocrinology*, 1996. PMID 8762732 DOI 10.1046/j.1365-2265.1996.722543.x (Acute synergy with GHRH(1-29)-NH2 in six men, altered responses to repeat challenges and loss of statistically demonstrable synergy after repeated combined administration.)

164. Massoud AF et al. Interaction of the growth hormone releasing peptide hexarelin with somatostatin.. *Clinical endocrinology*, 1997. PMID 9425393 DOI 10.1046/j.1365-2265.1997.3121128.x (Somatostatin infusion and withdrawal studies, including inhibition of separate and combined secretagogue responses. Does not support complete escape from inhibitory control.)

165. Massoud AF et al. Hexarelin induced growth hormone release is influenced by exogenous growth hormone.. *Clinical endocrinology*, 1995. PMID 8548947 DOI 10.1111/j.1365-2265.1995.tb02927.x (Reduced hexarelin-stimulated growth hormone response after recombinant growth hormone pretreatment in healthy men. Supports feedback sensitivity without establishing chronic combination outcomes.)

166. Matheny RW Jr et al. Minireview: Mechano-growth factor: a putative product of IGF-I gene expression involved in tissue repair and regeneration.. *Endocrinology*, 2010. PMID 20130113 DOI 10.1210/en.2009-1217 (Distinguishes IGF-I transcripts, precursor proteins, and synthetic MGF peptides. Reports the absence of an isolated analogous endogenous free peptide in the biological sources reviewed at that time.)

167. Mayo KE et al. Regulation of the pituitary somatotroph cell by GHRH and its receptor.. *Recent progress in hormone research*, 2000. PMID 11036940 (GHRH receptor biology and regulation of pituitary somatotroph function.)

168. Mazzarino M et al. Rapid and harmonized analytical workflow for the determination of peptidic and non-peptidic doping agents in dried and liquid blood matrices.. *The Analyst*, 2026. PMID 42328738 DOI 10.1039/d6an00455e (Matrix-dependent analytical stability, including AOD-9604 degradation in serum and plasma. Does not establish reconstitution instructions or a pharmaceutical beyond-use date.)

169. McDonald H et al. Hexarelin targets neuroinflammatory pathways to preserve cardiac morphology and function in a mouse model of myocardial ischemia-reperfusion.. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, 2020. PMID 32403043 DOI 10.1016/j.biopha.2020.110165 (Mouse ischemia-reperfusion research examining cardiac morphology, function and neuroinflammatory pathways. Findings remain model-specific.)

170. McKee KK et al. Molecular analysis of rat pituitary and hypothalamic growth hormone secretagogue receptors.. *Molecular endocrinology (Baltimore, Md.)*, 1997. PMID 9092793 DOI 10.1210/mend.11.4.9908 (Rat receptor cloning, seven-transmembrane structure and pituitary and hypothalamic expression.)

171. Meanti R et al. Protective Effects of Hexarelin and JMV2894 in a Human Neuroblastoma Cell Line Expressing the SOD1-G93A Mutated Protein.. *International journal of molecular sciences*, 2023. PMID 36674509 DOI 10.3390/ijms24020993 (Human-derived cell-line research involving mutant SOD1. The word human describes the cell line and does not make this a human clinical study.)

172. Mendell JR et al. A phase 1/2a follistatin gene therapy trial for becker muscular dystrophy.. *Molecular therapy : the journal of the American Society of Gene Therapy*, 2015. PMID 25322757 DOI 10.1038/mt.2014.200 (Primary uncontrolled human AAV-FS344 study in six participants with Becker muscular dystrophy. Reports intramuscular quadriceps vector administration, cohort-specific doses and follow-up, walking outcomes, biopsy findings, and clinical monitoring. Also describes precursor processing. Does not validate recombinant protein administration.)

173. Mendell JR et al. Follistatin Gene Therapy for Sporadic Inclusion Body Myositis Improves Functional Outcomes.. *Molecular therapy : the journal of the American Society of Gene Therapy*, 2017. PMID 28279643 DOI 10.1016/j.ymthe.2017.02.015 (Small human AAV-FS344 study with six treated participants and eight matched untreated comparators. Reports annualized walking outcomes, histological findings, vector dose, an exercise program, and associations between exercise participation and improvement. Does not isolate a protein treatment effect.)

174. Mericq V et al. Changes in appetite and body weight in response to long-term oral administration of the ghrelin agonist GHRP-2 in growth hormone deficient children.. *Journal of pediatric endocrinology & metabolism : JPEM*, 2003. PMID 14513874 DOI 10.1515/jpem.2003.16.7.981 (Appetite and BMI observations in ten children receiving 900 mcg/kg orally twice daily for 12 months, reported in PMID 14513874.)

175. Mills P et al. A synthetic mechano growth factor E Peptide enhances myogenic precursor cell transplantation success.. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2007. PMID 17845560 DOI 10.1111/j.1600-6143.2007.01927.x (Positive synthetic E-peptide findings involving human myogenic precursor transplantation into mice. Establishes related animal evidence without establishing PEG-MGF efficacy in people.)

