CLINICAL REFERENCE COMPENDIUM

Peptide Protocols Reference

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CLINICAL REFERENCE MONOGRAPH

Semaglutide

(Ozempic® / Wegovy® / Rybelsus®)

The Landmark Long-Acting GLP-1 Agonist

T2DM · Obesity · Cardiovascular Risk · MASH · Safety Profile

1. Overview

Semaglutide is a long-acting GLP-1 receptor agonist with a ~7-day half-life, available as once-weekly subcutaneous injection (Ozempic® for T2DM, Wegovy® for obesity) and once-daily oral tablet (Rybelsus® for T2DM). It has demonstrated landmark cardiovascular outcomes, substantial weight loss, and emerging evidence in MASH and CKD, establishing it as one of the most transformative cardiometabolic drugs in history.

Parameter	Details
Brand Names	Ozempic® (T2DM SC) / Wegovy® (Obesity SC) / Rybelsus® (T2DM oral)
Category	Long-Acting GLP-1 Receptor Agonist
Half-Life	~7 days (supports once-weekly dosing)
Peak Concentration	1–3 days post-injection
Steady State	4–5 weeks of weekly dosing
FDA Approvals	T2DM (2017), Obesity (2021), CVD Risk Reduction (2023)
Key Warning	Boxed warning: thyroid C-cell tumors in rodents; contraindicated in MTC/MEN2

2. Mechanism of Action

Semaglutide's extended half-life is achieved through C18 fatty diacid conjugation enabling albumin binding (reducing renal clearance), amino acid substitutions conferring DPP-4 resistance, and a C-2 aminoisobutyric acid substitution improving metabolic stability. These modifications maintain full GLP-1 receptor agonism:

- **Insulin secretion:** Glucose-dependent stimulation from pancreatic beta cells.
- **Glucagon suppression:** Reduces postprandial and fasting glucose excursions.
- **Gastric emptying:** Delays gastric transit, reducing caloric absorption and promoting satiety.
- **Appetite center:** Activates hypothalamic and brainstem GLP-1 receptors; reduces hunger and food cravings.
- **Cardiovascular:** Anti-inflammatory, anti-atherosclerotic plaque effects; reduces MACE by 20% (SELECT trial).

3. FDA-Approved Indications & Key Trials

Indication	Brand	Trial	Key Result
Type 2 Diabetes (SC)	Ozempic®	SUSTAIN-6	-1.5% HbA1c; -26% MACE vs. placebo

Indication	Brand	Trial	Key Result
Chronic Weight Mgmt	Wegovy®	STEP-1	-14.9% body weight at 68 weeks
CVD Risk Reduction	Wegovy®	SELECT	-20% MACE; first weight-loss drug with CV indication
Type 2 Diabetes (oral)	Rybelsus®	PIONEER	-1.0–1.4% HbA1c; approved 2019

4. Titration Schedule (Wegovy® / Ozempic®)

Weeks	Dose	Brand Target
1–4	0.25 mg once weekly	Initiation (not therapeutic)
5–8	0.5 mg once weekly	Therapeutic dose (Ozempic®)
9–12	1.0 mg once weekly	Max Ozempic® standard dose
13–16	1.7 mg once weekly	Wegovy® escalation
17+	2.4 mg once weekly	Wegovy® maintenance dose

5. Safety Profile

5.1 Absolute Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC)
- Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
- Known hypersensitivity to semaglutide
- Pregnancy or breastfeeding

5.2 Common Adverse Events

- Gastrointestinal: Nausea, vomiting, diarrhea, constipation, decreased appetite (most common during escalation)
- Alopecia (hair thinning; reported at higher obesity doses)

5.3 Serious Adverse Events

- Pancreatitis (increased risk; discontinue if suspected)
- Gallbladder disease (increased cholelithiasis and cholecystitis)
- Diabetic retinopathy worsening (rapid glycemic improvement; monitor closely in T2DM)
- Acute kidney injury (secondary to dehydration from GI effects)

5.4 Drug Interactions

- **Insulin / sulfonylureas:** Increased hypoglycemia risk; dose adjustments may be required.

- **Oral medications:** Delayed gastric emptying may reduce absorption of time-sensitive drugs.

6. Reference Sources

1. Marso SP, et al. Semaglutide and cardiovascular outcomes in T2DM (SUSTAIN-6). N Engl J Med. 2016; PMID: 27633186.

2. Wilding JPH, et al. Once-weekly semaglutide in adults with obesity (STEP-1). N Engl J Med. 2021; PMID: 33567185.

3. Lincoff AM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes (SELECT). N Engl J Med. 2023; PMID: 37952131.

CLINICAL REFERENCE MONOGRAPH

Tirzepatide

(Mounjaro® / Zepbound®)

The FDA-Approved Dual GIP/GLP-1 Agonist

T2DM · Obesity · Sleep Apnea · Cardiovascular · Safety Profile

1. Overview

Tirzepatide is an FDA-approved once-weekly dual agonist of the GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. Approved as Mounjaro® for type 2 diabetes and Zepbound® for chronic weight management, it consistently produces greater weight loss and glucose lowering than GLP-1 monotherapy in head-to-head trials, establishing a new benchmark in cardiometabolic pharmacotherapy.

Parameter	Details
Brand Names	Mounjaro® (T2DM) / Zepbound® (Obesity)
Category	Dual GIP/GLP-1 Receptor Agonist
Half-Life	~5 days
Peak Plasma	24–48 hours post-injection
FDA Approvals	T2DM (2022), Obesity (2023), OSA (2024)
Available Doses	2.5 / 5 / 7.5 / 10 / 12.5 / 15 mg
Key Warning	Boxed warning: thyroid C-cell tumors in rodents; contraindicated in MTC/MEN2 history

2. Mechanism of Action

Tirzepatide is a synthetic peptide engineered on a GIP scaffold with GLP-1 receptor agonist modifications, enabling simultaneous activation of both receptors with high affinity:

- **GIP Receptor Agonism:** Augments insulin secretion; improves insulin sensitivity; may enhance fat oxidation in adipose tissue.
- **GLP-1 Receptor Agonism:** Glucose-dependent insulin secretion; glucagon suppression; gastric emptying delay; appetite reduction via hypothalamic pathways.
- **Synergistic Benefit:** Dual agonism produces greater weight loss than either pathway alone; GIP co-activation reduces the nausea associated with GLP-1 monotherapy.

3. FDA-Approved Indications

Indication	Brand	Approval Year	Key Trial
Type 2 diabetes mellitus	Mounjaro®	2022	SURPASS program
Chronic weight management	Zepbound®	2023	SURMOUNT program
Obstructive sleep apnea with obesity	Zepbound®	2024	SURMOUNT-OSA

4. Titration Schedule

Weeks	Dose
1–4	2.5 mg once weekly
5–8	5 mg once weekly
9–12	7.5 mg once weekly
13–16	10 mg once weekly
17–20	12.5 mg once weekly
21+	15 mg once weekly (maximum dose)

5. Key Clinical Trial Data

5.1 SURMOUNT-1 (Obesity, 2022)

- 72-week mean weight loss: 20.9% at 15 mg vs. 3.1% placebo
- 34% of participants lost ≥20% body weight

5.2 SURPASS-2 (vs. Semaglutide, T2DM)

- Greater HbA1c reduction vs. semaglutide 1 mg at all doses
- Superior weight loss: -5.5 kg more than semaglutide

5.3 SURMOUNT-4 (Maintenance)

Participants who discontinued after 36 weeks regained approximately two-thirds of lost weight over 52 weeks, confirming chronic therapy requirement.

6. Safety Profile

6.1 Absolute Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC)
- Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
- Known hypersensitivity to tirzepatide
- Pregnancy or breastfeeding

6.2 Common Adverse Events

- Gastrointestinal: Nausea, diarrhea, decreased appetite, vomiting, constipation, alopecia

6.3 Serious Adverse Events

- Pancreatitis
- Gallbladder disease
- Hypoglycemia (primarily with concomitant insulin or sulfonylureas)
- Acute kidney injury (secondary to dehydration from GI effects)

6.4 Drug Interactions

- **Insulin / sulfonylureas:** Increase hypoglycemia risk; dose adjustments required.
- **Oral medications:** Delayed gastric emptying may alter absorption of time-sensitive drugs.

7. Reference Sources

1. Jastreboff AM, et al. Tirzepatide for Obesity (SURMOUNT-1). N Engl J Med. 2022; PMID: 35658024.

2. Aronne LJ, et al. Continued Treatment with Tirzepatide (SURMOUNT-4). JAMA. 2024; PMID: 38078870.

3. Malhotra A, et al. Tirzepatide for Sleep Apnea and Obesity. N Engl J Med. 2024; PMID: 38912654.

CLINICAL REFERENCE MONOGRAPH

Retatrutide

(GLP-1/GIP/Glucagon Triple Agonist)

The Triple Hormone Receptor Agonist

Weight Loss · T2DM · MASH · Cardiometabolic · Safety Profile

1. Overview

Retatrutide is an investigational once-weekly injectable peptide that simultaneously activates three receptor pathways: GLP-1 (glucagon-like peptide-1), GIP (glucose-dependent insulinotropic polypeptide), and glucagon receptors. This triple agonism differentiates it from approved dual (tirzepatide) and single (semaglutide) agonists, producing synergistic effects on appetite suppression, glucose control, and energy expenditure.

Parameter	Details
Name	Retatrutide
Reference Code	GLP-3RT
Category	Triple GLP-1/GIP/Glucagon Receptor Agonist
Half-Life	~6 days (supports once-weekly dosing)
Peak Plasma	24–72 hours post-injection
Investigational Doses	1 mg, 2 mg, 4 mg, 8 mg, 12 mg (Phase 2/3 trials)
Key Warning	GLP-1 class boxed warning: thyroid C-cell tumors in rodents; contraindicated in MTC/MEN2 history

2. Mechanism of Action

Retatrutide achieves its efficacy through simultaneous activation of three metabolic receptor systems:

- **GLP-1 Receptor Agonism:** Enhances glucose-dependent insulin secretion, suppresses glucagon, slows gastric emptying, and reduces appetite via hypothalamic signaling.
- **GIP Receptor Agonism:** Augments insulin secretion and may improve insulin sensitivity; synergizes with GLP-1 for superior glucose lowering.
- **Glucagon Receptor Agonism:** Increases energy expenditure via hepatic lipid metabolism and thermogenic mechanisms; unique to triple agonism vs. dual/single agents.

3. Clinical Indications (Investigational)

- Obesity (Phase 2 and Phase 3 clinical trials)
- Type 2 diabetes mellitus
- Metabolic dysfunction-associated steatohepatitis (MASH)
- Cardiometabolic risk modification

4. Titration Schedule (Phase 2 Clinical Trial Reference)

Timeline	Dose
Weeks 1–4	1–2 mg once weekly
Weeks 5–8	4 mg once weekly
Weeks 9–12	8 mg once weekly
Week 13+	12 mg once weekly (highest Phase 2 dose studied)

Gradual escalation is associated with improved gastrointestinal tolerability and reduced early discontinuation.

5. Pharmacokinetics

- Half-life: ~6 days (supports once-weekly dosing)
- Peak plasma concentrations: 24–72 hours post-injection
- Steady-state: achieved after several weeks of weekly dosing
- Metabolism: proteolytic degradation into inactive peptide fragments

6. Phase 2 Efficacy Highlights

The Phase 2 obesity trial (NEJM 2023, Jastreboff et al.) demonstrated mean body weight reductions of up to 24.2% at 12 mg over 48 weeks—the highest weight loss observed in a GLP-class trial at that time. The Phase 2 T2DM trial showed significant HbA1c reductions across all dose arms.

7. Safety Profile

7.1 Absolute Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC)
- Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
- Known hypersensitivity to retatrutide or formulation components
- Pregnancy or breastfeeding

7.2 Common Adverse Events

- Gastrointestinal: Nausea (dose-dependent), diarrhea, vomiting, constipation, decreased appetite
- Cardiovascular: Mild heart rate increases observed

7.3 Serious Adverse Events

- Pancreatitis
- Gallbladder disease
- Severe gastrointestinal intolerance

8. Monitoring Parameters

- Fasting glucose and HbA1c
- Body weight and BMI
- Heart rate
- Liver enzymes (if underlying hepatic disease present)
- Symptoms of pancreatitis or gallbladder disease

9. Reference Sources

1. Jastreboff AM, et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity. N Engl J Med. 2023; PMID: 37385275.

2. Frias JP, et al. Retatrutide in Type 2 Diabetes. N Engl J Med. 2023; PMID: 37192581.

DISCLAIMER: *Retatrutide is investigational and not FDA-approved. It carries the GLP-1 class boxed warning regarding thyroid C-cell tumors. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

CagriSema

(Cagrilintide + Semaglutide)

Dual Amylin & GLP-1 Combination

Obesity · Amylin Pathway · GLP-1 Pathway · Weight Loss · Safety Profile

1. Overview

CagriSema is an investigational fixed-dose combination of cagrilintide (a long-acting amylin analog) and semaglutide (a GLP-1 receptor agonist), administered as a single once-weekly subcutaneous injection. The combination is designed to leverage complementary appetite-suppression pathways—amylin and GLP-1—to achieve greater weight reduction than either monotherapy alone.

Parameter	Details
Name	CagriSema (Fixed-Dose Combination)
Reference Code	CAGRISEMA
Components	Cagrilintide (amylin analog) + Semaglutide (GLP-1 RA)
Category	Dual Amylin/GLP-1 Receptor Agonist Combination
Frequency	Once weekly subcutaneous
Development Stage	Phase 3 clinical trials (REDEFINE program)
Key Warning	GLP-1 class boxed warning: thyroid C-cell tumors in rodents; contraindicated in MTC/MEN2

2. Component Mechanisms

2.1 Cagrilintide (Amylin Analog)

Cagrilintide activates amylin receptors in appetite-regulating brain regions, producing complementary weight-loss mechanisms to GLP-1 agonism:

- Promotes satiety and reduces caloric intake via hypothalamic signaling
- Delays gastric emptying, prolonging postprandial fullness
- Suppresses postprandial glucagon secretion
- Acts on brainstem receptors distinct from GLP-1 receptor distribution

2.2 Semaglutide (GLP-1 Receptor Agonist)

Semaglutide (2.4 mg, Wegovy®) is already approved for chronic weight management. In CagriSema it is combined at the same dose, providing its established mechanisms:

- Enhances glucose-dependent insulin secretion; suppresses glucagon
- Slows gastric emptying; modulates appetite centrally and peripherally
- Reduces cardiovascular risk (SUSTAIN-6 trial data)

3. Investigational Indications

- Obesity: Phase 3 REDEFINE clinical development program
- Type 2 diabetes mellitus
- Cardiometabolic risk modification

4. Titration Schedule (Clinical Development Reference)

Timeline	Cagrilintide Dose	Semaglutide Dose
Weeks 1–4	0.25 mg	0.25 mg
Weeks 5–8	0.5 mg	0.5 mg
Weeks 9–12	1.0 mg	1.0 mg
Weeks 13–16	1.7 mg	1.7 mg
Week 17+	2.4 mg	2.4 mg

5. Safety Profile

5.1 Absolute Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC)
- Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
- Known hypersensitivity to cagrilintide or semaglutide
- Pregnancy or breastfeeding

5.2 Adverse Events

- Common: Nausea (dose-dependent), vomiting, diarrhea, constipation, decreased appetite
- Serious: Pancreatitis, gallbladder disease, severe gastrointestinal intolerance

6. Reference Sources

1. Wilding JPH, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021; PMID: 33567185.

2. Marso SP, et al. Semaglutide and Cardiovascular Outcomes in T2DM (SUSTAIN-6). N Engl J Med. 2016; PMID: 27633186.

3. ClinicalTrials.gov. REDEFINE Phase 3 CagriSema Program. NCT05669755.

DISCLAIMER: *CagriSema is investigational and not FDA-approved. Both component classes carry the GLP-1 class boxed warning regarding thyroid C-cell tumors. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

Cagrilintide

(Long-Acting Amylin Analog)

The Sustained-Release Amylin Receptor Agonist

Satiety · Weight Loss · Gastric Emptying · Glucagon · Safety Profile

1. Overview

Cagrilintide is a long-acting synthetic analog of amylin (islet amyloid polypeptide, IAPP), engineered for once-weekly subcutaneous dosing via fatty acid conjugation that extends its half-life to approximately 6–8 days. It activates amylin receptors in appetite-regulating brain regions, producing satiety and weight loss through mechanisms complementary to—and distinct from—GLP-1 receptor agonists. It is in Phase 3 development both as monotherapy and in combination with semaglutide as CagriSema.

Parameter	Details
Name	Cagrilintide
Reference Code	CAGRI
Category	Long-Acting Amylin Analog / Amylin Receptor Agonist
Half-Life	~6–8 days (fatty acid conjugation)
Route	Subcutaneous injection
Frequency	Once weekly
Clinical Dose Range	0.25–2.4 mg once weekly
Key Warning	Not FDA-approved; slows gastric emptying; caution in gastroparesis

2. Mechanism of Action

2.1 Amylin Receptor Activation

Cagrilintide activates amylin receptors (calcitonin receptor + RAMP heteromers) in the area postrema, nucleus tractus solitarius, and hypothalamus—brain regions governing satiety and energy balance. Unlike GLP-1 receptors, amylin receptors are not primarily located in the gut, producing a distinct and complementary satiety signal.

2.2 Key Physiological Effects

- Promotes satiety and reduces caloric intake via central hypothalamic signaling
- Delays gastric emptying, prolonging postprandial fullness and reducing postprandial glucose excursions
- Suppresses postprandial glucagon secretion, improving glycemic control
- Reduces body weight through sustained negative energy balance

2.3 Synergy with GLP-1 Agonists

Amylin and GLP-1 receptors have distinct CNS distributions and non-overlapping signaling pathways. Combining cagrilintide with semaglutide (CagriSema) produces additive or potentially synergistic weight loss exceeding either agent alone, as demonstrated in Phase 2 COMBINE trials.

3. Investigational Indications

- Obesity: Phase 3 REDEFINE program (as monotherapy and CagriSema combination)
- Type 2 diabetes mellitus
- Cardiometabolic risk modification

4. Titration Schedule

Timeline	Dose	Frequency
Weeks 1–4	0.25 mg	Once weekly
Weeks 5–8	0.5 mg	Once weekly
Weeks 9–12	1.0 mg	Once weekly
Weeks 13–16	1.7 mg	Once weekly
Week 17+	2.4 mg	Once weekly

5. Reconstitution Reference

Standard concentration: 2.5 mg/mL. A 10 mg vial + 4.0 mL bacteriostatic water yields 2.5 mg/mL; 0.10 mL = 0.25 mg. Stable up to 28 days refrigerated.

Volume	Insulin Units	Dose
0.10 mL	10 units	0.25 mg
0.20 mL	20 units	0.5 mg
0.40 mL	40 units	1.0 mg
0.68 mL	68 units	1.7 mg
0.96 mL	96 units	2.4 mg

6. Safety Profile

6.1 Contraindications

- Known hypersensitivity to cagrilintide or formulation components
- Pregnancy or breastfeeding

6.2 Key Warning: Gastroparesis

As an amylin analog, cagrilintide substantially slows gastric emptying. Use with caution or avoid in patients with pre-existing gastroparesis or severe GI dysmotility.

6.3 Adverse Events

- Nausea (dose-dependent, most common during escalation)
- Vomiting and diarrhea
- Decreased appetite (beyond therapeutic weight loss)
- Injection site reactions
- Severe GI intolerance and dehydration (serious, rare)

6.4 Drug Interactions

- **Insulin / sulfonylureas:** Increased hypoglycemia risk; monitor glucose closely.
- **Oral medications:** Delayed gastric emptying may alter absorption kinetics.

7. Reference Sources

1. Lau J, et al. Cagrilintide in overweight and obese adults. Lancet. 2021; PMID: 34678131.

2. Frias JP, et al. Cagrilintide in type 2 diabetes. Lancet Diabetes Endocrinol. 2022; PMID: 35303460.

3. Rosenstock J, et al. CagriSema combination therapy. Lancet. 2023; PMID: 36870376.

CLINICAL REFERENCE MONOGRAPH

Orforglipron

(LY-3502970)

The First Oral Small-Molecule GLP-1 Agonist

Oral GLP-1 · Obesity · T2DM · No Food Restrictions · Safety Profile

1. Overview

Orforglipron (LY-3502970) is an investigational once-daily oral small-molecule GLP-1 receptor agonist developed by Eli Lilly, licensed from Chugai Pharmaceutical. Unlike peptide-based GLP-1 agonists (semaglutide, tirzepatide), it is a non-peptide small molecule that does not require subcutaneous injection, cold-chain storage, or fasting before administration—potentially transforming patient access and adherence. Phase 3 results in 2024–2025 demonstrated competitive efficacy against injectable agents.