176. Mongongu C et al. Detection of LongR(3) -IGF-I, Des(1-3)-IGF-I, and R(3) -IGF-I using immunopurification and high resolution mass spectrometry for antidoping purposes.. *Drug testing and analysis*, 2021. PMID 33587816 DOI 10.1002/dta.3016 (Analytical characterization and oxidized forms in preparations of other IGF-I analogs. Retained only for related-material quality context, not PEG-MGF dosing, clearance, or detection windows.)

177. Mosa R et al. Hexarelin, a Growth Hormone Secretagogue, Improves Lipid Metabolic Aberrations in Nonobese Insulin-Resistant Male MKR Mice.. *Endocrinology*, 2017. PMID 28977588 DOI 10.1210/en.2017-00168 (Intraperitoneal treatment in MKR mice, with reported improvements in metabolic tolerance, triglycerides and body composition.)

178. Munafo A et al. Polyethylene glycol-conjugated growth hormone-releasing hormone is long acting and stimulates GH in healthy young and elderly subjects.. *European journal of endocrinology*, 2005. PMID 16061831 DOI 10.1530/eje.1.01965 (Adjacent evidence from a different, PEG-conjugated compound, including impaired glucose tolerance after repeated exposure in older participants.)

179. Nascif SO et al. Decreased ghrelin-induced GH release in thyrotoxicosis: comparison with GH-releasing peptide-6 (GHRP-6) and GHRH.. *Pituitary*, 2007. PMID 17410412 DOI 10.1007/s11102-007-0005-2 (Acute endocrine comparison in thyrotoxicosis and healthy controls. GHRP-6 did not increase glucose during this experiment, which does not exclude chronic metabolic effects.)

180. Neeland IJ et al. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies.. *Diabetes, obesity & metabolism*, 2024. PMID 38937282 DOI 10.1111/dom.15728 (Heterogeneous lean mass changes across GLP-1-based therapies and distinctions between lean tissue, muscle mass and function.)

181. Neyzi O et al. Growth response to growth hormone-releasing hormone(1-29)-NH2 compared with growth hormone.. *Acta paediatrica (Oslo, Norway : 1992). Supplement*, 1993. PMID 8329826 DOI 10.1111/j.1651-2227.1993.tb12828.x (Randomized pediatric dose comparison using daily totals divided into three SC administrations.)

182. Ng FM et al. Molecular and cellular actions of a structural domain of human growth hormone (AOD9401) on lipid metabolism in Zucker fatty rats.. *Journal of molecular endocrinology*, 2000. PMID 11116208 DOI 10.1677/jme.0.0250287 (Related AOD9401

fragment research involving lipid enzymes, adipocyte size and weight gain. Retained with explicit separation from direct AOD-9604 evidence.)

183. Ng FM et al. Metabolic studies of a synthetic lipolytic domain (AOD9604) of human growth hormone.. *Hormone research*, 2000. PMID 11146367 DOI 10.1159/000053183 (AOD-9604 at 500 mcg/kg orally once daily for 19 days in obese Zucker rats. Reports reduced weight gain and preserved insulin sensitivity in the experimental model.)

184. Ng FM et al. Hyperglycemic action of synthetic C-terminal fragments of human growth hormone.. *The American journal of physiology*, 1978. PMID 645904 DOI 10.1152/ajpendo.1978.234.5.E521 (Direct experiments including native hGH 176-191 in normal rats. Reports transient hyperglycaemia, increased insulin, and reduced insulin sensitivity. Does not establish human risk magnitude or fat loss efficacy.)

185. Nicholls AR et al. Growth Hormone and Insulin-Like Growth Factor-1.. *Frontiers of hormone research*, 2016. PMID 27347885 DOI 10.1159/000445173 (Provides historical context on growth-axis substances and performance-related misuse. Current prohibited status is established separately from the 2026 WADA list, rather than inferred from this review.)

186. Nielsen MJF et al. Renal or Hepatic Impairment Does Not Affect Pharmacokinetics, Safety, or Tolerability of Subcutaneous Cagrilintide.. *Clinical pharmacokinetics*, 2026. PMID 42228334 DOI 10.1007/s40262-026-01654-0 (Small organ-impairment pharmacokinetic studies. Single subcutaneous administrations were 0.6 mg for the renal study and 0.9 mg for the hepatic study, PMID 42228334.)

187. Nielsen TL et al. Antimyostatin Treatment in Health and Disease: The Story of Great Expectations and Limited Success.. *Cells*, 2021. PMID 33802348 DOI 10.3390/cells10030533 (Review of clinical translation limitations in myostatin-directed treatment through 2021. Supports distinguishing muscle mass outcomes from functional benefit and avoiding transfer of animal findings to untested clinical applications.)

188. Ogru E et al. The conformational and biological analysis of a cyclic anti-obesity peptide from the C-terminal domain of human growth hormone.. *The journal of peptide research : official journal of the American Peptide Society*, 2000. PMID 11152298 DOI 10.1034/j.1399-3011.2000.00771.x (Structural characterization of a related 15-residue cyclic fragment. Does not test shaking, routine storage, or a complete AOD-9604 preparation protocol.)

189. Okano M et al. Determination of growth hormone secretagogue pralmorelin (GHRP-2) and its metabolite in human urine by liquid chromatography/electrospray ionization tandem mass spectrometry.. *Rapid communications in mass spectrometry : RCM*, 2010. PMID 20552695 DOI 10.1002/rcm.4619 (Analytical detection of pralmorelin and a metabolite in human urine. Current prohibition is supported separately by WADA.)

190. Orlovius AK et al. AOD-9604 does not influence the WADA hGH isoform immunoassay.. *Drug testing and analysis*, 2013. PMID 24124033 DOI 10.1002/dta.1557 (Analytical anti-doping context only. Does not determine current prohibited status, human efficacy or a permissible exposure pattern.)

191. Overgaard RV et al. Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials.. *Clinical pharmacokinetics*, 2021. PMID 33969456 DOI 10.1007/s40262-021-01025-x (Oral exposure variability, formulation-dependent bioavailability and effects of administration conditions.)

192. Pandya N et al. Growth hormone (GH)-releasing peptide-6 requires endogenous hypothalamic GH-releasing hormone for maximal GH stimulation.. *The Journal of clinical endocrinology and metabolism*, 1998. PMID 9543138 DOI 10.1210/jcem.83.4.4711 (GHRH antagonist suppression of most, but not all, of the acute GHRP-6 growth hormone response in nine healthy men.)

193. Pang J et al. Hexarelin suppresses high lipid diet and vitamin D3-induced atherosclerosis in the rat.. *Peptides*, 2010. PMID 19931584 DOI 10.1016/j.peptides.2009.11.007 (Experimentally induced rat atherosclerosis model. Defines preclinical vascular evidence rather than cardiovascular prevention in humans.)

194. Perkovic V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes.. *The New England journal of medicine*, 2024. PMID 38785209 DOI 10.1056/NEJMoa2403347 (FLOW regimen, population, follow-up and reduction in the primary kidney-related composite.)

195. Peña JR et al. Localized delivery of mechano-growth factor E-domain peptide via polymeric microstructures improves cardiac function following myocardial infarction.. *Biomaterials*, 2015. PMID 25678113 DOI 10.1016/j.biomaterials.2014.12.050 (Mouse cardiac findings using E-peptide delivery from PEG-based polymeric microstructures. Supports distinguishing a PEG-containing delivery scaffold from a PEG-conjugated peptide.)

196. Philippou A et al. Expression of IGF-1 isoforms after exercise-induced muscle damage in humans: characterization of the MGF E peptide actions in vitro.. *In vivo (Athens, Greece)*, 2009. PMID 19567392 (Human muscle-biopsy expression changes after exercise-induced damage and separate synthetic E-peptide signaling experiments in cultured cells. It contains no PEG-MGF administration trial.)

197. Pi-Sunyer X et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management.. *The New England journal of medicine*, 2015. PMID 26132939 DOI 10.1056/NEJMoa1411892 (SCALE population, subcutaneous daily trial regimen, 56-week efficacy, and adverse-event findings.)

198. Pierno S et al. Growth hormone secretagogues modulate the electrical and contractile properties of rat skeletal muscle through a ghrelin-specific receptor.. *British journal of pharmacology*, 2003. PMID 12788817 DOI 10.1038/sj.bjp.0705284 (Direct skeletal muscle mechanistic research and failure of chronic secretagogue treatment to restore electrical and contractile properties in aged rats. Adds relevant non-hypertrophy muscle evidence.)

199. Pihoker C et al. Treatment effects of intranasal growth hormone releasing peptide-2 in children with short stature.. *The Journal of endocrinology*, 1997. PMID 9390009 DOI 10.1677/joe.0.1550079 (Uncontrolled pediatric growth study using 5 to 15 mcg/kg intranasally twice daily initially, then three times daily, reported in PMID 9390009.)

200. Podratz JL et al. Mechano growth factor interacts with nucleolin to protect against cisplatin-induced neurotoxicity.. *Experimental neurology*, 2020. PMID 32511954 DOI 10.1016/j.expneurol.2020.113376 (Identifies nucleolin as an MGF-binding partner in neuronal experiments.)

201. Popovic V et al. GH-releasing hormone and GH-releasing peptide-6 for diagnostic testing in GH-deficient adults.. *Lancet (London, England)*, 2000. PMID 11030292 DOI 10.1016/S0140-6736(00)02755-0 (Acute diagnostic testing in 125 patients and 125 healthy controls. Supports diagnostic investigation, not marketing approval or chronic recomposition treatment.)