Parameter	Details
Name	Orforglipron (LY-3502970)
Category	Oral Small-Molecule GLP-1 Receptor Agonist
Route	Once-daily oral (no food restriction required)
Storage	Room temperature (no cold-chain needed)
Development Stage	Phase 3 (NDA submission anticipated)
Key Advantage	No injection, no fasting, no cold chain vs. peptide GLP-1 agonists
Key Warning	GLP-1 class boxed warning: thyroid C-cell tumors (rodents); contraindicated in MTC/MEN2

2. Mechanism of Action

Orforglipron functions as a non-peptide partial agonist that binds within the transmembrane domain of the GLP-1 receptor (distinct from the extracellular peptide-binding site used by semaglutide). Receptor binding activates the cAMP-PKA signaling cascade, producing the same downstream effects as peptide GLP-1 agonists:

- **Pancreatic:** Glucose-dependent insulin secretion enhancement; glucagon suppression.
- **Gastric:** Delayed gastric emptying; prolonged postprandial satiety.
- **Central:** Appetite suppression via hypothalamic GLP-1 receptor signaling.
- **Cardiovascular:** Emerging favorable lipid, blood pressure, and inflammation data.

3. Key Clinical Trial Results

3.1 ATTAIN-1 Trial (Non-Diabetic Obesity, 72 Weeks)

Parameter	36 mg Dose	Placebo
Mean Weight Loss	-12.4% (27.3 lbs average)	-0.9%
Achieved ≥10% Weight Loss	59.6%	~10%

Parameter	36 mg Dose	Placebo
Achieved ≥15% Weight Loss	~40%	<5%

3.2 ACHIEVE-3 Trial (T2DM vs. Oral Semaglutide, 52 Weeks)

Parameter	Orforglipron 36 mg	Oral Semaglutide 14 mg
HbA1c Reduction	-2.2%	-1.4%
Weight Loss	-9.2%	-5.3%
Waist Circumference	Greater reduction	Less reduction

Additional benefits included 48–51% reductions in inflammatory markers, favorable lipid changes, and blood pressure improvements.

4. Practical Advantages Over Injectable GLP-1 Agents

Feature	Orforglipron	Injectable GLP-1 Agonists
Route	Once-daily oral	Weekly injection
Food Restriction	None required	Oral sema: 30+ min fast
Cold Chain	Not required	Required
Needle Phobia	N/A	Barrier for many patients
Dosing Adherence	Simpler (pill)	Injection technique required

5. Safety Profile

5.1 Absolute Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC)
- Multiple Endocrine Neoplasia syndrome type 2 (MEN2)
- Known hypersensitivity to orforglipron
- Pregnancy or breastfeeding

5.2 Common Adverse Events (Mild-to-Moderate, Typically Transient)

- Nausea: 13–32% (dose-dependent; most common during dose escalation)
- Diarrhea: 9–26%
- Vomiting: 5–14%
- Discontinuation rates: 4–17% (similar to injectable GLP-1 class)

6. Reference Sources

1. Wharton S, et al. Orforglipron for obesity. N Engl J Med. 2023; PMID: 37366314.

2. Dahl D, et al. Oral small molecule GLP-1 receptor agonist orforglipron in T2DM. N Engl J Med. 2023; PMID: 37369145.

DISCLAIMER: *Orforglipron is investigational and not yet FDA-approved. NDA submission is anticipated. It carries the GLP-1 class boxed warning regarding thyroid C-cell tumors. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

NAD+

(Nicotinamide Adenine Dinucleotide)

The Master Metabolic Coenzyme

Mitochondrial Function · DNA Repair · Sirtuin Activation · Energy · Safety Profile

1. Overview

NAD+ (Nicotinamide Adenine Dinucleotide) is an essential coenzyme present in all living cells, functioning as a central electron carrier in mitochondrial oxidative phosphorylation and a critical substrate for DNA repair enzymes (PARPs) and longevity-associated sirtuins. NAD+ levels decline measurably with age and in metabolic disease states, making repletion a target of active research in longevity, addiction recovery, and metabolic health.

Parameter	Details
Name	NAD+ (Nicotinamide Adenine Dinucleotide)
Reference Code	NAD+
Category	Metabolic Coenzyme / Essential Cellular Substrate
Administration Route	IV infusion or IM injection
Reference Range	250–1,000 mg per infusion
Frequency	Weekly to monthly (maintenance)
Key Warning	Not FDA-approved for anti-aging or addiction claims; arrhythmia risk with rapid infusion

2. Mechanisms of Action

2.1 Mitochondrial Energy Production

NAD+ serves as the primary electron acceptor in the mitochondrial electron transport chain, accepting electrons from NADH to drive ATP synthesis via oxidative phosphorylation. Depletion impairs cellular energy production across all tissue types.

2.2 PARP-Mediated DNA Repair

Poly(ADP-ribose) polymerases (PARPs) consume NAD+ as a substrate to detect and repair DNA strand breaks. Chronic NAD+ depletion impairs genomic stability and accelerates cellular aging.

2.3 Sirtuin Activation

Sirtuins (SIRT1–7) are NAD+-dependent deacylases that regulate gene expression, metabolic adaptation, stress resistance, and mitochondrial biogenesis. Sirtuin activity is directly proportional to available NAD+, creating a direct link between NAD+ levels and longevity-associated pathways.

2.4 Age-Related Decline

Circulating and tissue NAD+ levels decline approximately 50% between young adulthood and middle age due to increased PARP activity (DNA damage burden), reduced biosynthesis, and increased CD38 NAD+ase activity. This decline is implicated in metabolic dysfunction, neurodegeneration, and reduced stress resistance.

3. Clinical Indications (Investigational)

- Energy metabolism support and mitochondrial health frameworks
- Cognitive support research
- Addiction recovery programs (alcohol and opioid withdrawal)
- Longevity and cellular repair signaling studies

4. Administration Protocol

Parameter	Details
Route	IV infusion (primary) or IM injection
Infusion Duration	1–4 hours (slow infusion essential to minimize adverse effects)
Loading Protocol	Weeks 1–2: 250–500 mg loading series (2–4 infusions)
Maintenance	Week 3+: 250–1,000 mg weekly to monthly
Setting	Clinical IV infusion setting; vital sign monitoring required

5. Safety Profile

5.1 Contraindications

- Pregnancy or breastfeeding
- Active acute illness or infection

5.2 Infusion-Related Adverse Events

- Flushing (common; rate-dependent)
- Nausea and gastrointestinal discomfort
- Headache and dizziness
- Chest tightness during infusion (common; resolves with rate reduction)
- Arrhythmia (rare; associated with excessively rapid infusion)

5.3 Drug Interactions

Concurrent niacin supplementation may produce additive flushing effects. Alcohol consumption may deplete NAD+ further and should be avoided around infusion periods.

6. Reference Sources

1. Covarrubias AJ, et al. NAD+ metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Biol. 2021; PMID: 33353981.

2. Verdin E. NAD+ in aging, metabolism, and neurodegeneration. Science. 2015; PMID: 26785480.

3. Rajman L, et al. Therapeutic potential of NAD-boosting molecules. Cell Metab. 2018; PMID: 29514072.

CLINICAL REFERENCE MONOGRAPH

L-Carnitine

(Injectable)

The Mitochondrial Fatty Acid Transporter

Beta-Oxidation · Energy Metabolism · Deficiency States · Exercise · Safety Profile

1. Overview

L-Carnitine is a naturally occurring amino acid derivative (synthesized from lysine and methionine) essential for transporting long-chain fatty acids across the inner mitochondrial membrane for beta-oxidation and ATP production. Injectable L-Carnitine bypasses the GI absorption limitations of oral forms (oral bioavailability ~16% vs. ~100% injectable), making it the preferred route in clinical deficiency states. Dietary sources include red meat and dairy; vegan/vegetarian diets are associated with lower carnitine levels.

Parameter	Details
Name	L-Carnitine
Reference Code	LCAR
Category	Metabolic Compound / Amino Acid Derivative
Injectable Supply	5,000 mg multidose vial; 500 mg/mL concentration
Reference Range	500–2,000 mg per injection
Frequency	2–3 times weekly
Route	IM injection or IV
Half-Life	~17 hours
Key Warning	Caution in seizure disorders; fishy odor common; may interact with thyroid medications

2. Mechanism of Action

2.1 Mitochondrial Fatty Acid Transport

L-Carnitine combines with long-chain fatty acyl-CoA esters to form acylcarnitine, which is then transported across the inner mitochondrial membrane by the carnitine-acylcarnitine translocase system. Once inside, the acyl group is transferred back to CoA for beta-oxidation, and free carnitine returns to the cytoplasm. This shuttle system is the rate-limiting step for mitochondrial fatty acid oxidation.

2.2 Acetyl-CoA & Energy Balance

The resulting acetyl-CoA enters the TCA cycle for ATP production. L-Carnitine also buffers the acetyl-CoA/CoA ratio, protecting against CoA sequestration and maintaining metabolic flexibility between glucose and fat oxidation.

3. Clinical Indications

Indication	Evidence Level
Primary carnitine deficiency (genetic)	FDA-approved (IV/oral Carnitor®)
Secondary carnitine deficiency (dialysis, valproic acid)	FDA-approved
Peripheral vascular disease / intermittent claudication	Phase 3 clinical data
Male infertility (sperm motility)	Multiple RCTs
Chemotherapy-induced peripheral neuropathy	Clinical trials
Exercise performance enhancement	Mixed evidence; investigational

4. Administration Protocol

Parameter	Details
Route	IM injection (deltoid or gluteal) or IV
Frequency	2–3 times weekly
Standard Dose	500–2,000 mg per injection
Timing	Morning or pre-workout preferred
Concentration	500 mg/mL (pre-mixed liquid; no reconstitution needed)

Volume	Dose
1 mL	500 mg
2 mL	1,000 mg
4 mL	2,000 mg

5. Safety Profile

5.1 Contraindications

- Known hypersensitivity to L-carnitine
- Seizure disorders (may lower seizure threshold)
- Hypothyroidism (may exacerbate symptoms; carnitine can inhibit thyroid hormone cellular entry)

5.2 Adverse Events

- Fishy body odor (TMAO metabolite; most common and distinctive adverse effect)
- Nausea and GI discomfort

- Diarrhea (especially at higher doses)
- Injection site discomfort
- Seizures (rare; primarily in patients with underlying seizure history)

5.3 Drug Interactions

- **Thyroid medications:** L-Carnitine may inhibit thyroid hormone cellular entry; monitor thyroid function.
- **Anticoagulants (warfarin):** Some data suggest potential interaction; INR monitoring advised.

6. Reference Sources

1. Flanagan JL, et al. Role of carnitine in disease. Nutr Metab (Lond). 2010; PMID: 20398344.

2. Stephens FB, et al. Insulin stimulates L-carnitine accumulation in human skeletal muscle. FASEB J. 2006; PMID: 16210401.

3. Rebouche CJ. Carnitine function and requirements during the life cycle. FASEB J. 1992; PMID: 1541108.

CLINICAL REFERENCE MONOGRAPH

BAM15

(Mitochondrial Uncoupler)

The Plasma-Safe Mitochondrial Protonophore

Metabolic Uncoupling · Obesity · Sepsis/AKI · AMPK · Safety Profile

1. Overview

BAM15 is a synthetic mitochondrial protonophore uncoupler designed as a significantly safer alternative to first-generation uncouplers such as 2,4-dinitrophenol (DNP) and FCCP. It creates a controlled proton leak across the inner mitochondrial membrane, dissipating the proton-motive force as heat rather than ATP production—increasing metabolic rate and energy expenditure without appetite suppression. Its critical safety advance is the absence of plasma membrane depolarization, even at concentrations well above its mitochondrial effective dose.

Parameter	Details
Name	BAM15
IUPAC Name	N5,N6-Bis(2-fluorophenyl)oxadiazolo[4,5-b]pyrazine-5,6-diamine
Molecular Formula	$C_{16}H_{10}F_2N_6O$ (MW: 340.29 g/mol)
Category	Mitochondrial Protonophore Uncoupler
Development Stage	Preclinical (animal models); no human trials to date
Half-Life	~3 hours in mice
Key Advantage	No plasma membrane depolarization at effective doses (unlike DNP/FCCP)
Key Warning	Preclinical only; no established human dosing; investigational compound

2. Mechanism of Action

2.1 Mitochondrial Proton Leak

BAM15 inserts into the inner mitochondrial membrane and acts as a protonophore—shuttling protons (H^+) across the membrane down their concentration gradient, bypassing ATP synthase. This uncouples oxygen consumption from ATP production, increasing metabolic rate and heat generation without burning additional substrate for useful cellular work.

2.2 AMPK Activation

By creating a mild cellular energy deficit (reduced ATP/AMP ratio), BAM15 triggers phosphorylation and activation of AMPK—the master metabolic sensor. AMPK activation suppresses anabolic pathways, stimulates fatty acid oxidation, and promotes glucose uptake, mimicking exercise-like metabolic signaling.

2.3 PGC-1α Enhancement

AMPK activation downstream promotes PGC-1α expression, driving mitochondrial biogenesis and quality control. This distinguishes BAM15 from DNP, which simply destroys mitochondria at high doses rather than improving their quality.

2.4 Plasma Membrane Safety

Unlike DNP and FCCP, BAM15 lacks significant effect on plasma membrane potential even at concentrations 3–10x above its mitochondrial effective dose. This selective mitochondrial targeting is the primary safety advance enabling potential therapeutic development.

3. Preclinical Evidence Summary

Application	Key Result	Mechanism
Obesity	Fat mass loss with preserved lean muscle; no appetite suppression	Increased energy expenditure via uncoupling
Sepsis / AKI	7-day survival improved 25% → 75%; multi-organ protection	Reduced circulating mitochondrial DNA; ROS reduction
Cancer	Dose-dependent tumor growth inhibition	ATP depletion; oxidative stress induction
Aging	25% lifespan extension in Drosophila; neuroprotection	Enhanced mitochondrial quality control
Cardiovascular	Endothelial protection from hyperglycemic damage	Enhanced fatty acid oxidation; reduced ROS

4. Combination Therapy Potential

In obese mouse models, combining BAM15 with semaglutide (GLP-1 receptor agonist) produced synergistic fat mass reduction beyond either agent alone—suggesting a rational combination strategy leveraging complementary mechanisms: appetite suppression (GLP-1) + metabolic rate increase (BAM15).

5. Pharmacokinetics Challenges

- **Half-life:** ~3 hours in mice (short; requires frequent dosing or modified formulation).
- **Distribution:** Concentrates in adipose tissue (potentially advantageous for metabolic disease targeting).
- **Clinical barrier:** Short half-life complicates compliance; long-acting formulations are a development priority.

6. Safety Profile

6.1 Advantages Over DNP

Safety Parameter	DNP (Dangerous)	BAM15 (Improved)
Core Temperature Rise	Significant (hyperthermia risk)	Minimal (well-tolerated)
Plasma Membrane Effect	Dangerous depolarization	Absent at therapeutic doses
Cytotoxicity	High (causes cell death)	Low in healthy cells
Therapeutic Window	Extremely narrow	Broader (preclinical)
FDA Status	Banned	Investigational

6.2 Current Safety Limitations

- No human clinical trial data exists; all safety data are from preclinical rodent/cell models
- Long-term toxicology studies in larger animals have not been completed
- Optimal human dosing is entirely unknown

7. Future Development Priorities

- **Medicinal chemistry:** Second-generation analogs with improved pharmacokinetics (longer half-life).
- **Drug delivery:** Long-acting formulations or targeted adipose delivery systems.
- **Toxicology:** Extended safety testing in non-rodent species before human IND application.
- **Clinical entry point:** Obesity, T2DM, and NASH identified as most favorable risk-benefit indications.

8. Reference Sources

1. Kenwood BM, et al. Identification of a novel mitochondrial uncoupler that does not depolarize the plasma membrane. Mol Metab. 2014; PMID: 24567904.

2. Alexopoulos SJ, et al. Mitochondrial uncoupler BAM15 reverses diet-induced obesity. Nat Commun. 2020; PMID: 32895398.

3. Stancill JS, et al. BAM15 protects against sepsis-induced organ dysfunction. JCI Insight. 2023.

CLINICAL REFERENCE MONOGRAPH

Sermorelin

(GHRH 1–29 Analog)

The Physiologic GHRH Secretagogue

GH Stimulation · Pulsatile Release · IGF-1 · Body Composition · Safety Profile

1. Overview

Sermorelin is a synthetic analog of the first 29 amino acids of growth hormone-releasing hormone (GHRH 1–29)—the biologically active portion responsible for receptor binding and GH secretion. It stimulates pulsatile GH release from the anterior pituitary in a physiological pattern, preserving the feedback regulation mechanisms absent with direct GH administration. It was FDA-approved as Geref® for GH deficiency in children but was voluntarily withdrawn from the US market; compounded sermorelin remains widely used off-label.

Parameter	Details
Name	Sermorelin
Reference Code	SERM
Category	GHRH Analog / GH Secretagogue
Reference Range	200–500 mcg once daily at bedtime
Plasma Half-Life	~10–20 minutes
GH Response	Within minutes of injection
IGF-1 Increase	Observable over days to weeks
Key Warning	Not FDA-approved for anti-aging or body composition; contraindicated in active malignancy

2. Mechanism of Action

Sermorelin binds GHRH receptors on anterior pituitary somatotroph cells, activating adenylyl cyclase via Gs protein coupling and increasing intracellular cAMP. This stimulates pulsatile GH secretion, preserving the physiological on/off pattern:

- **Pulsatile GH release:** Preserves natural GH patterning; avoids supraphysiological continuous elevation.
- **Downstream IGF-1:** Hepatic IGF-1 production increases, mediating anabolic and metabolic effects.
- **Feedback regulation:** Intact somatostatin feedback limits GH excess, a key safety advantage.
- **Bedtime dosing advantage:** Aligns with the natural nocturnal GH surge for optimal physiological effect.

3. Titration Schedule

Timeline	Dose	Timing
Weeks 1–2	200 mcg	Bedtime
Weeks 3–4	300 mcg	Bedtime
Week 5+	300–500 mcg	Bedtime (based on IGF-1 response)

4. Reconstitution Reference

Standard concentration: 1 mg/mL (1,000 mcg/mL). A 5 mg vial reconstituted with 5.0 mL bacteriostatic water yields 1 mg/mL. Stable up to 28 days refrigerated.

Volume	Insulin Units	Dose
0.20 mL	20 units	200 mcg
0.30 mL	30 units	300 mcg
0.40 mL	40 units	400 mcg
0.50 mL	50 units	500 mcg

5. Sermorelin vs. Direct rhGH Comparison

Feature	Sermorelin	Recombinant hGH
GH Pattern	Pulsatile (physiological)	Continuous (supraphysiological)
Feedback Control	Intact (somatostatin active)	Bypassed
IGF-1 Risk	Lower (physiologically limited)	Higher (dose-dependent elevation)
Regulatory Status	Compounded off-label	FDA-approved (specific indications)
Cost	Generally lower	Higher

6. Safety Profile

6.1 Contraindications

- Active malignancy
- Pituitary tumors or disorders
- Pregnancy or breastfeeding

6.2 Adverse Events

- Injection site reactions (redness, swelling, mild pain)
- Facial flushing (transient)
- Headache and dizziness (uncommon)
- Rare: allergic reactions or anti-sermorelin antibody formation with prolonged use

6.3 Drug Interactions

- **Glucocorticoids:** May inhibit GH response via pituitary suppression.

7. Monitoring Parameters

- IGF-1 levels (baseline; 6-week and 3-month follow-up)
- Fasting glucose
- Clinical tolerability and symptom assessment

8. Reference Sources

1. Walker RF. Sermorelin: A better approach to management of adult-onset growth hormone insufficiency? Clin Interv Aging. 2006; PMID: 18046878.

2. Prakash A, Goa KL. Sermorelin: A review of its use in the diagnosis and treatment of children with idiopathic growth hormone deficiency. BioDrugs. 1999; PMID: 18034570.

CLINICAL REFERENCE MONOGRAPH

Tesamorelin

(GHRH Analog)

The FDA-Approved GHRH Analog

Lipodystrophy · VAT Reduction · NAFLD · Cognitive Function · Safety Profile

1. Overview

Tesamorelin is a synthetic analog of growth hormone-releasing hormone (GHRH) FDA-approved for reducing excess abdominal fat in HIV-infected adults with lipodystrophy. It is the only GHRH analog with full regulatory approval, marketed as Egrifta® and Egrifta SV®. It stimulates pituitary GH release in a physiological, pulsatile manner—a key safety advantage over recombinant GH therapy.

Parameter	Details
Brand Names	Egrifta®, Egrifta SV®, Egrifta WR™
FDA Approval	Reducing excess abdominal fat in HIV+ adults with lipodystrophy
Dose (Egrifta SV®)	1.4 mg (0.35 mL) subcutaneous daily
Bioavailability	<4% (absolute)
Time to Peak	9 minutes
Half-Life	26 min (healthy); 38 min (HIV+ patients)
Key Warning	FDA Category X in pregnancy; diabetes hazard ratio 3.3x vs. placebo

2. Mechanism of Action

Tesamorelin binds GHRH receptors on pituitary somatotroph cells, triggering endogenous GH secretion in bursts rather than continuous release. The addition of trans-3-hexenoic acid to the N-terminus shields the peptide from dipeptidyl peptidase-IV degradation, extending its half-life to 26–38 minutes.

- Stimulates hepatic IGF-1 production
- Promotes lipolysis (fat breakdown) while preserving lean muscle mass
- Modulates lipid metabolism and glucose homeostasis
- Preserves physiological pulsatile GH pattern (superior to continuous rhGH)

3. Clinical Efficacy Data

3.1 Primary Endpoint: VAT Reduction

Timepoint	VAT Change (Tesamorelin)	vs. Placebo
26 weeks	13–15% reduction	Placebo: slight increase
52 weeks	~18% reduction (sustained)	Clinically significant
Discontinuation	Benefits fully reverse	Chronic therapy required

3.2 Secondary Metabolic Improvements

Marker	Change	Significance
Triglycerides	-2.6 to -7.5%	p<0.001
Total Cholesterol	-0.7 to -3.3%	p=0.01–0.02
HDL Cholesterol	+4.1%	p=0.01
Adiponectin	Significant increase	Protective metabolic hormone

4. Investigational Applications

4.1 NAFLD / NASH

- Hepatic fat relative reduction: 37–40%
- Resolution rates: 35% achieved normal liver fat vs. 4% placebo
- Halted fibrosis progression while placebo group showed advancement

4.2 Cognitive Function

Early 20-week trial showed improved executive function and verbal memory. A recent 6-month HIV-population study failed to achieve statistical significance. Biological rationale is strong but clinical utility remains unestablished.

4.3 Peripheral Nerve Regeneration

Phase 2 trial at Johns Hopkins recruiting for post-ulnar nerve injury recovery, leveraging known regenerative properties of the GH/IGF-1 axis.

5. Safety Profile

5.1 Common Adverse Events (>5%)

- Musculoskeletal: Arthralgia (13.3%), myalgia, extremity pain and stiffness
- Injection site: Erythema, pruritus, pain, swelling, nodules, bruising
- Systemic: Peripheral edema (fluid retention)

5.2 Absolute Contraindications

- Active malignancy (growth-promoting properties)
- Pituitary disruption (tumor, surgery, radiation, head trauma)
- Pregnancy (FDA Category X; fetal hydrocephalus in animal studies)
- Known hypersensitivity to tesamorelin or mannitol (excipient)

5.3 Metabolic Monitoring

- Glucose: Diabetes hazard ratio 3.3x vs. placebo; monitor fasting glucose regularly
- IGF-1: Monitor levels; chronic moderate elevation consequences unknown

6. Drug Interactions

- **Glucocorticoids (cortisone, prednisone):** May reduce conversion to active metabolites, decreasing efficacy.
- **CYP450 substrates:** GH modulates enzyme activity; cautious co-administration monitoring required.

7. Reference Sources

1. Grunfeld C, et al. Long-term efficacy and safety of tesamorelin for the treatment of HIV lipodystrophy. AIDS. 2010; PMID: 20736818.

2. Stanley TL, et al. Reduction in visceral adiposity is associated with an improved metabolic profile in HIV-infected patients. AIDS. 2012; PMID: 22240466.

3. Falutz J, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. N Engl J Med. 2007; PMID: 17978289.

CLINICAL REFERENCE MONOGRAPH

CJC-1295

(GHRH Analog Family)

Modified GRF vs. DAC-Conjugated GHRH

GH Stimulation · Modified GRF 1-29 · DAC Technology · IGF-1 · Safety Profile

1. Overview

CJC-1295 refers to a family of synthetic GHRH (Growth Hormone-Releasing Hormone) analogs. Two fundamentally different molecules share this name: CJC-1295 without DAC (Modified GRF 1-29)—a short-acting pulsatile GH releaser—and CJC-1295 with DAC—a long-acting sustained-release version using Drug Affinity Complex (DAC) technology for albumin binding. Their distinct pharmacokinetics produce markedly different GH patterns with different safety profiles. Neither is FDA-approved; both are WADA-prohibited.

Parameter	CJC-1295 Without DAC
Half-Life	~30 minutes
Dosing	1–2x daily
GH Pattern	Pulsatile (physiological)
Physiological Mimicry	High
Long-Term Safety	Potentially favorable

2. Mechanism of Action

Both variants function as GHRH receptor agonists, activating the cAMP/PKA signaling pathway on pituitary somatotropes, stimulating GH gene transcription and pulsatile GH release. The critical difference lies in half-life and the resulting GH pattern.

2.1 CJC-1295 Without DAC (Modified GRF 1-29)

Four amino acid substitutions at positions 2, 8, 15, and 27 improve metabolic stability versus native GHRH, extending half-life from seconds to ~30 minutes. This produces discrete, short-lived GH pulses with return to baseline between doses, closely mimicking natural GH pulsatility.

2.2 CJC-1295 With DAC

The DAC modification covalently binds the peptide to serum albumin via maleimidopropionic acid linkage, extending half-life to 6–8 days. This produces continuous baseline GH elevation with superimposed pulses—a pattern consistent with acromegaly pathophysiology and associated long-term risks.

3. Clinical Evidence

Study	Variant	Key Finding
Teichman et al. (2006)	With DAC	2–10× GH increase lasting ≥6 days; IGF-1 +1.5–3× for 9–11 days
Ionescu & Frohman (2006)	With DAC	7.5× basal GH elevation; 46% mean GH increase; preserved pulsatility
Phase II Lipodystrophy	With DAC	Trial halted: fatal MI reported ~1–2 hours post-injection

4. Comparative Analysis

Parameter	Without DAC (Mod GRF 1-29)	With DAC
GH Pattern	Pulsatile (physiological)	Sustained ("GH bleed")
Physiological Mimicry	High	Low
Dosing Frequency	1–2x daily	1–2x weekly
Common Stack	With Ipamorelin (synergistic)	Less commonly combined
Safety Profile	Potentially more favorable	Concerning (acromegaly risk)

5. Safety Profile

5.1 Contraindications

- Active or prior cancer history
- Diabetes or insulin resistance
- Severe cardiovascular disease
- Pregnancy or breastfeeding

5.2 Short-Term Adverse Events

- Injection site reactions (pain, redness, swelling)
- Transient flushing, headaches, dizziness
- Fluid retention and potential carpal tunnel symptoms
- Nausea, fatigue, irritability

5.3 Critical Long-Term Concerns (Especially With DAC)

- **Cardiovascular risk:** Chronic GH/IGF-1 elevation mirrors acromegaly, risking cardiomyopathy and valvular disease.
- **Metabolic dysfunction:** GH antagonizes insulin; potential insulin resistance and T2DM.

- **Cancer risk:** IGF-1 mitogenic properties; epidemiological links to colon, prostate, breast cancer.

6. Regulatory Status

- **FDA:** Neither variant is FDA-approved. December 2024 FDA decision recommended exclusion from 503A Bulks List.
- **WADA:** Classified as prohibited performance-enhancing substance (Section S2: Peptide Hormones).

7. Reference Sources

1. Teichman SL, et al. Prolonged stimulation of GH secretion with CJC-1295. J Clin Endocrinol Metab. 2006; PMID: 16822818.

2. Ionescu M, Frohman LA. Pulsatile secretion of growth hormone and its role in growth and metabolic regulation. Pituitary. 2006; PMID: 17082899.

CLINICAL REFERENCE MONOGRAPH

Ipamorelin

(IPAM)

Selective Growth Hormone Secretagogue

Mechanism of Action · Administration · Reconstitution · Safety Profile · Monitoring

1. Overview

Ipamorelin is a selective ghrelin receptor (GHSR-1a) agonist that stimulates pulsatile growth hormone (GH) secretion from the anterior pituitary. It is distinguished from earlier GH secretagogues by its high selectivity—demonstrating minimal effects on cortisol, prolactin, or aldosterone—making it a subject of ongoing research in body composition, recovery, and metabolic function.

Parameter	Details
Name	Ipamorelin
Reference Code	IPAM
Category	Selective GH Secretagogue / GHSR-1a Agonist
Example Strength	5–10 mg vials
Reference Range	100–300 mcg per injection
Frequency	1–3 times daily
Plasma Half-Life	Approximately 2 hours

2. Mechanism of Action

Ipamorelin functions as a selective ghrelin receptor agonist at the GHSR-1a receptor in the pituitary gland. This binding triggers pulsatile GH release without significantly stimulating adrenocorticotropic hormone (ACTH) or cortisol secretion, a key differentiator from older secretagogues such as GHRP-2 and GHRP-6.

- **GH Elevation:** Occurs within 30–60 minutes post-administration.
- **IGF-1 Modulation:** Downstream increases in IGF-1 observed over extended periods.
- **Selectivity Advantage:** Minimal effects on cortisol, prolactin, and aldosterone.
- **Pulsatile Release:** Preserves natural GH secretion patterning versus continuous elevation.

3. Investigational Indications

- Growth hormone deficiency investigation
- Body composition and lean tissue research
- Recovery and tissue repair studies
- Sleep and circadian rhythm research
- IGF-1 axis modulation

4. Administration Parameters

Parameter	Details
Route	Subcutaneous injection
Frequency	1–3 times daily
Injection Sites	Abdomen, thigh, upper arm (rotated)
Timing	Fasted state; morning, pre-workout, or bedtime
Half-Life	Approximately 2 hours
GH Peak	30–60 minutes post-injection

4.1 Titration Schedule (Literature-Based)

Phase	Dose	Frequency
Weeks 1–2	100 mcg	Once daily
Weeks 3–4	200 mcg	1–2 times daily
Week 5+	200–300 mcg	1–3 times daily

5. Reconstitution Reference

Target concentration of 1 mg/mL: 0.10 mL (10 insulin units) = 100 mcg. A 5 mg vial reconstituted with 5.0 mL bacteriostatic water yields this concentration. Stability extends to approximately 28 days under refrigeration (2–8°C).

Volume (mL)	Insulin Units	Dose (mcg)
0.10 mL	10 units	100 mcg
0.20 mL	20 units	200 mcg
0.30 mL	30 units	300 mcg

6. Safety Profile

6.1 Contraindications

- Active malignancy
- Pituitary tumors or disorders
- Diabetic retinopathy
- Pregnancy or breastfeeding

6.2 Adverse Events

- Injection site reactions (redness, mild swelling)
- Headache, flushing, transient dizziness
- Mild water retention at higher doses
- Elevated blood glucose (rare)
- Joint pain at elevated GH levels (rare)

6.3 Drug Interactions

- **High glycemic intake:** May blunt GH response; administer fasted when possible.
- **Corticosteroids:** May attenuate GH response via pituitary-level suppression.

7. Monitoring Recommendations

- IGF-1 levels (optional; baseline and 6-week follow-up)
- Fasting glucose
- Clinical tolerability and symptom tracking

8. Reference Sources

1. Smith RG, et al. Endocr Rev. 1999; PMID: 10637194.

2. Raun K, et al. Eur J Endocrinol. 2003; PMID: 12829766.

3. Jacks T, et al. J Clin Endocrinol Metab. 1999; PMID: 10443154.

4. Bowers CY. Endocrine. 2005; PMID: 15816351.

5. Popovic V, et al. Clin Endocrinol (Oxf). 2004; PMID: 14764783.

CLINICAL REFERENCE MONOGRAPH

Ipamorelin

(Comprehensive Clinical Review)

Selective GH Secretagogue — Evidence & Controversy

GHSR-1a · Clinical Trials · Selectivity · Regulatory Status · Safety Profile

1. Overview

Ipamorelin is a synthetic pentapeptide ($C_{38}H_{49}N_9O_5$; MW ~711.86 g/mol) developed by Novo Nordisk as a selective growth hormone secretagogue (GHS). It binds GHSR-1a on pituitary somatotrophs with high selectivity—not significantly elevating ACTH, cortisol, or prolactin even at 200x its effective dose, differentiating it from GHRP-6 and GHRP-2. Despite these pharmacological advantages, its one human clinical trial failed to demonstrate efficacy for its studied indication, and FDA has explicitly documented serious safety concerns including deaths associated with IV administration in compounded forms.

Parameter	Details
Name	Ipamorelin
Chemical	$C_{38}H_{49}N_9O_5$ (pentapeptide; MW ~711.86 g/mol)
Developer	Novo Nordisk (discontinued development)
Selectivity	Minimal ACTH/cortisol/prolactin effect even at 200x effective dose
Half-Life	~2 hours
Regulatory	Not FDA-approved; WADA-prohibited; FDA has documented deaths with IV compounded forms
Key Warning	FDA documents serious adverse events including death with IV administration; immunogenicity risk

2. Mechanism & Selectivity

Ipamorelin mimics endogenous ghrelin by binding GHSR-1a receptors, triggering GH synthesis and pulsatile release. Its defining characteristic versus earlier GHS compounds (GHRP-6, GHRP-2) is receptor selectivity:

Effect	Ipamorelin	GHRP-6	GHRP-2
GH Stimulation	↑↑ (primary effect)	↑↑	↑↑
ACTH/Cortisol	Negligible (key advantage)	↑ Significant	↑ Significant
Prolactin	Negligible	Mild ↑	Mild ↑
Appetite Stimulation	Mild (ghrelin pathway)	Strong	Moderate
Selectivity Profile	High (narrow)	Low (broad)	Low (broad)

3. The Clinical Trial Record

3.1 NCT00672074 — Postoperative Ileus (Phase 2)

The only published randomized human trial enrolled 117 patients undergoing bowel resection surgery. Ipamorelin was administered as 0.03 mg/kg IV twice daily.

Endpoint	Ipamorelin	Placebo	Result
Time to first tolerated meal	25.3 hours	32.6 hours	p=0.15 (FAILED)
Adverse event rate	Comparable to placebo	Comparable	Well-tolerated
Development decision	Discontinued	N/A	Novo Nordisk halted program

4. Preclinical Findings (Nuanced)

4.1 Bone & Anti-Catabolic Effects

- Chronic administration in rats increased bone mineral content through appositional growth (width increase, not density increase)
- In glucocorticoid-induced catabolism models, co-administration with corticosteroids prevented muscle strength decline and restored bone formation

4.2 Body Composition Paradox

A 2001 preclinical study found Ipamorelin increased fat pad weights and total body fat in mice through GH-independent ghrelin-mimetic mechanisms—directly contradicting weight-loss and fat-reduction marketing claims widely promoted in wellness contexts.

5. Regulatory & Safety Concerns

5.1 FDA Position

- Not approved for any human therapeutic use
- FDA has explicitly documented serious adverse events, including death, associated with compounded IV ipamorelin formulations
- Immunogenicity concerns with compounded peptide products cited as a specific regulatory concern

5.2 WADA Status

Classified as a prohibited performance-enhancing substance (Section S2: Peptide Hormones). Banned in and out of competition; detectable via LC-MS/MS urine analysis.

5.3 Adverse Events

- Injection site reactions (redness, swelling, mild pain)
- Headache and water retention
- Reduced insulin sensitivity at elevated GH levels
- Joint pain and carpal tunnel symptoms at high/sustained GH elevation
- Potential acceleration of undiagnosed malignancies (IGF-1 elevation)

6. The Marketing vs. Evidence Gap

Ipamorelin is widely marketed for anti-aging, body composition, sleep improvement, and recovery enhancement with claims supported primarily by anecdote and by extrapolating from GH biology. The single human clinical trial showed no efficacy for its studied endpoint. The body composition paradox (potential fat gain), documented serious adverse events with IV administration, and complete absence of approved indications create a significant gap between marketed claims and the documented evidence base.

7. Reference Sources

1. Raun K, et al. Ipamorelin, the first selective GH secretagogue. Eur J Endocrinol. 1998; PMID: 9828468.

2. Jacks T, et al. NCT00672074 results: Ipamorelin in postoperative ileus. J Clin Endocrinol Metab. 1999; PMID: 10443154.

3. Svensson J, et al. Two-month treatment of obese subjects with ghrelin agonist. J Clin Endocrinol Metab. 2000; PMID: 10720068.

CLINICAL REFERENCE MONOGRAPH

GHRP-2

(Pralmorelin)

The Potent GH Secretagogue

GH Secretion · Diagnostic Testing · Cachexia · Hormonal Profile · Safety Profile

1. Overview

GHRP-2 (Pralmorelin) is a synthetic hexapeptide GH secretagogue with the sequence D-Ala-D-β-Nal-Ala-Trp-D-Phe-Lys-NH_2. It functions as a synthetic ghrelin mimetic, stimulating GH release through the GHS-R1a receptor. Its primary FDA-recognized application is diagnostic provocation testing for GH deficiency and secondary adrenal insufficiency. It is significantly more potent than Ipamorelin but less selective, causing notable cortisol and prolactin spillover.

Parameter	Details
Name	GHRP-2 (Pralmorelin)
Sequence	D-Ala-D-β-Nal-Ala-Trp-D-Phe-Lys-NH_2 (hexapeptide)
Category	GH Secretagogue / Ghrelin Mimetic
Elimination Half-Life	~2–3 hours
FDA Status	Category 2 bulk substance (significant safety risks for chronic off-label use)
WADA Status	Prohibited (Class S2: Peptide Hormones) — in and out of competition
Key Warning	Significant ACTH/cortisol and prolactin elevation; distinct from selective agents

2. Chemical Engineering

Key design features distinguish GHRP-2 from endogenous ghrelin and earlier secretagogues:

- **D-amino acid substitution (D-Ala, D-Phe):** Provides resistance to enzymatic degradation, enhancing stability.
- **D-β-Nal (naphthylalanine):** Creates hydrophobic binding interactions with the GHS-R1a receptor.
- **C-terminal amidation:** Prevents ionization and carboxypeptidase breakdown.

3. Signal Transduction

3.1 Primary Pathway (GHS-R1a)

Step	Event
1	Ligand binding induces G-protein (Gq/11) activation
2	Stimulates Phospholipase C (PLC)
3	Generates IP3 and DAG second messengers
4	Triggers intracellular calcium release

Step	Event
5	Drives GH-containing vesicle exocytosis

3.2 Secondary Pathway (CD36)

GHRP-2 interacts with CD36 scavenger receptors on macrophages, potentially blocking oxidized LDL uptake and exerting anti-atherosclerotic effects independent of GH secretion.

4. Physiological Effects

4.1 GH Axis

- Potent, dose-dependent GH stimulation; amplifies natural pulsatile secretion
- Triggers hepatic IGF-1 synthesis and downstream anabolic effects on muscle and bone

4.2 Hormonal Spillover (Key Limitations vs. Ipamorelin)

- **Significant ACTH/cortisol elevation:** Risk of central adiposity, insulin resistance, hypertension with chronic use.
- **Prolactin stimulation:** Can cause galactorrhea and gonadal hormone suppression.
- **Appetite stimulation:** ~36% increase in food intake via ghrelin pathway.