202. Popovic V et al. Absence of desensitization by hexarelin to subsequent GH releasing hormone-mediated GH secretion in patients with anorexia nervosa.. *Clinical endocrinology*, 1997. PMID 9231048 DOI 10.1046/j.1365-2265.1997.1650982.x (Documents an endocrine interaction study in anorexia nervosa. Population-specific findings should not be generalized into universal secretagogue adaptation rules.)

203. Prakash A et al. Sermorelin: a review of its use in the diagnosis and treatment of children with idiopathic growth hormone deficiency.. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*, 1999. PMID 18031173 DOI 10.2165/00063030-199912020-00007 (Historical diagnostic and pediatric treatment evidence, diagnostic limitations, and documented flushing and injection-site pain.)

204. Rafferty B et al. Growth hormone-releasing factor analogue (hGRF1-29NH2): immunoreactive-GRF plasma levels after intravenous and subcutaneous administration.. *The Journal of endocrinology*, 1985. PMID 2866222 DOI 10.1677/joe.0.107r005 (Rat pharmacokinetics and low SC systemic exposure. Does not establish a human bioavailability correction.)

205. Rafferty B et al. Pharmacokinetic evaluation of superactive analogues of growth hormone-releasing factor (1-29)-amide.. *Peptides*, 1988. PMID 2896343 DOI 10.1016/0196-9781(88)90029-0 (Rat half-life and SC bioavailability estimates for the parent fragment and substituted analogs.)

206. Rahim A et al. Growth hormone status during long-term hexarelin therapy.. *The Journal of clinical endocrinology and metabolism*, 1998. PMID 9589671 DOI 10.1210/jcem.83.5.4812 (Adult 16-week subcutaneous regimen, reversible attenuation of stimulated growth hormone release, unchanged IGF-1 and body-composition endpoints, and an increase in one bone formation marker. Does not establish a cycling recommendation.)

207. Rahim A et al. Does desensitization to hexarelin occur?. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 1998. PMID 10990150 DOI 10.1016/s1096-6374(98)80039-7 (Identifies 12 healthy elderly participants and reports the adult 16-week response attenuation and recovery. Related to the chronic-treatment findings, rather than an independent replication.)

208. Rahim A et al. The effect of chronic hexarelin administration on the pituitary-adrenal axis and prolactin.. *Clinical endocrinology*, 1999. PMID 10341859 DOI 10.1046/j.1365-2265.1999.00609.x (Pituitary-adrenal and prolactin findings during the adult repeated-treatment regimen. No significant increase in urinary free cortisol or prolactin response area, with reduced cortisol response area during treatment.)

209. Rahman OF et al. Therapeutic Peptides in Orthopaedics: Applications, Challenges, and Future Directions.. *Journal of the American Academy of Orthopaedic Surgeons. Global research & reviews*, 2026. PMID 41490200 DOI 10.5435/JAAOSGlobal-D-25-00236 (Narrative orthopaedic research context. Does not constitute a human AOD-9604 combination trial or establish clinical joint-repair efficacy.)

210. Raun K et al. Liraglutide, a long-acting glucagon-like peptide-1 analog, reduces body weight and food intake in obese candy-fed rats, whereas a dipeptidyl peptidase-IV inhibitor, vildagliptin, does not.. *Diabetes*, 2007. PMID 17192459 DOI 10.2337/db06-0565 (Verified rat dose, subcutaneous route, twice-daily frequency, treatment duration, food intake, and body-composition outcomes.)

211. Raun K et al. Ipamorelin, the first selective growth hormone secretagogue.. *European journal of endocrinology*, 1998. PMID 9849822 DOI 10.1530/eje.0.1390552 (Peptide sequence, antagonist pharmacology, rat pituitary activity and swine endocrine selectivity. Prolactin remained unaffected with all tested secretagogues.)

212. Reis-Barbosa PH et al. The dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist tirzepatide effects on body weight evolution, adiponectin, insulin and leptin levels in the combination of obesity, type 2 diabetes and menopause in mice.. *Diabetes, obesity & metabolism*, 2024. PMID 39113264 DOI 10.1111/dom.15820 (Ovariectomized obese-diabetic mouse model, daily SC research exposure and weight findings.)

213. Rigamonti AE et al. Six-week treatment with hexarelin in young dogs: evaluation of the GH responsiveness to acute hexarelin or GHRH administration, and of the orexigenic effect of hexarelin.. *European journal of endocrinology*, 1999. PMID 10474131 DOI 10.1530/eje.0.1410313 (Verified repeated subcutaneous dog exposure, changing growth hormone responsiveness and a different time course for appetite effects.)

214. Rosenstock J et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA.. *Lancet (London, England)*, 2023. PMID 37385280 DOI 10.1016/S0140-6736(23)01053-X (Diabetes regimens, active comparator design, HbA1c and weight changes, gastrointestinal event rates and absence of reported severe hypoglycaemia.)