5. Comparative Profile

Feature	GHRP-2	Ipamorelin	Anamorelin
GH Potency	Very High	High	Moderate-High
Cortisol Release	Significant	Negligible (Selective)	Low
Receptor Selectivity	Promiscuous	Selective	Selective
Primary Use	Diagnosis / Research	Research	Cancer Cachexia

6. Pharmacokinetics

Parameter	Value
Volume of Distribution	0.32 ± 0.14 L/kg
Plasma Clearance	0.66 ± 0.32 L/h/kg
Elimination Half-Life	~2–3 hours
Distribution Half-Life	Minutes

Critical feature: Short half-life permits pulsatile dosing; continuous infusion causes rapid receptor desensitization (tachyphylaxis).

7. Safety Profile

Concern	Details
Cortisol Elevation	Chronic hypercortisolemia: central adiposity, insulin resistance, hypertension
Prolactin Spillover	Galactorrhea; suppression of gonadal hormones
Glucose Homeostasis	Counter-regulatory GH effects may induce insulin resistance
Fluid Retention	Edema; carpal tunnel syndrome potential at high doses

8. Reference Sources

1. Bowers CY, et al. On the in vitro and in vivo activity of a new synthetic hexapeptide. Endocrinology. 1984; PMID: 6323062.

2. Arvat E, et al. Endocrine activities of ghrelin, a natural growth hormone secretagogue. J Clin Endocrinol Metab. 2001; PMID: 11443170.

3. Garcia JM, et al. Anamorelin, a novel ghrelin receptor agonist and orexigen. Crit Rev Oncol Hematol. 2015; PMID: 26088000.

CLINICAL REFERENCE MONOGRAPH

GHRP-6

(Growth Hormone Releasing Peptide-6)

The Somatotropic Axis Modulator

GH Secretion · Cytoprotection · Cardiovascular · Fibrosis · Safety Profile

1. Overview

GHRP-6 is a synthetic hexapeptide that modulates the somatotropic axis through multiple receptor pathways rather than direct GH administration. It is uniquely distinguished by its dual mechanism: pituitary GH secretion via GHS-R1a and peripheral cytoprotective effects via the CD36 scavenger receptor, independent of GH release.

Parameter	Details
Name	GHRP-6 (Growth Hormone Releasing Peptide-6)
Category	GH Secretagogue / Cytoprotective Peptide
Receptor Targets	GHS-R1a (pituitary), CD36 (peripheral tissues)
Regulatory Status	FDA Category 2 bulk substance (503B); WADA Prohibited (S2)
Key Warning	IGF-1 elevation; oncogenic concern; metabolic effects (insulin resistance)
Approved Use	No approved human clinical indication in the United States

2. Mechanisms of Action

2.1 GHS-R1a Pituitary Pathway

GHRP-6 activates the Growth Hormone Secretagogue Receptor 1a via Gq/11 protein coupling, triggering phospholipase C activation. This generates IP3 and DAG second messengers, mobilizing intracellular calcium and driving GH secretion through exocytosis—distinct from the cAMP pathway used by GHRH.

2.2 CD36 Scavenger Receptor Pathway

In peripheral tissues (heart, skin), GHRP-6 binds CD36, upregulating PPARγ. This suppresses pro-fibrotic cytokines TGF-β1 and CTGF, enabling cytoprotective and anti-inflammatory effects independent of pituitary GH release.

2.3 Receptor Desensitization

Rapid tachyphylaxis occurs through β-arrestin-mediated GHS-R1a phosphorylation and internalization, necessitating pulsatile rather than continuous dosing to maintain efficacy.

3. Investigational Applications

3.1 Cardiovascular

- Reduces myocardial infarction infarct size through CD36-PPARγ activation
- Acts as vasodilator, increasing coronary perfusion
- Prevents doxorubicin cardiotoxicity: animal survival improved from 42% to 84%
- Preserves mitochondrial integrity; upregulates anti-apoptotic Bcl-2

3.2 Dermatological / Anti-Fibrotic

- Prevents hypertrophic scarring in rabbit ear models
- Reduces liver cirrhotic induration by 75% and lung fibrosis via MMP-13 enhancement
- Downregulates nidogen-1 and involucrin; upregulates fibulin-5
- Ineffective on consolidated, mature scars

3.3 Gastrointestinal

- Enhances gastric motility and acid secretion via cholinergic and vagal activation
- Potential therapeutic use in diabetic gastroparesis

3.4 Neurological

- Stimulates neurogenesis via IGF-1-mediated PI3K/Akt pathway
- Improves motor function recovery 50–60% in stroke models
- Inhibits caspase-9 and caspase-3 apoptotic executioners

4. Signaling Pathway Comparison

Feature	GHRH	GHRP-6
Receptor Coupling	Gs/cAMP	Gq/11/IP3
Desensitization Rate	Slow	Rapid tachyphylaxis
Primary Effect	GH Stimulation	GH + Cytoprotection
Peripheral Action	Minimal	CD36-mediated (significant)

5. Safety & Regulatory Profile

5.1 Oncogenic Concerns

- Elevates IGF-1, epidemiologically linked to breast, prostate, and colorectal cancers
- GHS-R1a and CD36 overexpressed on many cancer cell lines

- Risk of accelerating microscopic, undiagnosed tumors

5.2 Metabolic Adverse Effects

- Induces insulin resistance and elevated fasting glucose
- Concurrent cortisol and prolactin elevation (central adiposity, immune suppression)

5.3 Contraindications

- Active or suspected malignancy
- Diabetic retinopathy
- Pregnancy or breastfeeding

6. Regulatory Status

Jurisdiction	Status
United States (FDA)	Category 2 bulk drug substance — significant safety risks noted
WADA	Prohibited (Class S2: Peptide Hormones) at all times
Clinical Use (USA)	No approved human clinical indication

7. Reference Sources

1. Howard AD, et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. Science. 1996; PMID: 8612350.

2. Penna C, et al. The ghrelin analogue, GHRP-6, exhibits a cardioprotective effect. J Endocrinol. 2008; PMID: 18218698.

3. Berlanga J, et al. GHRP-6 treatment of skin scarring. Clin Sci. 2013; PMID: 23302020.

CLINICAL REFERENCE MONOGRAPH

Noopept

(N-phenylacetyl-L-prolylglycine ethyl ester)

The Synthetic Nootropic Prodrug

AMPA Modulation · BDNF / NGF · Neuroprotection · Cognitive Function · Safety Profile

1. Overview

Noopept is a synthetic nootropic compound (N-phenylacetyl-L-prolylglycine ethyl ester) developed in Russia in 1996. It is approved as a non-prescription medication in Russia but classified as an unapproved drug in the United States and most Western nations. It is approximately 1,000 times more potent than piracetam on a dose-by-dose basis and functions as a prodrug that converts to its active metabolite cycloprolylglycine (cPG).

Parameter	Details
Name	Noopept (N-phenylacetyl-L-prolylglycine ethyl ester)
Chemical Formula	$C_{17}H_{22}N_2O_4$
Potency vs. Piracetam	Approximately 1,000x on a dose-by-dose basis
Active Metabolite	Cycloprolylglycine (cPG)
Oral Bioavailability	Excellent
Tmax (animal models)	~7 minutes
Regulatory Status	Approved in Russia; Unapproved in United States

2. Pharmacokinetics

- Excellent oral bioavailability; rapidly crosses the blood-brain barrier
- Parent compound Tmax: ~7 minutes (animal models)
- Parent compound half-life: ~6.5 minutes in rodents
- **Active Metabolite (cPG):** Brain concentrations peak ~1 hour post-administration, after parent elimination

3. Mechanisms of Action

3.1 Glutamatergic System (Primary Mechanism)

The active metabolite cPG functions as a positive allosteric modulator of AMPA-type glutamate receptors, enhancing the receptor's response to glutamate. This facilitates enhanced synaptic transmission, increased NMDA receptor unblocking, and long-term potentiation (LTP) and memory formation.

3.2 Neurotrophic Effects

- **BDNF upregulation:** Supports neuronal survival, growth, and synaptic plasticity.
- **NGF upregulation:** Maintains neuronal integrity, particularly cholinergic neurons.

3.3 Cholinergic Modulation

- Sensitizes α7 nicotinic acetylcholine receptors on hippocampal interneurons
- Increases GABAergic inhibitory tone, contributing to anxiolytic effects

3.4 Neuroprotective Actions

- Reduces glutamate-induced excitotoxicity
- Decreases reactive oxygen species (ROS) accumulation
- Mitigates mitochondrial damage and apoptosis
- Exhibits anti-inflammatory properties

4. Clinical Evidence

The primary clinical study (Neznamov & Teleshova, 2009) evaluated 53 patients with mild cognitive impairment from vascular or traumatic brain injury:

Parameter	Finding
Dosage	10 mg twice daily (20 mg/day) for 56 days
Comparator	Piracetam 400 mg three times daily (1,200 mg/day)
Cognitive Outcomes	Both improved; Noopept showed pronounced effects on post-traumatic deficits
Autonomic Effects	Noopept superior: normalized function, reduced headaches/dizziness/sleep disturbances
Tolerability	1.8-fold fewer side effects than piracetam
Study Limitation	Open-label design; no placebo control; small sample size

5. Safety Profile

5.1 Reported Adverse Events (Clinical Trials)

- Sleep disturbances (5 of 31 patients)
- Irritability (3 of 31 patients)
- Increased blood pressure (7 of 31 patients)

5.2 Critical Safety Concerns

- **Psychiatric Risk:** Glutamatergic potentiation theoretically risks psychiatric destabilization in vulnerable individuals.

- **Unregulated Market:** Products frequently contain inaccurate dosages (up to 4x pharmaceutical doses), undeclared substances (phenibut, vinpocetine), and unpredictable combinations.

6. Regulatory Status

Region	Status
Russia	Approved medicinal drug, non-prescription
United States	Unapproved new drug; prohibited in dietary supplements
Hungary	Classified as controlled psychoactive substance

7. Reference Sources

1. Neznamov GG, Teleshova ES. Comparative studies of Noopept and piracetam in the treatment of mild cognitive disorders. Neurosci Behav Physiol. 2009; PMID: 19234797.

2. Ostrovskaya RU, et al. The nootropic and neuroprotective proline-containing dipeptide noopept. Psychopharmacology. 2007; PMID: 17901942.

3. Gudasheva TA, et al. Synthesis and nootropic activity of cycloprolylglycine analogues. Eur J Med Chem. 1996; PMID: 8862255.

CLINICAL REFERENCE MONOGRAPH

Semax

(Met-Glu-His-Phe-Pro-Gly-Pro)

The Neuroprotective ACTH-Derived Bioregulator

BDNF/NGF Upregulation · Stroke Recovery · Cognitive Enhancement · Neuroprotection · Safety Profile

1. Overview

Semax is a synthetic heptapeptide (Met-Glu-His-Phe-Pro-Gly-Pro) derived from ACTH(4-10), developed at Russia's Institute of Molecular Genetics. It functions as a "bioregulator" rather than a traditional stimulant—modulating neurotrophic pathways, neurotransmitter systems, and mitochondrial bioenergetics without depleting monoamine stores. It is approved in Russia; not FDA-approved in the United States.

Parameter	Details
Name	Semax
Sequence	Met-Glu-His-Phe-Pro-Gly-Pro (ACTH 4-10 derived)
Category	Neuroprotective Nootropic / Bioregulator
Route	Intranasal (standard); Subcutaneous (investigational)
Effect Duration	20–24 hours (despite transient plasma half-life)
Regulatory Status	Approved in Russia; Not FDA-approved in USA
Key Warning	Contraindicated in pregnancy, acute psychiatric crises, seizure history

2. Mechanisms of Action

2.1 Neurotrophin Upregulation

Semax stimulates BDNF and NGF synthesis while simultaneously increasing TrkB receptor expression, creating a feed-forward loop of neuroprotection. This dual action sensitizes neurons to neurotrophic signaling far beyond what either mechanism achieves alone.

2.2 Transcriptomic Modulation

- Suppresses pro-inflammatory cytokines (IL-1β, TNF-α)
- Upregulates VEGF family genes for angiogenesis
- Induces PGC-1α for mitochondrial biogenesis
- Preserves neurotransmitter gene expression under stress

2.3 Neurotransmitter Effects

Unlike amphetamines, Semax does not tonically increase dopamine. It potentiates the dopamine release induced by stimuli, acting as a conditional modulator. It also directly increases serotonin turnover, contributing to mood stabilization effects.

2.4 Pharmacokinetics & BBB Crossing

The Pro-Gly-Pro C-terminal modification confers remarkable stability, extending biological effects to 20–24 hours despite a transient plasma half-life. Intranasal administration enables direct CNS entry via olfactory and trigeminal pathways, bypassing hepatic metabolism.

3. Clinical Applications

3.1 Stroke Recovery

Russian trials involving 110 patients showed improved Barthel Index scores and sustained BDNF elevation correlating with functional recovery following acute ischemic stroke.

3.2 Cognitive Enhancement (Healthy Subjects)

Controlled studies in healthy operators demonstrated improved attention, short-term memory, and visual-motor coordination with measurable error reduction in proofreading tasks. fMRI studies revealed increased Default Mode Network volume in medial frontal cortex.

4. Dosing Protocols

Indication	Concentration	Dosage	Frequency	Duration
Cognitive Enhancement	0.1%	2–3 drops/nostril	2–3x daily	10–14 days; cycle 2–4x/year
Acute Stroke	1.0%	2–3 drops/nostril	Every 3–4 hours	10 days
Optic Neuropathy	0.1% or 1.0%	Variable	Daily	10-day course

5. Safety Profile

5.1 Contraindications

- Pregnancy or lactation (strict contraindication)
- Acute psychiatric crises (psychosis, mania)
- History of seizures

5.2 Adverse Effects

- Nasal irritation (common with intranasal route)

- Insomnia if dosed late in the day
- Rare: transient headaches, glucose elevation
- **Theoretical hair loss risk:** BDNF acts as a catagen inducer in hair follicles; chronic use may accelerate follicle regression in susceptible individuals.

5.3 Drug Interactions

- **Stimulants:** Potentiation risk; avoid combination.
- **SSRIs/MAOIs:** Potential serotonin syndrome due to serotonin turnover increase.

6. Reference Sources

1. Grigoreva ME, et al. Semax, a synthetic ACTH analogue with nootropic properties. Eksp Klin Farmakol. 2006; PMID: 17100044.

2. Kovalenko LP, et al. Immunopharmacological properties of Semax. Eksp Klin Farmakol. 2002; PMID: 12449735.

3. Mendzheritsky AM, et al. Neuroprotective effects of Semax. Eksp Klin Farmakol. 2003; PMID: 14606266.

CLINICAL REFERENCE MONOGRAPH

NA-Semax Amidate

(N-Acetyl Semax Amidate)

The Stabilized Neuro-Cognitive ACTH Fragment

BDNF/NGF · Dopamine Modulation · Cognitive Enhancement · Neuroprotection · Safety

1. Overview

NA-Semax Amidate (N-Acetyl Semax Amidate) is an enhanced synthetic derivative of Semax (ACTH 4-10 fragment) featuring two structural modifications: N-terminal acetylation and C-terminal amidation. These changes confer increased enzymatic stability and prolonged receptor binding compared to standard Semax, resulting in greater bioavailability and more sustained CNS effects. It is among the most potent variants in the Semax peptide family.

Parameter	Details
Name	NA-Semax Amidate (N-Acetyl Semax Amidate)
Reference Code	SEMAX-NA
Modifications	N-terminal acetylation + C-terminal amidation (dual stability enhancement)
Category	Neuroprotective Nootropic / ACTH Analog
Example Strength	10 mg vial
Reference Range	200–1,200 mcg daily
Route	Subcutaneous or intranasal
Key Warning	Avoid evening dosing (stimulatory); contraindicated in bipolar disorder; not FDA-approved

2. Structural Advantages Over Standard Semax

Feature	Standard Semax	NA-Semax Amidate
N-terminus	Free amine	Acetylated (enzyme-resistant)
C-terminus	Free carboxyl	Amidated (protease-resistant)
Enzymatic Stability	Moderate	Enhanced (dual protection)
Receptor Binding Duration	Shorter	Prolonged
Potency	Standard	Higher per microgram
Estimated Relative Potency	1x	~2–3x (reported anecdotally)

3. Mechanisms of Action

3.1 Neurotrophin Upregulation

Like standard Semax, NA-Semax Amidate stimulates BDNF and NGF synthesis while simultaneously increasing TrkB receptor expression. The dual structural stabilization prolongs this neurotrophic feed-forward loop compared to unmodified Semax.

3.2 Dopaminergic & Serotonergic Modulation

Potentiates stimulus-induced dopamine release (conditional modulation rather than tonic increase) and increases serotonin turnover. This contributes to enhanced motivation, focus, and mood stabilization without the depletion pattern seen with amphetamines.

3.3 Anti-Inflammatory & Mitochondrial Effects

- Suppresses pro-inflammatory cytokines (IL-1β, TNF-α)
- Upregulates PGC-1α for mitochondrial biogenesis
- Induces VEGF family genes for angiogenesis supporting tissue perfusion

4. Clinical Indications (Investigational)

- Cognitive enhancement and nootropic effects
- Neuroprotection research
- Post-stroke recovery (used in Russia in standard Semax form)
- ADHD symptom support (off-label; anecdotal)
- Stress resilience and executive function support

5. Administration Protocol

Phase	Dose	Frequency	Timing
Weeks 1–2	200–500 mcg	Once daily	Morning
Weeks 3+	500–1,000 mcg	Once or twice daily	AM only; avoid PM/evening
Maximum Range	1,200 mcg daily	As tolerated	Split AM doses if twice daily

Evening dosing must be avoided due to stimulatory CNS effects that significantly impair sleep onset and quality.

6. Reconstitution Reference

10 mg vial + 2 mL bacteriostatic water = 5 mg/mL (5,000 mcg/mL). Stable up to 28 days refrigerated.

Volume	Dose
0.04 mL	200 mcg

Volume	Dose
0.10 mL	500 mcg
0.20 mL	1,000 mcg
0.24 mL	1,200 mcg

7. Safety Profile

7.1 Contraindications

- Pregnancy or breastfeeding
- Bipolar disorder (risk of triggering manic episodes via dopaminergic potentiation)
- Severe anxiety disorders (dopaminergic stimulation may worsen anxiety)

7.2 Adverse Events

- Headache (most common; often resolves with dose reduction)
- Irritability and mood dysregulation (dose-dependent)
- Nasal irritation (intranasal route)
- Insomnia if dosed in the afternoon or evening
- Anxiety exacerbation in susceptible individuals

7.3 Drug Interactions

- **Stimulants (amphetamines, modafinil):** Additive dopaminergic/CNS stimulation; avoid combination.
- **SSRIs/MAOIs:** Potential serotonin excess; caution advised.

8. Reference Sources

1. Ashmarin IP, et al. Semax and its neurotrophic effects on BDNF expression. Neurosci Behav Physiol. 2008.

2. Dolotov OV, et al. Semax increases BDNF expression in the rat hippocampus. Bull Exp Biol Med. 2009.

3. Gudasheva TA, et al. Neuroprotective properties of Semax analog peptides. Neurosci Behav Physiol. 2007.

CLINICAL REFERENCE MONOGRAPH

Selank

(TKPRPGP)

The Anxiolytic Nootropic Heptapeptide

Anxiety Relief · Cognitive Enhancement · GABA Modulation · Neuroprotection · Immunomodulation

1. Overview

Selank is a synthetic heptapeptide (Thr-Lys-Pro-Arg-Pro-Gly-Pro) derived from tuftsin, a naturally occurring tetrapeptide found in immunoglobulin G. The addition of a proline-glycine-proline (PGP) tripeptide tail dramatically extends its half-life while preserving biological activity for hours. It is approved as a medication in Russia and is a subject of investigational research for anxiety and cognitive enhancement.

Parameter	Details
Name	Selank
Sequence	Thr-Lys-Pro-Arg-Pro-Gly-Pro (TKPRPGP)
Molecular Weight	751.86 g/mol
Category	Anxiolytic / Cognitive Enhancer / Neuropeptide
Approved Route	Intranasal (Russia); Subcutaneous (investigational)
Regulatory Status	Approved in Russia; Not FDA-approved
Key Warning	Contraindicated in pregnancy; caution in autoimmune disorders

2. Mechanisms of Action

2.1 GABAergic Modulation

Selank functions as a positive allosteric modulator of GABA-A receptors, enhancing endogenous GABA binding affinity rather than forcing receptor activation. This produces anxiolysis without sedation—a key distinction from benzodiazepines.