215. Rosenstock J et al. Cagrilintide-semaglutide (CagriSema) as an add-on to basal insulin in adults with type 2 diabetes (REIMAGINE 3): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study.. *Lancet (London, England)*, 2026. PMID 42251856 DOI 10.1016/S0140-6736(26)01022-6 (REIMAGINE 3, 274 participants receiving basal insulin, 40-week glycemic and weight outcomes, and absence of reported severe hypoglycemia under trial conditions.)

216. Roumi M et al. Kinetics and disposition of hexarelin, a peptidic growth hormone secretagogue, in rats.. *Drug metabolism and disposition: the biological fate of chemicals*, 2000. PMID 10611139 (Rat peptide pharmacokinetics, terminal half-life, clearance,

distribution and excretion. Does not establish human half-life or stability of a reconstituted preparation. No DOI was returned by PubMed esummary.)

217. Roumi M et al. Radioimmunoassay for hexarelin, a peptidic growth hormone secretagogue, and its pharmacokinetic studies.. *Peptides*, 1995. PMID 8545255 DOI 10.1016/0196-9781(95)02022-o (Dog pharmacokinetic measurements using a hexarelin radioimmunoassay, including an approximately 120-minute intravenous terminal half-life.)

218. Rubino DM et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial.. *JAMA*, 2022. PMID 35015037 DOI 10.1001/jama.2021.23619 (STEP 8 semaglutide outcomes, permitted lower maintenance exposure for intolerance and gastrointestinal event frequency.)

219. Rutledge C et al. Liraglutide Protects Against Diastolic Dysfunction and Improves Ventricular Protein Translation.. *Cardiovascular drugs and therapy*, 2024. PMID 37382868 DOI 10.1007/s10557-023-07482-9 (Cardiac and lean-muscle findings in an angiotensin II mouse model; journal publication year corrected from online-first year.)

220. Sackmann-Sala L et al. Activation of the GH/IGF-1 axis by CJC-1295, a long-acting GHRH analog, results in serum protein profile changes in normal adult subjects.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2009. PMID 19386527 DOI 10.1016/j.ghir.2009.03.001 (Exploratory serum proteomics analysis in 11 healthy men before and one week after CJC-1295 administration.)

221. Safwan M et al. Gastrointestinal safety of semaglutide and tirzepatide vs. placebo in obese individuals without diabetes: a systematic review and meta analysis.. *Annals of Saudi medicine*, 2025. PMID 40189856 DOI 10.5144/0256-4947.2025.129 (Pooled gastrointestinal adverse-event risk and nonsignificant pancreatic and biliary findings for tirzepatide.)

222. Samms RJ et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice.. *The Journal of clinical investigation*, 2021. PMID 34003802 DOI 10.1172/JCI146353 (Preclinical GIPR-dependent insulin sensitization and white-adipose glucose disposal.)

223. Sanyal AJ et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis.. *The New England journal of medicine*, 2025. PMID 40305708 DOI 10.1056/NEJMoa2413258 (ESSENCE interim histological outcomes, studied subcutaneous regimen and limits of inference about long-term clinical liver outcomes.)

224. Sanyal AJ et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial.. *Nature medicine*, 2024. PMID 38858523 DOI 10.1038/s41591-024-03018-2 (Liver substudy population, weekly subcutaneous doses, relative liver-fat changes and normalization rates at week 24.)

225. Schneck K et al. Population pharmacokinetics of the GIP/GLP receptor agonist tirzepatide.. *CPT: pharmacometrics & systems pharmacology*, 2024. PMID 38356317 DOI 10.1002/psp4.13099 (Population pharmacokinetic model pooling 19 studies and approximately five-day half-life.)

226. Secher A et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss.. *The Journal of clinical investigation*, 2014. PMID 25202980 DOI 10.1172/JCI75276 (Rodent brain uptake and neuronal mechanisms, with limits on extrapolation to human appetite regulation.)

227. Semenistaya E et al. Determination of growth hormone releasing peptides metabolites in human urine after nasal administration of GHRP-1, GHRP-2, GHRP-6, Hexarelin, and Ipamorelin.. *Drug testing and analysis*, 2015. PMID 25869809 DOI 10.1002/dta.1787 (Documents nasal ipamorelin exposure in one human volunteer during analytical research, contradicting the claim that all human exposure was intravenous.)

228. Shah N et al. Tripartite neuroendocrine activation of the human growth hormone (GH) axis in women by continuous 24-hour GH-releasing peptide infusion: pulsatile, entropic, and nyctohemeral mechanisms.. *The Journal of clinical endocrinology and metabolism*, 1999. PMID 10372723 DOI 10.1210/jcem.84.6.5687 (Changes in GH burst mass, amplitude and basal secretion during continuous IV infusion at 1 mcg/kg per hour for 24 hours, reported in PMID 10372723.)