2.2 Enkephalinase Inhibition

Competitive inhibition of enkephalin-degrading enzymes (neprilysin, aminopeptidase N) preserves endogenous Leu-enkephalin, restoring natural opioid signaling dysregulated in anxiety disorders. Clinical data confirmed biochemical restoration correlated with anxiety score reduction.

2.3 Neurotrophic Regulation

Selank rapidly upregulates BDNF (Brain-Derived Neurotrophic Factor) in the hippocampus, providing neuroprotection against chronic stress-induced atrophy and enhancing memory consolidation.

2.4 Dopaminergic & Serotonergic Tuning

- **DRD1/DRD2 modulation:** Enhances working memory and cognitive flexibility.

- **Serotonergic metabolism:** Increases serotonin turnover rates, contributing to mood stabilization.

2.5 Immunomodulation

Modulates IL-6 expression and Th1/Th2 cytokine balance, producing demonstrable antiviral effects in preclinical data.

3. Comparative Profile

Feature	Selank	Benzodiazepines	SSRIs
Cognitive Effect	Enhanced (nootropic)	Impaired (sedation)	Variable
Energy Effect	Stimulating	Sedating	Neutral/variable
Dependence Risk	None observed	High	Discontinuation syndrome
Onset	Minutes to days	Minutes	Weeks

4. Clinical Evidence

Zozulia et al. (2008) enrolled 62 patients (Selank n=30, Medazepam n=32) with generalized anxiety disorder and neurasthenia. Using Hamilton Anxiety Rating Scale, Zung Self-Rating Scale, and CGI assessments, Selank reduced anxiety while simultaneously reducing asthenia, whereas Medazepam induced sedation and cognitive slowing. Biochemically, Selank significantly increased Leu-enkephalin half-life and concentration.

5. Administration Routes

Route	Details
Intranasal (Medical Standard)	Targets brain via olfactory bulb; onset 10–15 minutes; approved in Russia
Subcutaneous (Investigational)	Systemic exposure; higher immunogenicity risk vs. intranasal route

6. Safety Profile

6.1 Contraindications

- Pregnancy or lactation (strictly contraindicated; BDNF effects on fetal development)

- Autoimmune disorders (caution due to Th1/Th2 modulation)

6.2 Immunogenicity Concern

The synthetic PGP tail may trigger Anti-Drug Antibodies (ADAs) that recognize it as foreign, potentially neutralizing Selank or cross-reacting with endogenous tuftsin. This is the primary long-term safety concern with subcutaneous administration.

7. Reference Sources

1. Zozulia AA, et al. Efficacy and possible mechanisms of Selank action in anxiety. Eksp Klin Farmakol. 2008; PMID: 18447292.

2. Semenova TP, et al. Neurotropic effects of Selank, analog of tuftsin. Eksp Klin Farmakol. 2010; PMID: 21469474.

3. Kozlovskaya MM, et al. BDNF modulation by Selank in the hippocampus. Ross Fiziol Zh. 2010.

CLINICAL REFERENCE MONOGRAPH

NA-Selank

(N-Acetyl Selank)

The Acetylated Anxiolytic Nootropic Heptapeptide

GABA Modulation · Anxiety Relief · BDNF · Cognitive Enhancement · Safety Profile

1. Overview

NA-Selank (N-Acetyl Selank) is a structurally enhanced derivative of Selank featuring N-terminal acetylation, which increases resistance to enzymatic degradation and enhances CNS penetration compared to the parent compound. Like Selank, it derives from tuftsin (immunoglobulin G fragment) with a Pro-Gly-Pro stabilizing tail, but the acetyl modification extends its bioactive half-life and is reported to produce more pronounced and sustained anxiolytic and nootropic effects per microgram.

Parameter	Details
Name	NA-Selank (N-Acetyl Selank)
Reference Code	SELANK-NA
Modification	N-terminal acetylation for enhanced stability and CNS penetration
Category	Anxiolytic / Cognitive Enhancer / Neuropeptide
Typical Strength	10 mg vial
Reference Range	250–1,000 mcg once daily
Route	Subcutaneous or intranasal
Key Warning	Not FDA-approved; contraindicated in pregnancy; caution with benzodiazepines

2. Structural Advantage Over Standard Selank

N-terminal acetylation of Selank confers two key advantages: resistance to aminopeptidase-mediated N-terminal cleavage (the primary route of peptide degradation), and increased lipophilicity that enhances passive diffusion across the blood-brain barrier. These properties result in a reported 2–3x potency advantage over standard Selank at equivalent doses.

3. Mechanisms of Action

3.1 GABAergic System Modulation

NA-Selank acts as a positive allosteric modulator of GABA-A receptors, enhancing endogenous GABA binding without direct receptor activation. This produces anxiolysis without sedation or the tolerance/dependence seen with benzodiazepines.

3.2 Enkephalinase Inhibition

Competitively inhibits enkephalin-degrading enzymes (neprilysin, aminopeptidase N), preserving endogenous Leu-enkephalin and restoring natural opioid signaling dysregulated in chronic anxiety states.

3.3 Neurotrophic & Immunomodulatory Effects

- **BDNF upregulation:** Hippocampal neuroprotection against chronic stress-induced atrophy.
- **IL-6 modulation:** Balances Th1/Th2 cytokine ratio; demonstrable antiviral effects in preclinical models.
- **Dopaminergic tuning:** DRD1/DRD2 modulation enhancing working memory and cognitive flexibility.
- **Serotonergic metabolism:** Increases serotonin turnover, contributing to mood stabilization.

4. Clinical Indications (Investigational)

- Generalized anxiety disorder and stress modulation
- Cognitive enhancement and nootropic support
- Learning and memory consolidation
- Stress-related cognitive impairment
- Anxiolytic effect without sedation or performance impairment

5. Administration Protocol

Phase	Dose	Frequency	Route
Weeks 1–2	250–500 mcg	Once daily	Morning (SC or intranasal)
Weeks 3+	500–750 mcg	Once daily	Adjusted per response
Maximum	1,000 mcg daily	As tolerated	SC or intranasal

6. Reconstitution Reference

10 mg vial + 2 mL bacteriostatic water = 5 mg/mL (5,000 mcg/mL). Stable up to 28 days refrigerated.

Volume	Insulin Units	Dose
0.05 mL	5 units	250 mcg
0.10 mL	10 units	500 mcg
0.15 mL	15 units	750 mcg
0.20 mL	20 units	1,000 mcg

7. Safety Profile

7.1 Contraindications

- Pregnancy or breastfeeding
- Known hypersensitivity to Selank or components

7.2 Adverse Events

- Fatigue (uncommon; may indicate excessive GABAergic effect)
- Nasal irritation (intranasal route; common but mild)
- Headache (uncommon)

7.3 Drug Interactions

- **Benzodiazepines:** Moderate additive anxiolytic effect; risk of excessive sedation if combined.
- **Alcohol:** Additive CNS depression via GABAergic potentiation; avoid.

8. Monitoring Parameters

- Anxiety levels and mood tracking
- Sleep quality
- Cognitive performance assessment

9. Reference Sources

1. Zozulya AA, et al. Effects of Selank on GABAergic neurotransmission. Bull Exp Biol Med. 2003.

2. Volkova AV, et al. Effects of Selank on BDNF expression in anxiety models. Neurosci Behav Physiol. 2011.

3. Andreeva LA, et al. Clinical use of Selank in anxiety disorders. Zh Nevrol Psikhiatr Im S S Korsakova. 2005.

CLINICAL REFERENCE MONOGRAPH

DSIP

(Delta Sleep-Inducing Peptide)

The Neuro-Metabolic Sleep Modulator

Sleep Architecture · HPA Axis · Neuroprotection · Withdrawal · Safety Profile

1. Overview

DSIP is a nonapeptide first isolated in 1974 from rabbit cerebral venous blood during induced sleep states. It functions as a pleiotropic neuro-metabolic modulator with sleep-organizing, stress-protective, and neuroprotective characteristics. Unlike conventional sedatives, DSIP acts as a sleep organizer rather than a crude sedative, preserving normal sleep architecture including REM cycles.

Parameter	Details
Name	Delta Sleep-Inducing Peptide (DSIP)
Peptide Sequence	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu (WAGGDASGE)
Molecular Weight	~849 Daltons
Category	Neuropeptide / Neuro-Metabolic Modulator
Reference Range	100–250 mcg per dose
Route	Subcutaneous injection
In Vitro Half-Life	~15 minutes (in vivo bioactivity persists hours)

2. Pharmacokinetics & BBB Permeability

Despite a short in vitro half-life of ~15 minutes (cleaved by aminopeptidases), DSIP maintains in vivo bioactivity for hours through downstream signaling cascades. It crosses the blood-brain barrier through two distinct mechanisms:

- **Passive Transmembrane Diffusion:** Non-saturable lipophilic transport in brain parenchyma.
- **Saturable Choroid Plexus Transport:** High-affinity, low-capacity transport (Kt ~5.0 nM).

3. Mechanisms of Action

3.1 Glutamate-GABA Modulation

- Blocks NMDA receptor-mediated calcium influx, reducing excitotoxicity
- Potentiates GABAergic currents in hippocampus and cerebellum

3.2 Opioid System Interaction

Exhibits agonistic activity on opiate receptors while modulating endogenous enkephalin/endorphin systems. Functionally distinct from morphine: no respiratory depression or euphoria observed.

3.3 Antioxidant Mechanisms

- Enhances mitochondrial oxidative phosphorylation efficiency
- Upregulates endogenous antioxidant enzymes (SOD, catalase, glutathione peroxidase)
- Reduces lipid peroxidation markers

3.4 HPA Axis Regulation

- Inhibits ACTH secretion at pituitary level
- Reduces cortisol/corticosterone levels
- Prevents stress-induced monoamine depletion

4. Physiological Effects

4.1 Sleep Architecture

- Increases delta EEG power (0.5–4 Hz frequency band)
- Enhances sleep spindles (12–14 Hz), associated with memory consolidation
- Organizes sleep rather than inducing sedation; preserves REM cycles

4.2 Endocrine Effects

- Stimulates LH release (potential testosterone secretagogue pathway)
- Stimulates GH and GHRH; inhibits somatostatin

5. Clinical Applications (Investigational)

5.1 Withdrawal Syndromes

A study of 107 inpatients (47 alcohol, 60 opioid) reported marked improvement in 87% of alcohol withdrawal cases and 97% of opioid withdrawal cases, with rapid symptom alleviation and good tolerability.

5.2 Sleep Disorders

Improved sleep efficiency and reduced sleep latency; enhanced daytime alertness without benzodiazepine-type hangover or residual sedation.

5.3 Pain Management

A European Neurology study found DSIP significantly lowered pain levels in 6 of 7 patients with migraines, vasomotor headaches, and psychogenic pain syndromes.

6. Administration Protocol

Parameter	Details
Route	Subcutaneous injection
Reference Range	100–250 mcg per dose
High-Dose Note	>500 mcg may produce paradoxical alertness
Onset	Sleep pressure typically 60–120 minutes post-injection
Cycling	3 days on / 1 day off to prevent desensitization

7. Safety Profile

7.1 Contraindications

- Autoimmune disorders
- Pregnancy or lactation

7.2 Drug Interactions

- **Benzodiazepines / Alcohol:** Synergistic GABA potentiation; risk of unpredictable sedation.
- **Opioids:** Concurrent use is dangerous; receptor modulation may alter tolerance thresholds.

7.3 Immunogenicity

Exogenous peptides may trigger antibodies that cross-react with endogenous DSIP or homologous proteins. This represents the primary long-term safety concern with repeated administration.

8. Reference Sources

1. Schoenenberger GA, Monnier M. Characterization of a delta-EEG-inducing peptide. Proc Natl Acad Sci USA. 1977; PMID: 266176.

2. Graf MV, Kastin AJ. Delta-sleep-inducing peptide (DSIP): an update. Peptides. 1986; PMID: 3526111.

3. Nakamura A, et al. DSIP suppression of opioid withdrawal. Pharmacol Biochem Behav. 1982; PMID: 6818063.

CLINICAL REFERENCE MONOGRAPH

Pinealon

(PIN)

The Pineal Bioregulator Peptide

Neuroprotection · Circadian Regulation · Cognitive Aging · Sleep · Safety Profile

1. Overview

Pinealon is a synthetic tripeptide (Ala-Glu-Asp) derived from pineal gland peptide extracts, categorized as a cognitive and pineal bioregulator peptide within the Khavinson peptide series. It is researched for its potential to modulate pineal gland function, support melatonin synthesis, and exert neuroprotective and antioxidant effects.

Parameter	Details
Name	Pinealon
Reference Code	PIN
Peptide Sequence	Ala-Glu-Asp (tripeptide)
Example Strength	10 mg vial (varies by manufacturer)
Reference Range	100–500 mcg daily
Dosing Frequency	Once daily (evening typical)
Primary Warning	May increase melatonin activity; causes drowsiness; evening dosing recommended; not FDA-approved

2. Mechanism of Action

Pinealon is part of the Khavinson peptide bioregulator series, which proposes that short peptides can penetrate cell membranes and interact with DNA to modulate gene expression in a tissue-specific manner. Proposed mechanisms include:

- **Pineal Gland Modulation:** May support melatonin synthesis and circadian rhythm regulation.
- **Neuroprotection:** Preclinical data indicate antioxidant activity with potential protective effects against age-associated neurodegeneration.
- **Circadian Rhythm Support:** Proposed influence on the sleep-wake cycle via pineal signaling pathways.
- **Cognitive Aging:** Investigational support for cognitive function in aging populations.

3. Clinical Indications (Literature / Off-Label)

- Sleep regulation and quality improvement
- Neuroprotection research
- Cognitive aging support
- Circadian rhythm modulation

4. Administration Protocol

Parameter	Details
Route	Subcutaneous injection
Frequency	Once daily
Injection Sites	Abdomen or thigh
Timing	Evening, 1–2 hours before bedtime
Initial Dose	100–200 mcg
Titrated Dose	200–500 mcg based on response

5. Pharmacokinetics

- Short systemic half-life (hours)
- Sleep-related effects typically observable within days of initiation
- Long-term neuroprotective effects remain investigational and are not confirmed in controlled clinical trials

6. Reconstitution Reference

A 10 mg vial diluted in 2 mL bacteriostatic water yields 5 mg/mL (5,000 mcg/mL) concentration.

Volume	Insulin Units	Dose (mcg)
0.02 mL	2 units	100 mcg
0.04 mL	4 units	200 mcg
0.06 mL	6 units	300 mcg
0.08 mL	8 units	400 mcg
0.10 mL	10 units	500 mcg

7. Safety Profile

7.1 Contraindications

- Pregnancy or breastfeeding
- Known hypersensitivity to any component

7.2 Potential Adverse Events

- Drowsiness (dose-dependent; primary concern)
- Vivid dreams or altered dream patterns

7.3 Drug Interactions

Mild additive sedative effects may occur when combined with sedatives, hypnotics, or other agents affecting melatonin pathways. Caution is advised.

8. Monitoring Parameters

- Sleep quality and pattern tracking
- Cognitive function assessment
- Circadian rhythm patterns

9. Reference Sources

1. Khavinson VK, et al. Pineal peptide bioregulators and gene expression modulation. Bull Exp Biol Med. 2003; PMID: 12937682.

2. Khavinson V, et al. Pineal peptides and neuroendocrine regulation. Neuro Endocrinol Lett. 2001; PMID: 11524632.

CLINICAL REFERENCE MONOGRAPH

Pinealon

(EDR / Glu-Asp-Arg)

The Neuroprotective Pineal Bioregulator

Oxidative Stress · Neuroprotection · ERK Signaling · Epigenetics · Safety Profile

1. Overview

Pinealon (EDR peptide, T-33) is a synthetic tripeptide (L-glutamic acid–L-aspartic acid–L-arginine) developed from the Khavinson peptide bioregulator series at the St. Petersburg Institute of Bioregulation and Gerontology. While the brief reference guide version describes its sleep and circadian effects, the comprehensive evidence base centers on neuroprotection, oxidative stress reduction, and potential epigenetic gene regulation in aging and neurological models.

Parameter	Details
Name	Pinealon (EDR Tripeptide / T-33)
Sequence	Glu-Asp-Arg (L-glutamic acid–L-aspartic acid–L-arginine)
Molecular Formula	$C_{15}H_{26}N_6O_8$ (MW: ~418.40 g/mol)
Category	Neuroprotective Pineal Bioregulator
Reference Range	5 mg daily for 10–20 day cycles
Route	Subcutaneous (most common); IM and IV in research contexts
Key Warning	Active malignancy is an absolute contraindication; research predominantly from one scientific group

2. Mechanisms of Action

2.1 Oxidative Stress Reduction

Dose-dependent suppression of reactive oxygen species (ROS) accumulation demonstrated across multiple cell types including PC12 neuronal cells, cerebellar neurons, and hippocampal cultures. This represents the most consistently replicated mechanism in the Pinealon literature.

2.2 ERK 1/2 Signaling Modulation

Protective delay of stress-induced ERK 1/2 pathway activation in cerebellar neurons. This modulation affects the timing and magnitude of mitogen-activated protein kinase signaling, potentially protecting neurons from oxidative-stress-triggered apoptosis.

2.3 Cell Death Prevention

Protection against both necrotic and apoptotic cell death via caspase-3 modulation. In PC12 cells exposed to H_2O_2, Pinealon produced dose-dependent cell viability improvement compared to controls.

2.4 Proposed Genomic Regulation

Consistent with the Khavinson bioregulator theory, Pinealon is proposed to penetrate cell nuclei and bind to CNG DNA sequences, epigenetically modulating gene expression profiles relevant to cellular aging, repair, and neuronal function. This mechanism remains theoretical without direct confirmation in independent laboratories.

3. Preclinical Evidence

Model	Key Finding	Status
PC12 + H_2O_2	Dose-dependent cell viability improvement	Published; replicated
Pregnant rats (hyperhomocysteinemia)	Offspring showed superior Morris water maze learning	Published
5xFAD Alzheimer's mice	Prevented dendritic spine loss in hippocampus	Published
Macaque cognition	Reduced learning time over 10-day protocol	Published (primates)
Hypoxic stress model	Increased neuronal survival under low-oxygen conditions	Published

4. Human Clinical Research

4.1 Traumatic Brain Injury Study (72 Patients)

59.4% of patients showed improved working memory; additionally improved headache duration and EEG alpha-wave activity. Critical limitation: lacks methodological transparency regarding randomization and blinding.

4.2 Elderly Cohort (32 Participants)

Reported improvements in biological age markers. However, a competing peptide (Vesugen) showed greater effects in the same study, suggesting Pinealon's effects may be modest in this population.

4.3 Research Limitations

- Vast majority of studies conducted by the same interconnected research group without independent international replication
- Available human trials lack blinding, randomization, or placebo controls
- Primary publications for major claims (including telomere data) not available in accessible peer-reviewed databases
- Long-term effects in humans unknown for chronic or cyclical use

5. Comparison to Related Bioregulators

Peptide	Structure	Primary Target	Main Application
Pinealon	Tripeptide (EDR)	CNS cellular repair / ROS reduction	Neuroprotection
Epitalon	Tetrapeptide (AEDG)	Telomerase activation	Anti-aging / longevity
Semax	Heptapeptide	BDNF upregulation	Cognitive enhancement
Selank	Heptapeptide	GABA-A modulation	Anxiety reduction

6. Administration Protocol

Parameter	Details
Route	Subcutaneous (most common); IM and IV in research
Cycle Length	10–20 day cycles; with off-periods
Reference Dose	5 mg once daily during cycle
Timing	Evening (potential circadian interactions)
Reconstitution	10 mg + 2 mL BW = 5 mg/mL; stable 28 days refrigerated

7. Safety Profile

7.1 Contraindications

- Active malignancy or recent cancer history (cell proliferation effects)
- Pregnancy or breastfeeding
- Seizure disorders (theoretical lowered seizure threshold)

7.2 Adverse Events

- Injection site reactions (redness, itching, swelling)
- Transient headaches and vivid dreams
- Insomnia (if dosed at morning)
- General fatigue (uncommon)

7.3 Supply Chain Risk

Products are not manufactured under GMP standards and are primarily sold as research chemicals. Contamination or incorrect dosages are realistic risks in the unregulated market.

8. Reference Sources

1. Khavinson VK, et al. Neuroprotective effects of EDR peptide in hypoxia. Bull Exp Biol Med. 2014.

2. Khavinson VK, et al. Peptide EDR protects neurons from H2O2-induced death. Neuro Endocrinol Lett. 2011.

3. Khavinson VK, Morozov VG. Peptides of pineal gland and thymus prolong human life. Neuro Endocrinol Lett. 2003; PMID: 14730303.

DISCLAIMER: *Pinealon is not FDA-approved. Research derives primarily from one investigator group without independent international replication. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

PE 22-28

(TREK-1 Antagonist)

The Rapid-Onset Antidepressant Peptide

TREK-1 Inhibition · Serotonin Pathway · BDNF/Neurogenesis · Depression · Safety Profile

1. Overview

PE 22-28 is a synthetic heptapeptide derived from Spadin, an endogenous fragment of neurotensin receptor 3 (Sortilin). It functions as a selective antagonist of the TREK-1 potassium channel (K2P2.1), representing a mechanistically novel antidepressant approach entirely distinct from monoamine reuptake inhibition. Preclinical data suggest rapid onset of antidepressant and pro-neurogenic effects within 3–5 days.

Parameter	Details
Name	PE 22-28
Sequence	Gly-Val-Ser-Trp-Gly-Leu-Arg (GVSWGLR)
Molecular Weight	~773–802 Da
Target	TREK-1 potassium channel (K2P2.1)
IC50	~0.12 nM (more potent than parent Spadin at 40–60 nM)
Effect Half-Life	>24 hours (once-daily dosing feasible)
Reference Dose	50–100 mcg daily SC (anecdotal protocols)

2. Target: TREK-1 Channel

TREK-1 is a background potassium leak channel maintaining negative resting membrane potential. It is highly expressed in the prefrontal cortex, hippocampus, and dorsal raphe nucleus—brain regions central to mood regulation. The channel is polymodally regulated through mechanosensitivity, lipid activation, and temperature/pH sensing.

3. Mechanism of Action

PE 22-28 functions as a state-dependent allosteric antagonist (not a pore blocker), selectively antagonizing arachidonic acid activation of TREK-1:

- **Neuronal Depolarization:** Removes inhibitory K+ leak in serotonergic neurons.
- **Enhanced Serotonergic Firing:** Increases dorsal raphe nucleus neuron activity and serotonin output.
- **BDNF Cascade:** Elevates cAMP-PKA-CREB phosphorylation, triggering BDNF transcription.

Contrast with SSRIs: While SSRIs cause initial suppression via autoreceptor feedback, PE 22-28 directly depolarizes soma, overriding inhibitory inputs and producing rapid-onset effects.

4. Preclinical Efficacy

Model	Result
Forced Swim Test	30–50% reduction in immobility after 4 days
Novelty Suppressed Feeding	Significant reduction in eating latency
Dentate Gyrus Neurogenesis	Doubles BrdU+ progenitor cells within 4 days
Synaptic Markers	Increases PSD-95 and synapsin expression
Ischemia / Reperfusion	Neuroprotection via BDNF upregulation

5. Administration

Parameter	Details
Route	Subcutaneous injection
Reference Dose	50–100 mcg daily
Cycling	2 weeks on / 2 weeks off to mitigate desensitization
Onset	Mood lifting and cognitive improvement within 3–5 days (anecdotal)
Common Stack	PE 22-28 + Selank + Semax (complementary neurochemical coverage)

6. Safety Considerations

6.1 Cardiac Concerns

TREK-1 knockout mice exhibit prolonged QT intervals. The channel contributes to ventricular repolarization reserve. Blockade theoretically risks QT prolongation and Torsades de Pointes, particularly in compromised cardiac tissue. This is the primary serious safety concern.

6.2 Smooth Muscle Effects

TREK-1 knockout models show bladder hypertrophy and non-voiding contractions, and enhanced GI contractility with risk of cramping or hypermotility.

6.3 Contraindications

- History of cardiac arrhythmias, Long QT syndrome, or recent myocardial infarction
- Active epilepsy
- Overactive bladder or interstitial cystitis
- Irritable bowel syndrome with cramping
- Pregnancy (no teratogenic safety data)

7. Reference Sources

1. Borsotto M, et al. Targeting two-pore domain K+ channels TREK-1 and TASK-3 for the treatment of depression. Sci Rep. 2015; PMID: 25858814.

2. Djillani A, et al. Spadin analogue PE-22-28: a TREK-1 channel blocker with antidepressant properties. Front Pharmacol. 2017; PMID: 28769809.

CLINICAL REFERENCE MONOGRAPH

Dihexa

(PNB-0408)

The HGF/c-Met System Potentiator

Synaptic Plasticity · Cognitive Enhancement · Neuroprotection · c-Met Signaling · Safety Profile

1. Overview

Dihexa (PNB-0408) is an oligopeptide derived from angiotensin IV, engineered to resolve the pharmacokinetic limitations of native AngIV (plasma half-life of seconds). It functions as a positive allosteric modulator of the HGF/c-Met receptor system with exceptionally high binding affinity and oral bioavailability—remarkable properties for a neuropeptide.

Parameter	Details
Name	Dihexa (PNB-0408)
Chemical Formula	$C_{27}H_{44}N_4O_5$ (MW: 504.67 Da)
Category	HGF/c-Met Potentiator / Nootropic Peptide
Binding Affinity	Kd = 65 pM (exceptionally high)
Half-Life	~12 days (IV); ~8.8 days (IP) in rodents
Oral Bioavailability	Yes (unlike most neuropeptides)
Key Warning	c-Met is an oncogene; active malignancy is an absolute contraindication

2. Mechanism of Action

Dihexa functions as a positive allosteric modulator of the HGF/c-Met system, facilitating HGF dimerization and activating downstream PI3K/AKT and MEK/ERK signaling pathways critical for neuroprotection and synaptic plasticity. Unlike direct agonists, its allosteric mechanism preserves the physiological regulation of the c-Met pathway.

- **PI3K/AKT Pathway:** Promotes neuronal survival, anti-apoptotic signaling.
- **MEK/ERK Pathway:** Drives synaptic plasticity and memory consolidation.
- **BBB Penetration:** Confirmed via tritiated labeling studies.
- **Dendritic Spine Density:** Increased nearly 3-fold over 5 days in hippocampal cultures.

3. Preclinical Evidence

3.1 Cognitive Models

In aged rats (22–26 months), Dihexa at 2 mg/kg/day showed significantly improved performance in Morris Water Maze spatial learning tasks. In hippocampal cultures, it was seven orders of magnitude more powerful than BDNF in increasing dendritic spine density.

3.2 Disease Models

Model	Finding
APP/PS1 Alzheimer's	Reduced neuroinflammation; lowered IL-1β and TNF-α
6-OHDA Parkinson's	Suggested neuroprotection of dopaminergic neurons
Zebrafish Ototoxicity	Protected hair cells from gentamicin damage

4. Clinical Trial Data

LIFT-AD Phase 2/3 Trial (312 patients, 26 weeks) with fosgonimeton (an oral HGF/c-Met activator):

Endpoint	Result
Primary (Global Statistical Test)	Failed (p=0.70)
ADAS-Cog11 (cognition)	Trend favoring treatment; not significant (p=0.35)
ADCS-ADL23 (function)	Trend favoring treatment; not significant (p=0.61)
p-Tau217 biomarker	Significant reduction (p<0.01) — notable finding

SHAPE Trial (Parkinson's/Lewy Body Dementia): Primary endpoint failed; cognitive improvement seen in a patient subset.

5. Safety Profile

5.1 Contraindications

- Active malignancy or high cancer risk (c-Met is an oncogene; overactivation could promote tumor growth)
- Uncontrolled cardiovascular disease
- Severe psychiatric disorders
- Liver or kidney pathology
- Pregnancy or developmental stages

5.2 Adverse Events (Anecdotal)

- Overstimulation, anxiety, tension headaches (excessive dosing)
- Irritability, sleep disruption
- Potential withdrawal effects with abrupt cessation

6. Anecdotal Administration (Nootropic Community)

Parameter	Details
Route	Subcutaneous injection or transdermal
Reported Dose	Low microgram range; precise protocols not standardized
Reported Benefits	Enhanced mental stamina, verbal fluency, creative problem-solving
Adverse Reports	Overstimulation, headaches, irritability at higher doses

7. Reference Sources

1. Bhatt DL, et al. HGF/c-Met system and synaptic plasticity. J Pharmacol Exp Ther. 2013; PMID: 23378574.

2. McCoy AT, et al. Evaluation of Dihexa in cognitive function. J Alzheimers Dis. 2013.

DISCLAIMER: *Dihexa is not FDA-approved. It is an investigational compound with no established human safety profile. c-Met oncogene activation is a serious theoretical risk. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

BPC-157

(Body Protection Compound-157)

The Gastric Juice-Derived Healing Peptide

Tendon Repair · GI Healing · Angiogenesis · Nitric Oxide · Safety Profile

1. Overview

BPC-157 is a synthetic 15-amino acid peptide derived from a protein found in human gastric juice. Despite its predominantly preclinical evidence base, it has attracted significant research interest for its multi-tissue healing properties including tendon, ligament, muscle, and gastrointestinal repair. Animal models consistently demonstrate accelerated healing across tissue types, though human clinical data remain limited and largely absent from peer-reviewed literature.

Parameter	Details
Name	BPC-157 (Body Protection Compound-157)
Sequence	15-amino acid peptide derived from human gastric juice protein
Category	Healing & Recovery / Gastroprotective Peptide
Example Strength	10 mg vial
Dosing Range	250–500 mcg daily; up to 500 mcg twice daily (investigational)
Route	Subcutaneous injection (systemic); oral (GI-targeted)
Estimated Half-Life	~4 hours (limited modeling)
Key Warning	Not FDA-approved; data predominantly preclinical; contraindicated in active malignancy

2. Mechanisms of Action

2.1 Nitric Oxide (NO) Pathway Modulation

BPC-157 modulates nitric oxide synthesis, influencing vascular tone, endothelial function, and tissue perfusion. This is believed to be a central mechanism through which it promotes both GI protection and musculoskeletal healing.

2.2 Angiogenesis & Collagen Production

Promotes blood vessel formation (angiogenesis) and enhances collagen synthesis, providing the structural substrate for tissue repair. Animal studies demonstrate significant acceleration of tendon-to-bone healing through these mechanisms.

2.3 Growth Hormone Receptor Upregulation

May upregulate growth hormone receptor expression in specific tissues, amplifying local anabolic signaling independent of systemic GH levels.

2.4 Gastrointestinal Cytoprotection

Derived from gastric juice, BPC-157 exhibits potent gastroprotective properties in animal models—reducing NSAID-induced ulceration, promoting intestinal anastomosis healing, and counteracting intestinal inflammation through multiple pathways.

3. Investigational Applications

Indication Area	Evidence Level
Tendon and ligament repair	Preclinical (strong animal data)
Muscle recovery and repair	Preclinical
Gastrointestinal mucosal healing	Preclinical (strongest evidence base)
Post-surgical anastomosis healing	Preclinical
Inflammatory bowel disease	Preclinical
Neuroprotection	Preclinical (early-stage)

4. Administration Protocol

Parameter	Details
Route	Subcutaneous injection (systemic effects); oral capsules (GI-targeted)
Frequency	Once or twice daily
Injection Sites	Near injury area for targeted effect; abdomen for systemic distribution
Reconstitution	10 mg + 2 mL BW = 5 mg/mL; stable 28 days refrigerated

Volume	Insulin Units	Dose
0.05 mL	5 units	250 mcg
0.10 mL	10 units	500 mcg

5. Safety Profile

5.1 Contraindications

- Active malignancy (theoretical angiogenic promotion concerns)
- Pregnancy or breastfeeding

5.2 Adverse Events

Generally mild in animal models and anecdotal human use. Reported adverse effects include injection site reactions, mild nausea, and headache (rare). No serious adverse events have been reported in limited human observational contexts.

5.3 Critical Limitation

The compound is not FDA-approved and the evidence base is predominantly preclinical. Human pharmacokinetic data are extremely limited. Long-term safety in humans has not been established.

6. Reference Sources

1. Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157. Curr Neuropharmacol. 2016; PMID: 26517050.

2. Chang CH, et al. The promoting effect of pentadecapeptide BPC 157 on tendon healing. J Appl Physiol. 2011; PMID: 21030673.

3. Sikiric P, et al. Stable gastric pentadecapeptide BPC 157. Curr Pharm Des. 2011; PMID: 21548875.

CLINICAL REFERENCE MONOGRAPH

TB-500

(Thymosin Beta-4)

The Systemic Tissue Repair Peptide

Angiogenesis · Actin Regulation · Soft Tissue Repair · Anti-Inflammatory · Safety Profile

1. Overview

TB-500 is a synthetic version of Thymosin Beta-4 (Tβ4), a naturally occurring 43-amino acid peptide found in virtually all nucleated mammalian cells. It is one of the most abundant peptides in human platelets and wound fluid, suggesting a key role in tissue repair signaling. Preclinical evidence indicates TB-500 facilitates cell migration, angiogenesis, actin regulation, and anti-inflammatory signaling. A notable pharmacological feature is its systemic distribution of effects regardless of injection site.

Parameter	Details
Name	TB-500 (Thymosin Beta-4 / Tβ4)
Category	Healing & Recovery Peptide
Example Strength	10 mg vial
Loading Phase	2–2.5 mg twice weekly (Weeks 1–6)
Maintenance Phase	2–2.5 mg once weekly (ongoing)
Route	Subcutaneous injection
WADA Status	Prohibited substance
Key Warning	Not FDA-approved; contraindicated in active malignancy

2. Mechanisms of Action

2.1 Actin Sequestration & Cell Mobility

The primary biochemical role of Thymosin Beta-4 is sequestering G-actin (monomeric actin), regulating the actin cytoskeleton. This modulates cell migration, shape, and division—processes fundamental to wound repair and tissue regeneration.

2.2 Angiogenesis Promotion

TB-500 upregulates matrix metalloproteinases and promotes vascular endothelial cell migration, stimulating new blood vessel formation (angiogenesis) that is essential for tissue repair and regeneration.

2.3 Anti-Inflammatory Signaling

Reduces pro-inflammatory cytokines including TNF-α and IL-1β, modulating the acute inflammatory phase of healing and promoting transition to regenerative repair processes.

2.4 Systemic Distribution

Unlike many peptides that act locally, TB-500 appears to distribute systemically regardless of injection site, enabling treatment of multiple injury sites from a single injection location.

3. Investigational Indications

- Soft tissue injury (tendon, ligament, muscle) research
- Post-surgical recovery investigations
- Chronic wound and ulcer healing studies
- Hair regrowth research (limited supporting evidence)
- Cardiac tissue repair (preclinical myocardial injury models)

4. Administration Protocol

Phase	Dose	Frequency	Duration
Loading	2–2.5 mg	Twice weekly	Weeks 1–6
Maintenance	2–2.5 mg	Once weekly	Ongoing

5. Reconstitution Reference

10 mg vial + 2 mL bacteriostatic water = 5 mg/mL concentration. Stable up to 28 days refrigerated (2–8°C).

Volume	Insulin Units	Dose
0.40 mL	40 units	2.0 mg
0.45 mL	45 units	2.25 mg
0.50 mL	50 units	2.5 mg

6. Safety Profile

6.1 Contraindications

- Active malignancy (theoretical cell proliferation and angiogenic concerns)
- Pregnancy or breastfeeding
- Active systemic infections

6.2 Adverse Events

- Injection site reactions (redness, mild swelling)
- Temporary lethargy (uncommon)
- Sensation of head rush or light-headedness (uncommon)

7. Reference Sources

1. Goldstein AL, et al. Thymosin beta4: a multi-functional regenerative peptide. Expert Opin Biol Ther. 2012; PMID: 22416909.

2. Malinda KM, et al. Thymosin beta-4 accelerates wound healing. J Invest Dermatol. 1999; PMID: 10071287.

3. Smart N, et al. Thymosin beta4 induces adult epicardial progenitor mobilization and neovascularization. Nature. 2007; PMID: 17460664.

CLINICAL REFERENCE MONOGRAPH

TB-500

(Thymosin β-4 — Comprehensive)

Full-Spectrum Tissue Regeneration Evidence Review

Wound Healing · Cardiovascular · Neurological · Oncogenic Paradox · Phase II Data

1. Overview

TB-500 represents either synthetic full-length Thymosin Beta-4 (Tβ4) or, more specifically, its N-acetylated 17–23 amino acid active fragment (Ac-LKKTETQ)—the core actin-binding domain. Tβ4 is present in virtually all mammalian nucleated cells (~4.9 kDa; 43 amino acids), with particularly high concentrations in platelets, wound fluid, and immune cells. It is the most clinically advanced regenerative peptide, with completed Phase II/III trials for chronic wounds and ophthalmic repair, Phase I cardiovascular safety data, and preclinical evidence for neurological applications.

Parameter	Details
Full Name	Thymosin Beta-4 (Tβ4) / Active Fragment: Ac-LKKTETQ (aa 17–23)
Molecular Weight	~4.9 kDa (full 43-aa peptide)
Most Advanced Indication	Chronic wounds / Neurotrophic Keratopathy (Phase II/III)
Ophthalmic Status	RGN-259 granted FDA Orphan Drug Designation
Cardiovascular	Phase I safety completed; indirect human evidence
WADA Status	Prohibited (Class S2) at all times
Key Warning	Absolute contraindication in active malignancy (oncogenic paradox confirmed)

2. Molecular Mechanisms by Active Fragment

Fragment	Pathway	Effect
Amino acids 1–15	PI3K/Akt/ILK (Integrin-Linked Kinase)	Cell survival; anti-apoptosis
Amino acids 1–4 (Ac-SDKP)	NF-κB inhibition	Anti-inflammation; reduced TNF-α, IL-8
Amino acids 17–23	VEGF signaling	Angiogenesis; new vessel formation
Amino acids 17–23	MMP-1/2/9 regulation	Matrix remodeling; anti-fibrosis
Full peptide	G-actin sequestration	Cell migration; cytoskeletal remodeling

3. Clinical Evidence by System

3.1 Dermal & Ocular (Most Advanced)

- Phase II/III trials completed for chronic wounds (pressure ulcers, venous stasis ulcers, epidermolysis bullosa)
- **RGN-259 (ophthalmic drops):** FDA Orphan Drug Designation for Neurotrophic Keratopathy.
- **Phase II/III dry eye syndrome:** Demonstrated efficacy and safety.

- **Preclinical wound closure:** Accelerated healing in normal, aged, diabetic, and steroid-impaired animal models.

3.2 Cardiovascular (Phase I + Preclinical)

- **Phase I trial:** Established safety and tolerability in healthy volunteers.
- **Myocardial infarction (preclinical):** Improved LV function, reduced scarring, promoted angiogenesis, reactivated cardiac progenitor cells.
- **REGENERATIVE-IHD (indirect):** Elevated circulating Tβ4 post-stem cell therapy correlated with improved cardiac symptoms at 6 months.

3.3 Neurological (Preclinical Only)

- **TBI models:** Early administration (≤6h) reduced cortical lesion volume by up to 30%; delayed (24h) promoted long-term functional recovery.
- **Stroke (MCAo):** Delayed administration improved neurological recovery through 56 days; optimal dose 3.75 mg/kg in rodents.
- **Mechanisms:** Stimulated angiogenesis, oligodendrogenesis, and neurogenesis in injured CNS tissue.

3.4 Musculoskeletal (Theoretical)

Widely used off-label in sports medicine despite limited dedicated research for tendon, muscle, and ligament applications. The plausible biological mechanisms (actin regulation, anti-inflammation, angiogenesis) support the theoretical rationale but formal clinical evidence for musculoskeletal indications is absent.

4. The Oncogenic Paradox

This is the most clinically significant safety concern for systemic TB-500 use:

Cancer Context	Tβ4 Behavior	Clinical Implication
Solid tumors (colon, pancreas, breast, lung, glioma)	Overexpressed; correlates with invasion, metastasis, poor prognosis	Active malignancy: ABSOLUTE contraindication
Tumor angiogenesis	Promotes HIF-1α stabilization; VEGF upregulation	Could accelerate tumor vascularization
Multiple myeloma	Lower expression → shorter event-free survival	Paradoxically protective in some hematologic cancers
Clinical recommendation	Full cancer history required before use	Absolute contraindication for known malignancy

5. Pharmacokinetics & Regulatory Status

- **Human Phase I pharmacokinetics:** Dose-proportional plasma response; no accumulation over 14-day dosing.
- **Adverse events across Phase I/II:** Infrequent; consistently mild-to-moderate.
- **FDA status:** Unapproved investigational compound; increased compounding pharmacy scrutiny for purity and immune reactions.
- **WADA status:** Explicitly prohibited Class S2 (Peptide Hormones) for all athletes.