229. Shioura K et al. Administration of a Synthetic Peptide Derived from the E-domain Region of Mechano-Growth Factor Delays Decompensation Following Myocardial Infarction.. *International journal of cardiovascular research*, 2014. PMID 25606570 DOI 10.4172/2324-8602.1000169 (Cardiovascular findings following a stabilized synthetic MGF E-domain analog in a mouse myocardial-infarction model. It does not establish results for an unspecified PEG-MGF conjugate.)

230. Sigalos JT et al. The Safety and Efficacy of Growth Hormone Secretagogues.. *Sexual medicine reviews*, 2018. PMID 28400207 DOI 10.1016/j.sxmr.2017.02.004 (Class-level feedback physiology, glucose and insulin-sensitivity concerns, and limitations of long-term cancer and mortality evidence.)

231. Sisson EM et al. Liraglutide: clinical pharmacology and considerations for therapy.. *Pharmacotherapy*, 2011. PMID 21923591 DOI 10.1592/phco.31.9.896 (Albumin binding, prolonged absorption, pharmacology, and approximately 13-hour elimination half-life.)

232. Soule S et al. Incorporation of D-Ala2 in growth hormone-releasing hormone-(1-29)-NH2 increases the half-life and decreases metabolic clearance in normal men.. *The Journal of clinical endocrinology and metabolism*, 1994. PMID 7962295 DOI 10.1210/jcem.79.4.7962295 (Human IV pharmacokinetics, including a 4.3-minute disappearance half-time for the unmodified fragment.)

233. Stanley TL et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial.. *JAMA*, 2014. PMID 25038357 DOI 10.1001/jama.2014.8334 (Six-month VAT and liver-fat outcomes, including the early fasting-glucose increase and later group comparisons.)

234. Stanley TL et al. Effects of tesamorelin on non-alcoholic fatty liver disease in HIV: a randomised, double-blind, multicentre trial.. *The lancet. HIV*, 2019. PMID 31611038 DOI 10.1016/S2352-3018(19)30338-8 (HIV-associated fatty liver trial; hepatic fat outcomes, histology assessment, and randomized plus open-label study phases.)

235. Sumner CJ et al. Inhibition of myostatin does not ameliorate disease features of severe spinal muscular atrophy mice.. *Human molecular genetics*, 2009. PMID 19477958 DOI 10.1093/hmg/ddp253 (Negative disease-model evidence. Transgenic follistatin overexpression produced little additional muscle mass and no motor or survival benefit in severe spinal muscular atrophy mice. Supports limits on claims of universal functional benefit.)

236. Sun F et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis.. *Diabetes research and clinical practice*, 2015. PMID 26358202 DOI 10.1016/j.diabres.2015.07.015 (Modest resting heart-rate increases with liraglutide in diabetes trials.)

237. Sun X et al. Identification and utility exploration of a highly potent and long-acting bullfrog GLP-1 analogue in GLP-1 and amylin combination therapy.. *Peptides*, 2024. PMID 38582303 DOI 10.1016/j.peptides.2024.171203 (Mouse semaglutide comparator and combination weight outcomes. Does not establish a complete semaglutide dosing schedule from the abstract.)

238. Svensson J et al. The GH secretagogues ipamorelin and GH-releasing peptide-6 increase bone mineral content in adult female rats.. *The Journal of endocrinology*, 2000. PMID 10828840 DOI 10.1677/joe.0.1650569 (Continuous subcutaneous rat exposure for 12 weeks. Greater bone mineral content reflected larger bone dimensions without increased volumetric density.)

239. Teichman SL et al. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults.. *The Journal of clinical endocrinology and metabolism*, 2006. PMID 16352683 DOI 10.1210/jc.2005-1536 (Two small randomized human studies, subcutaneous administration, pharmacokinetics, prolonged GH and IGF-1 responses, selected reported dose levels and short-term tolerability. The publication year is 2006; electronic publication occurred in 2005. Does not establish athletic benefits or long-term safety.)

240. Tewari K et al. Peptide Supplements and Their Therapeutic Applications in Sports Medicine.. *The American journal of sports medicine*, 2026. PMID 42578445 DOI 10.1177/03635465261464420 (Scoping review including CJC-1295. Supports the predominance of animal research across the included literature and inadequate human evidence for musculoskeletal claims. Pooled findings and risks from other compounds are not CJC-1295-specific estimates.)

241. Thevis M et al. Mass spectrometric characterization of a biotechnologically produced full-length mechano growth factor (MGF) relevant for doping controls.. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society*, 2014. PMID 25466910 DOI 10.1016/j.ghir.2014.10.004 (Characterization of a modified full-length MGF-related protein, including terminal lysine loss and an R109H substitution. Supports construct-specific identity concerns and historical relevance to doping controls.)