6. Reference Sources

1. Goldstein AL, et al. Thymosin beta4: a multi-functional regenerative peptide. Expert Opin Biol Ther. 2012; PMID: 22416909.

2. Smart N, et al. Thymosin beta4 induces adult epicardial progenitor mobilization. Nature. 2007; PMID: 17460664.

3. Xiong Y, et al. Thymosin beta4 treatment after traumatic brain injury reduces lesion volume and promotes long-term recovery. J Neurosurg. 2011; PMID: 21950868.

CLINICAL REFERENCE MONOGRAPH

GHK-Cu

(Copper Peptide)

The Tissue Regeneration & Healing Peptide

Collagen Synthesis · Wound Healing · Angiogenesis · Skin Rejuvenation · Safety Profile

1. Overview

GHK-Cu is a naturally occurring tripeptide (glycyl-L-histidyl-L-lysine) that binds copper ions. First isolated from human plasma, it is found at elevated concentrations at sites of tissue injury and is believed to play a role in wound healing, collagen remodeling, and anti-inflammatory signaling. Topical applications are more extensively studied than systemic injectable use.

Parameter	Details
Name	GHK-Cu (Copper Peptide)
Reference Code	GHK-CU
Peptide Sequence	Glycyl-L-histidyl-L-lysine + Cu^{2+}
Category	Healing & Recovery / Regenerative Peptide
Example Strength	100 mg vial
Reference Range	1–3 mg daily (investigational)
Key Warning	Contraindicated in Wilson disease or copper hypersensitivity

2. Mechanism of Action

GHK-Cu binds divalent copper ions (Cu^{2+}) and is proposed to modulate a wide range of biological processes through gene expression regulation and growth factor signaling:

- **Collagen Synthesis Stimulation:** Upregulates collagen I, III, and IV production via fibroblast activation.
- **Angiogenesis:** Stimulates vascular endothelial growth factor (VEGF) and promotes new capillary formation.
- **Anti-Inflammatory Modulation:** Downregulates TNF-alpha and other pro-inflammatory cytokines.
- **Gene Expression Regulation:** Proposed to influence over 4,000 human genes in preclinical studies.
- **Antioxidant Activity:** Copper-binding may enhance superoxide dismutase (SOD) activity.

3. Investigational Indications

Indication Area	Research Status
Skin rejuvenation and anti-aging	Topical — Commercially used
Wound healing acceleration	Preclinical / Early investigational
Hair growth promotion	Preclinical / Investigational

Indication Area	Research Status
Anti-aging signaling research	Preclinical
Systemic injectable applications	Investigational only

4. Administration (Investigational)

Parameter	Details
Route	Subcutaneous (investigational); Topical (primary evidence base)
Frequency	Once daily
Injection Site	Abdomen, thigh, or near treatment area
Timing	Any time of day
Reference Range	1–3 mg daily (injectable, investigational)

5. Reconstitution Reference

A 100 mg vial reconstituted with 5 mL bacteriostatic water yields 20 mg/mL (20,000 mcg/mL). Stability: up to 28 days refrigerated at 2–8°C.

Volume	Insulin Units	Dose
0.05 mL	5 units	1 mg (1,000 mcg)
0.10 mL	10 units	2 mg (2,000 mcg)
0.15 mL	15 units	3 mg (3,000 mcg)

6. Safety Profile

6.1 Contraindications

- Copper sensitivity or hypersensitivity
- Wilson disease (impaired copper metabolism)
- Pregnancy or breastfeeding

6.2 Adverse Events

- Injection site reactions (redness, mild irritation)
- Mild nausea (uncommon)
- Copper toxicity risk at extreme doses (theoretical)

6.3 Drug Interactions

High-dose zinc supplementation may competitively interfere with copper absorption and reduce the bioavailability of copper available for GHK-Cu binding. Clinically significant interactions at therapeutic doses remain poorly characterized.

7. Reference Sources

1. Pickart L, et al. The human tri-peptide GHK and tissue remodeling. J Biomater Sci Polym Ed. 1999; PMID: 10204041.

2. Maquart FX, et al. Copper peptides and collagen synthesis. Biochim Biophys Acta. 2006; PMID: 16412581.

3. Pickart L, et al. GHK-Cu gene expression modulation. Biochim Biophys Acta. 2011; PMID: 21219841.

CLINICAL REFERENCE MONOGRAPH

GHK-Cu

(Copper Peptide — Comprehensive)

Master Regulator of Cellular Regeneration

Gene Expression · Collagen · Wound Healing · Anti-Aging · Oncogenic Paradox

1. Overview

GHK-Cu (glycyl-L-histidyl-L-lysine complexed with copper) is a naturally occurring tripeptide discovered by Dr. Loren Pickart in 1973, who found it could restore youthful protein synthesis patterns in aged tissue. Plasma concentrations decline significantly with age—from ~200 ng/mL at age 20 to ~80 ng/mL by age 60—suggesting a physiological role in tissue maintenance and regeneration. Preclinical evidence shows GHK-Cu modulates approximately 4,000 human genes (31.2% of those studied), making it one of the most pleiotropic peptides in the Khavinson-adjacent bioregulator literature.

Parameter	Details
Name	GHK-Cu (Glycyl-L-Histidyl-L-Lysine Copper Complex)
Discovery	Dr. Loren Pickart, 1973
Endogenous Plasma Level	~200 ng/mL (age 20) → ~80 ng/mL (age 60)
Genes Modulated	~4,000 human genes (31.2% of those studied; preclinical)
Category	Regenerative / Tissue Repair / Anti-Aging Peptide
Topical Use	Well-established; 1–3% concentration
Injectable Use	Investigational; not FDA-approved for systemic use

2. Molecular Mechanisms

2.1 Gene Expression Modulation

GHK-Cu's most remarkable property is its broad influence on gene expression. Bioinformatics analysis suggests it simultaneously upregulates wound healing, anti-inflammatory, and tissue regeneration genes while downregulating oncogenes, inflammatory mediators, and genes associated with aggressive cancer phenotypes—producing a paradoxical anti-cancer gene signature despite its pro-angiogenic activity.

2.2 Extracellular Matrix Regulation

- Stimulates synthesis of collagen types I, III, IV, and VII
- Promotes elastin and proteoglycan production
- Regulates matrix metalloproteinases (MMPs) for balanced ECM remodeling

2.3 Signaling Pathways

- Activates TGF-β (transforming growth factor) for tissue repair
- Suppresses NF-κB inflammatory pathways
- Modulates SIRT1/STAT3 (longevity/cellular stress response)

- Activates Wnt/β-catenin pathways (cell proliferation and differentiation)

2.4 Antioxidant Delivery

Delivers bioavailable copper to superoxide dismutase (SOD) enzymes, enhancing catalytic antioxidant defense. Also directly neutralizes lipid peroxidation byproducts including 4-hydroxynonenal (4-HNE).

3. Clinical Evidence (Topical Applications)

Study	Population	Protocol	Key Result
Wrinkle Reduction RCT	71 women	12-week topical GHK-Cu	Improved laxity, clarity, firmness; reduced fine lines
Wrinkle Volume Study	40 women	8-week comparison vs. control	55.8% wrinkle volume reduction; 32.8% depth reduction
Procollagen Study	Clinical	1-month topical	Increased procollagen in 70% of participants
Hair Density Trial	Clinical	6-month topical	27% increase in hair density

4. Therapeutic Potential (Preclinical)

- **Wound healing:** Accelerated closure across normal, aged, diabetic, and steroid-impaired animal models.
- **Pulmonary protection:** Suppressed TNF-α and IL-6 in acute lung injury models.
- **GI healing:** Ulcerative colitis models showed SIRT1 pathway-mediated mucosal healing.
- **Neuroprotection:** Emerging preclinical evidence; mechanism under investigation.

5. The Oncogenic Paradox

GHK-Cu presents a complex oncological profile that must be understood before systemic use:

Context	GHK-Cu Effect	Implication
Solid tumors (colon, pancreas, breast, lung)	Downregulates oncogenic gene expression	Anti-cancer gene signature
Angiogenesis	Pro-angiogenic (VEGF upregulation)	Could support tumor vascularization
Clinical recommendation	Contraindicated in active cancer	Absolute contraindication for systemic use

6. Delivery Considerations

Topical efficacy is more dependent on the delivery system than peptide concentration alone. Key delivery strategies include liposomal encapsulation (bypasses skin barrier), microemulsions (enhanced penetration), and microneedling (direct dermal delivery). Avoid co-application with low-pH products (vitamin C serums, AHAs) which can degrade the copper complex.

7. Safety Profile

7.1 Contraindications

- Wilson disease (absolute contraindication for systemic use—impaired copper metabolism)
- Active cancer or recent cancer history (oncogenic paradox; absolute contraindication for systemic)
- Copper metabolism disorders

7.2 Adverse Events

- Topical: Generally safe; mild irritation, redness, and itching at high concentrations
- Systemic/injectable: Copper toxicity risk requires monitoring

7.3 Drug Interactions

- **High-dose zinc supplementation:** Competitively inhibits copper absorption.
- **Chelating agents (EDTA):** Render GHK-Cu ineffective by binding the copper.

8. Reference Sources

1. Pickart L, Margolina A. Regenerative and protective actions of the GHK-Cu peptide. Int J Mol Sci. 2018; PMID: 30081536.

2. Pickart L, et al. The human tripeptide GHK-Cu in prevention of oxidative stress. Rejuvenation Res. 2012; PMID: 22510740.

3. Maquart FX, et al. Stimulation of collagen synthesis by glycyl-histidyl-lysine copper. J Invest Dermatol. 1993; PMID: 8478975.

CLINICAL REFERENCE MONOGRAPH

SS-31

(Elamipretide)

The Mitochondrial Cardiolipin Stabilizer

Mitochondrial Function · Heart Failure · ATP Production · ROS Reduction · Safety Profile

1. Overview

SS-31 (Elamipretide) is a synthetic tetrapeptide (D-Arg-Dmt-Lys-Phe-NH_2) from the Szeto-Schiller peptide family, engineered to target the inner mitochondrial membrane with high selectivity. It is the most clinically advanced mitochondrial-targeted peptide in development, with completed Phase 2 trials in heart failure and mitochondrial myopathy. Its unique mechanism—stabilizing cardiolipin to restore electron transport chain efficiency—addresses a fundamental driver of mitochondrial dysfunction across multiple disease states.

Parameter	Details
Name	SS-31 (Elamipretide)
Sequence	D-Arg-Dmt-Lys-Phe-NH_2 (tetrapeptide)
Target	Cardiolipin in the inner mitochondrial membrane
Category	Mitochondrial Targeted Peptide
Route	Subcutaneous injection
Investigational Dosing	10–40 mg once daily (varies by trial)
Development Stage	Phase 2 completed (heart failure, mitochondrial myopathy)
Key Warning	Not FDA-approved; investigational only; contraindicated in pregnancy

2. Mechanism of Action

2.1 Cardiolipin Targeting

Cardiolipin is a unique phospholipid found almost exclusively in the inner mitochondrial membrane, essential for organizing and stabilizing the respiratory chain supercomplexes. In disease states and aging, cardiolipin is oxidized and peroxidized, causing respiratory chain disorganization and elevated reactive oxygen species (ROS) production.

2.2 Electron Transport Chain Restoration

By binding selectively to cardiolipin via electrostatic and hydrophobic interactions, SS-31 prevents cardiolipin peroxidation and stabilizes the inner membrane architecture. This restores electron transport chain supercomplex organization, improving electron transfer efficiency, reducing electron leak, and increasing ATP production.

2.3 ROS Reduction

Stabilization of the electron transport chain reduces electron leak to oxygen, dramatically decreasing superoxide and hydrogen peroxide generation. This breaks the vicious cycle of oxidative stress → mitochondrial damage → increased ROS → further damage.

3. Clinical Applications (Investigational)

Indication	Trial	Key Finding
Heart Failure with Reduced EF	MMAD Trial (Phase 2)	Improved 6-minute walk test; favorable cardiac remodeling markers
Primary Mitochondrial Myopathy	MMPOWER-3 (Phase 2)	Improved walk test distance; improved fatigue measures
Mitochondrial Dysfunction	Multiple Phase 2	Well-tolerated across disease populations
Age-related bioenergetic decline	Investigational	Preclinical evidence of mitochondrial rejuvenation

4. Administration Protocol

Parameter	Details
Route	Subcutaneous injection
Frequency	Once daily
Typical Sites	Abdomen or thigh (rotate)
Investigational Dosing	10–40 mg once daily (trial-dependent)
Setting	Clinical or supervised; no hospital requirement in Phase 2

5. Safety Profile

5.1 Contraindications

- Pregnancy or breastfeeding
- Known hypersensitivity to elamipretide or components

5.2 Adverse Events (Phase 2 Trial Data)

- Injection site reactions: pain, erythema, induration (most common)
- Headache (uncommon)
- Nausea (uncommon)
- No major organ toxicity or serious adverse events attributed to study drug in completed trials

5.3 Drug Interactions

No major pharmacokinetic drug interactions reported in clinical trials to date. Mechanism of action (mitochondrial membrane targeting) does not involve cytochrome P450 pathways.

6. Reference Sources

1. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Br J Pharmacol. 2014; PMID: 24117398.

2. Butler J, et al. Effects of elamipretide on left ventricular function in patients with heart failure. JACC Heart Fail. 2020; PMID: 32035882.

3. Karaa A, et al. Elamipretide in patients with primary mitochondrial myopathy. Neurology. 2018; PMID: 29572380.

CLINICAL REFERENCE MONOGRAPH

ARA-290

(Cibinetide)

The Tissue-Protective EPO Mimetic

Neuropathy · IRR Activation · Sarcoidosis · Metabolic · Safety Profile

1. Overview

ARA-290 (Cibinetide) is a synthetic 11-amino acid peptide modeled after the helix-B surface domain of erythropoietin (EPO). It was engineered specifically to activate tissue-protective pathways without stimulating red blood cell production—addressing the major limitation of EPO therapy. It holds Orphan Drug Designation and Fast Track status for sarcoidosis-associated small fiber neuropathy.

Parameter	Details
Name	ARA-290 (Cibinetide)
Category	Tissue-Protective EPO Mimetic / Neuroprotective Peptide
Target Receptor	Innate Repair Receptor (IRR: EPOR + βc/CD131 heteromer)
IV Half-Life	1.1–2.3 minutes
SC Half-Life	17–27 minutes
SC Bioavailability	11–25% relative to IV
Regulatory Status	Orphan Drug Designation + Fast Track (sarcoidosis); Investigational

2. Mechanism of Action

2.1 The Innate Repair Receptor (IRR)

ARA-290 selectively binds the IRR—a heteromeric receptor composed of one EPOR subunit and one beta-common receptor subunit (βc/CD131). Unlike the homodimeric EPO receptor on bone marrow cells, the IRR is upregulated in injured tissues during stress or inflammation, enabling targeted tissue-protective signaling.

2.2 Key Signaling Pathways

- **JAK2/STAT3 Axis:** Promotes neurotrophic factor expression and anti-apoptotic genes.
- **NF-κB Inhibition:** Suppresses pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6).
- **TRPV1 Antagonism:** Provides direct pain relief by blocking nociceptive channels.

Despite rapid clearance, biological effects persist hours to days via a "hit-and-run" agonist mechanism.

3. Clinical Trial Data

3.1 Sarcoidosis-Associated Small Fiber Neuropathy (Phase 2b)

Parameter	Result
Protocol	4 mg daily SC for 28 days

Parameter	Result
Corneal Nerve Fiber Density (CNFD)	~23% increase from baseline
SFNSL Score	Significant improvement
6-Minute Walk Test	Significant increase in distance

3.2 Type 2 Diabetes Neuropathy (Phase 2)

Parameter	Result
Protocol	4 mg daily SC for 28 days + 28-day observation
HbA1c & Lipids	Improved; effects persisting post-treatment
Neuropathic Pain	Significant reduction (PainDetect questionnaire)

4. EPO vs. ARA-290 Comparison

Feature	rhEPO	ARA-290
Primary Target	Bone marrow (EPOR homodimer)	Injured tissue (IRR heteromer)
RBC Effect	Stimulates production	None
Thrombotic Risk	High	Low
rtPA Safety	Contraindicated	Safe (no increased hemorrhage)
Clinical Status	Approved (anemia)	Investigational (Orphan Drug)

5. Safety Profile

5.1 Hematological Safety

No evidence of erythropoiesis observed across all trials, even at 8 mg daily. No drug-related thrombotic events reported—a critical safety advantage over EPO therapy. No anti-ARA-290 antibodies detected in clinical studies.

5.2 Adverse Events

- Mild injection site reactions (pain, erythema, pruritus)
- Transient systemic symptoms (nausea, headache, fatigue)
- Possible Herxheimer-like reaction during initial administration days

5.3 Absolute Contraindication

Active malignancy: Tumors expressing the IRR could theoretically gain anti-apoptotic signaling. All clinical trials excluded patients with cancer within 5 years.

6. Reference Sources

1. Brines M, et al. Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor. Proc Natl Acad Sci USA. 2004; PMID: 15277674.

2. Dahan A, et al. Safety and efficacy of ARA-290 in sarcoidosis patients with small fiber neuropathy. Mol Med. 2013; PMID: 23868317.

3. Ziegler D, et al. ARA-290 in type 2 diabetes peripheral neuropathy. Diabetes Care. 2015; PMID: 25855301.

CLINICAL REFERENCE MONOGRAPH

KPV

(Lys-Pro-Val)

The Alpha-MSH Anti-Inflammatory Fragment

NF-κB Inhibition · IBD Research · Dermatology · Antimicrobial · Safety Profile

1. Overview

KPV is a tripeptide derived from amino acids 11–13 of alpha-melanocyte-stimulating hormone (α-MSH), itself derived from pro-opiomelanocortin (POMC). It retains the parent hormone's immune-modulating and anti-inflammatory properties while minimizing the pigmentation effects associated with full-length α-MSH. It is positioned as an emerging investigational therapeutic for inflammatory and infectious conditions.

Parameter	Details
Name	KPV (Lysine-Proline-Valine)
Sequence	α-MSH fragment (positions 11–13)
Category	Healing & Recovery / Anti-Inflammatory Peptide
Example Strength	10 mg vial
Reference Range	200–500 mcg daily (investigational)
Frequency	Once daily
Route	Subcutaneous
Key Warning	Not FDA-approved for systemic injectable use

2. Mechanisms of Action

2.1 NF-κB Pathway Inhibition

KPV competes for binding sites on Importin-α3, blocking nuclear translocation of NF-κB and suppressing the expression of pro-inflammatory genes. This is the primary anti-inflammatory mechanism underlying its therapeutic potential.

2.2 PepT1 Transporter System

KPV utilizes the H+-coupled oligopeptide transporter 1 (PepT1) for active cellular uptake. This transporter is upregulated in inflamed colonic tissue, creating an inherent disease-targeted delivery advantage for inflammatory bowel conditions.

2.3 MC1R Receptor Activation

As an α-MSH fragment, KPV binds melanocortin 1 receptors (MC1R) on immune and skin cells, triggering cAMP elevation—a signal that suppresses inflammatory responses.

2.4 Antimicrobial Activity

KPV disrupts fungal signaling, particularly in Candida albicans, by elevating intracellular cAMP and preventing the transition from yeast to invasive hyphal forms.

3. Investigational Indications

Indication Area	Proposed Mechanism / Status
Inflammatory Bowel Disease	NF-κB inhibition; PepT1-targeted delivery; preclinical
Psoriasis	IL-8, IL-23, IL-17 suppression via NF-κB modulation
Wound Healing	Inflammatory control + tissue regeneration support
Vitiligo	MC1R activation stimulates melanocyte pigment production
Vaginal Candidiasis	cAMP elevation inhibits hyphal transition; Phase 1/2a
Respiratory Inflammation	Importin-α3-dependent TNF-α reduction in bronchial cells

4. Administration Protocol

Parameter	Details
Route	Subcutaneous
Injection Site	Abdomen
Frequency	Once daily
Timing	Any time of day
Reference Range	200–500 mcg daily

5. Reconstitution Reference

A 10 mg vial + 2 mL bacteriostatic water yields 5 mg/mL (5,000 mcg/mL). Stability: up to 28 days refrigerated at 2–8°C.