242. Thorner M et al. Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. Geref International Study Group.. *The Journal of clinical endocrinology and metabolism*, 1996. PMID 8772599 DOI 10.1210/jcem.81.3.8772599 (Open-label pediatric growth study. Distinguishes 110 enrolled children from 86 eligible for efficacy analysis.)

243. Tolis G et al. Growth hormone release by the novel GH releasing peptide hexarelin in patients with homozygous beta-thalassemia.. *Journal of pediatric endocrinology & metabolism : JPEM*, 1997. PMID 9364340 DOI 10.1515/jpem.1997.10.1.35 (Documents investigation of growth hormone release in beta-thalassemia. Included to define the human research populations, not to establish adult training benefits.)

244. Tomas FM et al. Insulin-like growth factor-I and more potent variants restore growth of diabetic rats without inducing all characteristic insulin effects.. *The Biochemical journal*, 1993. PMID 7683875 DOI 10.1042/bj2910781 (Supports increased growth and nitrogen balance in diabetic rats, with greater growth potency for low-binding-protein variants. Also documents failure to reproduce all characteristic insulin effects. The highlighted maximum comparator dose is native IGF-I.)

245. Tomas FM et al. Superior potency of infused IGF-I analogues which bind poorly to IGF-binding proteins is maintained when administered by injection.. *The Journal of endocrinology*, 1996. PMID 8708565 DOI 10.1677/joe.0.1500077 (Reports 320 mcg/day and 400 mcg/day in normal and catabolic rats, respectively, administered subcutaneously by continuous infusion or once- or twice-daily injection for seven days. Supports schedule-dependent efficacy and limited superiority for reversal of carcass muscle loss.)

246. Tomas FM et al. Effects of insulin and insulin-like growth factors on protein and energy metabolism in tumour-bearing rats.. *The Biochemical journal*, 1994. PMID 8053901 DOI 10.1042/bj3010769 (Documents increased tumour growth, reduced food intake and circulating glucose, and lack of improved host muscle protein accretion with IGF exposure, particularly LR3, in tumour-bearing rats. Does not establish human cancer incidence.)

247. Torsello A et al. Hexarelin stimulation of growth hormone release and mRNA levels in an infant and adult rat model of impaired GHRH function.. *Neuroendocrinology*, 1997. PMID 9067986 DOI 10.1159/000127168 (Age-dependent rat endocrine responses, including suppressed challenge responses after repeated exposure in young-adult animals. Does not establish uniform adaptation across ages.)

248. Urva S et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists.. *Diabetes, obesity & metabolism*, 2020. PMID 32519795 DOI 10.1111/dom.14110 (Initial gastric-emptying delay, attenuation with repeated exposure and residual delay during escalation in diabetes.)

249. Urva S et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial.. *Lancet (London, England)*, 2022. PMID 36354040 DOI 10.1016/S0140-6736(22)02033-5 (Approximately six-day half-life, dose-proportional exposure, fixed and escalating research regimens, and 12-week study duration.)

250. Urva S et al. The novel GIP, GLP-1 and glucagon receptor agonist retatrutide delays gastric emptying.. *Diabetes, obesity & metabolism*, 2023. PMID 37311727 DOI 10.1111/dom.15167 (Retatrutide-associated delayed gastric emptying.)

251. van Can J et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults.. *International journal of obesity (2005)*, 2014. PMID 23999198 DOI 10.1038/ijo.2013.162 (Human mechanistic regimens, appetite, energy intake, gastric emptying, and lack of increased energy expenditure.)

252. Van den Berghe G et al. The somatotropic axis in critical illness: effect of continuous growth hormone (GH)-releasing hormone and GH-releasing peptide-2 infusion.. *The Journal of clinical endocrinology and metabolism*, 1997. PMID 9024260 DOI 10.1210/jcem.82.2.3736 (Endocrine responses to GHRP-2 and GHRH in critical illness, including additional GH and IGF-I responses with their combination.)

253. Villegas Meza AD et al. Injectable Peptides in Sports Medicine: A Structured Narrative Review of Evidence, Safety, and Antidoping Implications.. *JBJS reviews*, 2026. PMID 42160466 DOI 10.2106/JBJS.RVW.26.00027 (Investigational status of GH-axis secretagogues for sports medicine, uncertain safety, product quality concerns and antidoping implications. Its evidence classification and indication-specific conclusions should not be treated as universal approval determinations.)

254. Vittone J et al. Effects of single nightly injections of growth hormone-releasing hormone (GHRH 1-29) in healthy elderly men.. *Metabolism: clinical and experimental*, 1997. PMID 9005976 DOI 10.1016/s0026-0495(97)90174-8 (Uncontrolled adult study with increased nocturnal GH, unchanged IGF-I and DEXA body composition, and limited functional findings.)

255. Wade JD et al. Effect of C-terminal chain shortening on the insulin-antagonistic activity of human growth hormone 177--191.. *Acta endocrinologica*, 1982. PMID 6751009 DOI 10.1530/acta.0.1010010 (Insulin-antagonistic activity of chemically modified GH fragments in rats. Does not show that ordinary AOD-9604 handling generates those derivatives.)

256. Wang L et al. Growth hormone releasing peptide-6 (GHRP-6) ameliorates acute lung injury and its subsequent evolvement to interstitial fibrosis.. *International immunopharmacology*, 2026. PMID 41534456 DOI 10.1016/j.intimp.2026.116204 (Mouse models of acute lung injury and subsequent fibrotic changes. Findings remain preclinical.)

257. Westberg C et al. Hexarelin--evaluation of factors influencing oral bioavailability and ways to improve absorption.. *The Journal of pharmacy and pharmacology*, 2001. PMID 11578108 DOI 10.1211/0022357011776540 (Experimental intestinal degradation, lysine deamidation and low permeability relevant to oral absorption. Does not provide a validated storage specification.)

258. Wilding J et al. AOD-9604 Metabolic.. *Current opinion in investigational drugs (London, England : 2000)*, 2004. PMID 15134286 (Historical development review describing early human research. FDA corroborates its study using 25, 50 or 100 mcg/kg intravenously at weekly study visits across four periods.)

259. Wilding JPH et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity.. *The New England journal of medicine*, 2021. PMID 33567185 DOI 10.1056/NEJMoa2032183 (STEP 1 population, subcutaneous once-weekly regimen, weight outcomes, escalation and gastrointestinal discontinuations.)

260. Wilding JPH et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension.. *Diabetes, obesity & metabolism*, 2022. PMID 35441470 DOI 10.1111/dom.14725 (Exploratory withdrawal follow-up, extension sample size, cessation of lifestyle intervention and approximately two-thirds average weight regain.)

261. Wilton P et al. Pharmacokinetics of growth hormone-releasing hormone(1-29)-NH2 and stimulation of growth hormone secretion in healthy subjects after intravenous or intranasal administration.. *Acta paediatrica (Oslo, Norway : 1992). Supplement*, 1993. PMID 8329825 DOI 10.1111/j.1651-2227.1993.tb12827.x (Human IV and intranasal experiments, low intranasal bioavailability, and GH elevation lasting longer than circulating peptide exposure.)

262. Wu Z et al. Antilipogenic action of synthetic C-terminal sequence 177-191 of human growth hormone.. *Biochemistry and molecular biology international*, 1993. PMID 8358331 (Related GH fragment inhibited lipogenesis without significantly increasing glycerol release in the reported rat adipose assay. Supports distinguishing lipogenesis from lipolysis.)

263. Xia Y et al. The biology of activin: recent advances in structure, regulation and function.. *The Journal of endocrinology*, 2009. PMID 19273500 DOI 10.1677/JOE-08-0549 (Activin biology, structural regulation by binding proteins, and reproductive, metabolic, and immune functions. Supports mechanistic discussion and precautionary concerns, not a confirmed adverse-event incidence or formal follistatin contraindication list.)

264. Xu XB et al. GH-releasing peptides improve cardiac dysfunction and cachexia and suppress stress-related hormones and cardiomyocyte apoptosis in rats with heart failure.. *American journal of physiology. Heart and circulatory physiology*, 2005. PMID 15951341 DOI 10.1152/ajpheart.01042.2004 (Rat cardiac findings in a study including GHRP-2 at 100 mcg/kg SC twice daily for three weeks, reported in PMID 15951341.)

265. Yamauchi T et al. Efficacy and safety of co-administered cagrilintide and semaglutide versus semaglutide alone in adults with overweight or obesity with or without type 2 diabetes in Japan and Taiwan (REDEFINE 5): a multicentre, randomised, active-controlled, phase 3a trial.. *The lancet. Diabetes & endocrinology*, 2026. PMID 42009015 DOI 10.1016/S2213-8587(25)00402-4 (REDEFINE 5, 331 participants in Japan and Taiwan, 68-week combination-versus-semaglutide outcomes using the primary trial product estimand.)

266. Yokota-Nakagi N et al. Estradiol Replacement Improves High-Fat Diet-Induced Obesity by Suppressing the Action of Ghrelin in Ovariectomized Rats.. *Nutrients*, 2020. PMID 32224927 DOI 10.3390/nu12040907 (GHRP-6 increased high-fat diet intake and arcuate nucleus activation in placebo-treated ovariectomized rats, with different responses after estradiol replacement.)

267. Zhao X et al. Growth hormone-releasing peptide 6 (GHRP-6) hydrogel for acute kidney injury therapy via metabolic regulation.. *Journal of nanobiotechnology*, 2025. PMID 41327290 DOI 10.1186/s12951-025-03888-9 (A self-assembling GHRP-6 hydrogel in experimental kidney injury, tubular-cell metabolism and mTOR-P70 signaling. Formulation-specific preclinical findings.)

Recomposition is sequencing.

Fat loss and hypertrophy compounds, in the order the body accepts them.