Volume	Insulin Units	Dose
0.04 mL	4 units	200 mcg
0.06 mL	6 units	300 mcg
0.08 mL	8 units	400 mcg
0.10 mL	10 units	500 mcg

6. Safety Profile

6.1 Contraindications

- Pregnancy or breastfeeding
- Known hypersensitivity to any component

6.2 Adverse Events

- Injection site reactions (redness, mild irritation)
- Mild gastrointestinal upset (uncommon)
- Local hypersensitivity in transdermal applications

6.3 Potential Concerns

- Theoretical risk of incomplete pathogen clearance if antimicrobial activity insufficient
- Possible anti-drug antibody formation with prolonged synthetic dimer use
- Drug interactions: potential additive immunomodulatory effects with immunosuppressants

7. Reference Sources

1. Catania A, et al. Alpha-MSH in systemic inflammation. Front Neuroendocrinol. 2004; PMID: 15380241.

2. Brzoska T, et al. Alpha-MSH and melanocortin receptors: Mechanisms of anti-inflammatory action. Ann N Y Acad Sci. 2008; PMID: 18991866.

3. Shah NB, et al. Nanoparticle KPV delivery for colitis. Biomaterials. 2012; PMID: 22197566.

CLINICAL REFERENCE MONOGRAPH

LL-37

(Human Cathelicidin AMP)

Humanity's Singular Cathelicidin Peptide

Antimicrobial · Wound Healing · Immunomodulation · Biofilm Disruption · Safety Profile

1. Overview

LL-37 is humanity's only cathelicidin antimicrobial peptide, encoded by the CAMP gene on chromosome 3. Unlike other mammals that possess multiple cathelicidin variants, humans depend exclusively on this molecule for a broad spectrum of immune defense, wound healing, and regenerative signaling. It exhibits concentration-dependent effects: protective at appropriate levels but pathogenic when overexpressed in conditions such as psoriasis and lupus.

Parameter	Details
Name	LL-37 (Human Cathelicidin / hCAP18 C-terminal fragment)
Sequence	NH_2-LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES-COOH
Amino Acids	37 amino acids; ~4.5 kDa
Net Charge	Positive (+6 at physiological pH)
Structure	Amphipathic α-helix upon membrane contact
Reference Range	50–200 mcg daily (investigational SC)
Key Warning	Potent immunomodulatory; may exacerbate inflammatory/autoimmune activity

2. Biogenesis

The inactive precursor hCAP18 (18 kDa) undergoes proteolytic cleavage by tissue-specific enzymes to yield active LL-37. In neutrophils, Proteinase 3 mediates activation. In skin, Kallikrein 5 and 7 catalyze release. Alternative fragments such as KR-12 retain antimicrobial activity with reduced host cell toxicity.

3. Mechanisms of Action

3.1 Direct Antimicrobial Activity

- **Bacteria:** Disrupts gram-positive and gram-negative cell membranes; effective against multidrug-resistant strains.
- **Fungi:** Targets Candida albicans through membrane disruption and calcium dysregulation.
- **Viruses:** Neutralizes enveloped viruses (influenza, HIV, RSV); blocks SARS-CoV-2 entry.
- **Biofilms:** Prevents bacterial attachment and eradicates established biofilm structures.

3.2 Immunomodulatory Receptor Engagement

Receptor	Cell Type	Effect
FPRL1/FPR2	Phagocytes, lymphocytes	Chemotaxis; angiogenesis

Receptor	Cell Type	Effect
P2X7	Immune cells	Autophagy; cytokine release
EGFR	Epithelial cells	Proliferation; wound healing
TLR4	Macrophages	Anti-inflammatory (LPS neutralization)
TLR9/7/8	Dendritic cells	Pro-inflammatory (self-nucleic acid activation)

4. Wound Healing & Clinical Evidence

LL-37 stimulates keratinocyte migration and proliferation via EGFR transactivation and induces angiogenesis independent of VEGF.

Trial	Protocol	Outcome
Venous Leg Ulcers	Topical 0.5–1.6 mg/mL	6-fold and 3-fold higher healing rates vs. placebo
Diabetic Foot Ulcers	Topical application	Enhanced healing via increased granulation index
Dose-Response Note	3.2 mg/mL showed no benefit	Biphasic dose-response curve; higher ≠ better

5. Pathogenic Roles (Disease Contexts)

Condition	LL-37 Status	Mechanism
Psoriasis	Overexpressed	Self-DNA complexation; TLR9/7/8 activation; type I interferon loop
Lupus (SLE)	Overexpressed (NETs)	Autoantigen formation; breach of immune tolerance
Atherosclerosis	Elevated systemic	Promotes LDL uptake; foam cell formation
Cancer (ovarian/lung)	Overexpressed	Growth factor signaling via EGFR/ErbB2
Cancer (colorectal)	Downregulated	Tumor suppressive via caspase-independent apoptosis

6. Administration Protocol

Parameter	Details
Route	Subcutaneous injection
Frequency	Once daily

Parameter	Details
Titration	Weeks 1–2: 50–100 mcg; Weeks 3+: 100–200 mcg
Caution	May exacerbate inflammatory flares; contraindicated in active autoimmune disease

7. Safety Profile

7.1 Contraindications

- Pregnancy or breastfeeding
- Active autoimmune or inflammatory disorders

7.2 Adverse Events

- Injection site reactions (redness, mild swelling)
- Transient flu-like symptoms and fatigue
- Inflammatory flare patterns in susceptible individuals
- Theoretical autoimmune activation

8. Reference Sources

1. Zanetti M. Cathelicidins, multifunctional peptides of the innate immunity. J Leukoc Biol. 2004; PMID: 14726498.

2. Ramos R, et al. Wound healing activity of LL-37. J Invest Dermatol. 2011; PMID: 21544283.

3. Heilborn JD, et al. The cathelicidin anti-microbial peptide LL-37 is involved in re-epithelialization. J Invest Dermatol. 2003; PMID: 12708249.

DISCLAIMER: *LL-37 is not FDA-approved for systemic injectable use. This monograph provides educational content only and does not constitute medical advice, diagnosis, or treatment recommendations. Due to its potent immunomodulatory activity, clinical supervision is essential.*

CLINICAL REFERENCE MONOGRAPH

Thymosin Alpha-1

(TA-1 / Zadaxin®)

The Thymic Immune Modulating Peptide

T-Cell Maturation · Hepatitis B/C · Immune Enhancement · Antiviral · Safety Profile

1. Overview

Thymosin Alpha-1 (TA-1) is a naturally occurring 28-amino acid peptide derived from thymosin fraction 5, originally isolated from thymic tissue. It functions as a primary regulator of T-cell maturation and adaptive immune response. Marketed as Zadaxin®, it is approved in over 35 countries for hepatitis B, hepatitis C, and as an immunological adjuvant for vaccines—though not FDA-approved in the United States. Its immunomodulatory properties have driven investigational interest across oncology, infectious disease, and immune deficiency contexts.

Parameter	Details
Name	Thymosin Alpha-1 (TA-1)
Brand Name	Zadaxin® (approved in 35+ countries; not FDA-approved in USA)
Source	Synthetic; originally isolated from thymic tissue
Category	Immune Modulating Peptide / Thymic Hormone Analog
Reference Dose	1.6 mg subcutaneously, 2–3 times weekly
Route	Subcutaneous injection
Key Warning	Significant immunosuppressant interaction; contraindicated in organ transplant recipients on immunosuppression

2. Mechanism of Action

2.1 T-Cell Maturation Enhancement

TA-1 augments thymic processing and T-cell maturation via Toll-like receptor 9 (TLR9) signaling in dendritic cells and direct stimulation of T-cell precursors. This restores T-lymphocyte-mediated immune surveillance in immunocompromised and immunosenescent states.

2.2 Cytokine Network Modulation

- Increases IL-2 production and IL-2 receptor expression on T cells
- Enhances interferon-α and IFN-γ production, supporting antiviral immune responses
- Upregulates MHC class I and II expression on dendritic cells, improving antigen presentation
- Promotes Th1 immune polarization (cellular immunity) for viral clearance

2.3 NK Cell Activation

TA-1 enhances natural killer (NK) cell cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC), providing broad innate immune enhancement complementary to its adaptive effects.

3. Clinical Applications

Indication	Status	Evidence
Hepatitis B (chronic)	Approved (Zadaxin®) in 35+ countries	Multiple Phase 3 RCTs; improved seroconversion rates
Hepatitis C	Approved (combo with interferon)	Phase 3 data supporting combination therapy
Vaccine adjuvant	Approved uses in some countries	Improved vaccine immunogenicity in elderly
Oncology (adjuvant)	Investigational	Phase 2 data in melanoma, hepatocellular carcinoma
COVID-19 / Sepsis	Investigational	Phase 2/3 survival benefit in Chinese trials

4. Administration Protocol

Parameter	Details
Route	Subcutaneous injection
Frequency	2–3 times weekly
Sites	Abdomen or thigh
Reference Dose	1.6 mg per injection
Timing	Flexible; consistency in schedule is important

5. Safety Profile

5.1 Contraindications

- Organ transplant recipients on immunosuppressive therapy (TA-1 immune stimulation will oppose immunosuppression)
- Pregnancy or breastfeeding

5.2 Adverse Events

- Injection site reactions (redness, mild swelling; most common)
- Fatigue and mild flu-like symptoms (immune activation response)
- Rare: autoimmune exacerbation in predisposed individuals

5.3 Drug Interactions

- **Immunosuppressants:** Significant antagonism; concurrent use will reduce immunosuppressant efficacy and risk transplant rejection.

- **Corticosteroids:** May blunt TA-1 immune stimulation.

6. Monitoring Parameters

- T-cell counts (CD4/CD8 ratio where clinically indicated)
- Viral load assessment in hepatitis patients
- General immune function markers and liver function tests

7. Reference Sources

1. Garaci E, et al. Thymosin alpha 1 in the treatment of cancer: from basic research to clinical application. Int J Immunopharmacol. 2000; PMID: 10714998.

2. King R, et al. Thymosin alpha-1 for treatment of chronic hepatitis B. Expert Rev Anti Infect Ther. 2010; PMID: 20377335.

3. Liu F, et al. Thymosin alpha-1 in COVID-19 patients. Clin Immunol. 2020; PMID: 32544665.

CLINICAL REFERENCE MONOGRAPH

Epitalon

(Ala-Glu-Asp-Gly)

The Telomerase-Activating Longevity Tetrapeptide

Telomere Biology · Pineal Modulation · Antioxidant · Circadian · Safety Profile

1. Overview

Epitalon (Epithalon) is a synthetic tetrapeptide (Ala-Glu-Asp-Gly) originally derived from the pineal peptide extract Epithalamin, developed by Professor Vladimir Khavinson at the St. Petersburg Institute of Bioregulation and Gerontology. It is the most studied peptide in the Khavinson bioregulator series and the only one with published data specifically addressing telomerase activation and telomere elongation in human somatic cells—a landmark finding in longevity research.

Parameter	Details
Name	Epitalon (Epithalon)
Reference Code	EPIT
Sequence	Ala-Glu-Asp-Gly (tetrapeptide)
Category	Longevity / Pineal Bioregulator / Telomerase Activator
Reference Range	5 mg daily for 10–20 day cycles
Route	Subcutaneous (most common); IM and IV in research contexts
Frequency	Once daily during defined cycles
Key Warning	Contraindicated in active malignancy (theoretical telomerase activation concern)

2. Mechanisms of Action

2.1 Telomerase Activation

Epitalon has been shown in vitro and in cell culture studies to upregulate hTERT (human telomerase reverse transcriptase) expression, increasing telomerase enzyme activity in human somatic cells. In a landmark 2003 study (Khavinson et al.), Epitalon increased telomerase activity in human fetal fibroblasts and elongated telomeres in aged cells—the first demonstration of pharmacological telomere extension in human cells.

2.2 Pineal Gland Modulation

As a pineal-derived peptide, Epitalon modulates melatonin synthesis and secretion. Declining melatonin with age is associated with impaired circadian rhythms, reduced antioxidant defense, and accelerated aging. Epitalon partially restores melatonin production in aged individuals and animal models.

2.3 Antioxidant Activity

Epitalon reduces oxidative stress markers including lipid peroxidation products (MDA) and increases superoxide dismutase (SOD) activity in animal studies. This antioxidant protection is proposed as an additional anti-aging mechanism.

2.4 Epigenetic & Gene Expression Effects

Consistent with the Khavinson bioregulator theory, Epitalon is proposed to interact with DNA promoter regions of specific genes, modulating age-related changes in gene expression profiles related to cell cycle regulation and stress response.

3. Administration Parameters

Parameter	Details
Route	Subcutaneous (most common); IM and IV in research contexts
Frequency	Once daily during defined cycle
Cycle Length	10–20 day cycles (per published human studies)
Reference Dose	5 mg per injection
Timing	Evening administration (circadian interaction)
Stability	Up to 28 days refrigerated after reconstitution

4. Reconstitution Reference

Standard target concentration: 5 mg/mL. A 10 mg vial + 2 mL bacteriostatic water yields 5 mg/mL; 0.10 mL (10 units) = 0.5 mg. For 5 mg dose: 1.0 mL (100 units).

5. Published Human Research

Khavinson VK and colleagues published multiple human studies at the St. Petersburg Institute demonstrating:

- Increased telomerase activity and telomere length in aged human somatic cells in vitro
- Reduced incidence of age-related retinal degeneration in patients over 60 (10-year follow-up)
- Improved circadian melatonin profiles and sleep architecture in elderly subjects
- Reduced all-cause mortality in elderly cohorts vs. controls in observational studies

6. Safety Profile

6.1 Contraindications

- Active malignancy or recent cancer history (theoretical concern: telomerase overactivation in cancer cells)
- Pregnancy or breastfeeding
- Known hypersensitivity to peptide components

6.2 Adverse Events

Generally well-tolerated in published human studies with no significant adverse events reported at standard 5 mg/day dosing. Reported adverse effects are minimal:

- Injection site reactions (mild, transient)
- Headache (uncommon)
- Drowsiness (uncommon)

7. Reference Sources

1. Khavinson VK, et al. Peptide Ala-Glu-Asp-Gly induces telomerase activity and telomere elongation in human somatic cells. Bull Exp Biol Med. 2003; PMID: 12640523.

2. Khavinson VK, Morozov VG. Peptides of pineal gland and thymus prolong human life. Neuro Endocrinol Lett. 2003; PMID: 14730303.

3. Anisimov VN, et al. Effect of Epitalon on biomarkers of aging in rats. Exp Gerontol. 2010; PMID: 21146590.

DISCLAIMER: *Epitalon is not FDA-approved. While peer-reviewed human studies exist, the evidence base is predominantly from one research group. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

FOXO4-DRI

(Senolytic Peptide)

The Targeted Senescent Cell Eliminator

Senolysis · p53 Pathway · Aging & Frailty · Organ Protection · Safety Profile

1. Overview

FOXO4-DRI is a senolytic peptide engineered to selectively eliminate senescent cells—cells that have ceased dividing but remain metabolically active, secreting pro-inflammatory factors (the SASP: senescence-associated secretory phenotype). It represents a breakthrough approach in geroscience, targeting a root mechanism of biological aging rather than its downstream symptoms.

Parameter	Details
Name	FOXO4-DRI (D-Retro-Inverso Peptide)
Design	Mirror-image D-amino acids in reversed sequence; protease-resistant
Target Mechanism	FOXO4-p53 axis disruption; selective pro-apoptotic signaling in senescent cells
Evidence Base	Preclinical only; no peer-reviewed human clinical trial data
Primary Warning	p53 modulation carries substantial risk; no human safety data available
Regulatory Status	Not FDA-approved; experimental research compound only

2. Mechanism of Action

2.1 The FOXO4-p53 Axis in Senescent Cells

Senescent cells overexpress FOXO4, which binds and sequesters p53 in the cell nucleus, preventing it from triggering apoptosis. This allows senescent cells to survive indefinitely despite harboring damage, accumulating in tissues over time and driving chronic inflammation.

2.2 Competitive Inhibition by FOXO4-DRI

FOXO4-DRI is engineered as a D-Retro-Inverso peptide constructed from mirror-image amino acids in reversed sequence, dramatically increasing resistance to enzymatic degradation. The peptide enters cells and competitively binds p53, displacing endogenous FOXO4 and liberating p53's pro-apoptotic function, leading to selective elimination of senescent cells while sparing healthy cells.

3. Preclinical Evidence Summary

Research Area	Key Finding	Potential Application
Systemic Aging	Doubled running distance; restored fur density in aged mice	Reversal of age-related frailty
Kidney Function	Restored renal filtering capacity	Chronic kidney disease

Research Area	Key Finding	Potential Application
Liver Protection	Neutralized chemotherapy-induced damage	Adjuvant during cancer treatment
Osteoarthritis	Removed >50% senescent chondrocytes	Enhanced joint repair
Hypogonadism	Increased serum testosterone in aged mice	Age-related testosterone deficiency
Pulmonary Fibrosis	Reduced collagen deposition in lungs	Idiopathic pulmonary fibrosis

4. Critical Safety Concerns

4.1 Theoretical Risks

- **Impaired Beneficial Senescence:** Acute senescence is essential for wound healing and tumor suppression; systemic elimination could interfere.
- **p53 Pathway Modulation:** Any unintended interaction with p53 in healthy cells risks severe consequences including unwanted apoptosis.
- **Immune Overwhelm:** Rapid clearance of numerous senescent cells could saturate immune clearance capacity.

4.2 Absolute Contraindications

- Active malignancy or recent cancer history
- Pregnancy or breastfeeding
- Autoimmune conditions (immune activation risk)
- Post-surgical or active wound healing states

5. Translational Status & Barriers

No peer-reviewed human clinical trial data exists. All evidence derives from animal models, which frequently fail to predict human outcomes. Key barriers include high manufacturing costs for complex D-amino acid peptide synthesis, the need for reliable biomarkers to identify senescent cell burden in individuals, and the requirement for combination strategies pairing senolytic with pro-regenerative agents.

6. Most Promising Investigational Indications

- Chronic kidney disease
- Chemotherapy-induced organ damage (adjuvant oncology)
- Osteoarthritis and cartilage degeneration
- Male late-onset hypogonadism

- Idiopathic pulmonary fibrosis

7. Reference Sources

1. Baar MP, et al. Targeted apoptosis of senescent cells restores tissue homeostasis. Cell. 2017; PMID: 28340339.

2. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020; PMID: 32686219.

CLINICAL REFERENCE MONOGRAPH

MOTS-c

(Mitochondrial-Derived Peptide)

The Mitokine Metabolic Regulator

AMPK Activation · Metabolic Health · Muscle & Bone · Neuroprotection · Safety Profile

1. Overview

MOTS-c is a 16-amino acid mitochondrial-derived peptide encoded by a short open reading frame within the 12S rRNA gene. Described as a "mitokine," it functions as a hormone-like signaling molecule that orchestrates metabolic adaptations. Circulating endogenous MOTS-c declines with age and increases post-exercise, suggesting a role in the molecular mechanisms underlying exercise benefits.

Parameter	Details
Name	MOTS-c (Mitochondrial Open Reading Frame of the 12S rRNA-c)
Amino Acids	16-amino acid peptide
Category	Mitochondrial-Derived Peptide / Mitokine
Regulatory Status	FDA prohibits compounding; WADA banned (performance-enhancing)
Anecdotal Reference Range	5–10 mg subcutaneous weekly or pre-exercise
Key Warning	Active malignancy contraindicated; oncology paradox (tumor-suppressive in some, risk in others)

2. Mechanisms of Action

2.1 Primary: Folate-AICAR-AMPK Axis

MOTS-c inhibits the folate cycle, causing accumulation of AICAR (5-aminoimidazole-4-carboxamide ribonucleotide). AICAR acts as an AMPK agonist, activating the cell's master metabolic sensor without actual energy depletion—effectively creating perceived metabolic stress and triggering downstream adaptive responses.

2.2 Secondary Pathways

- **Nuclear translocation:** Targets ARE elements for NRF2-mediated antioxidant gene expression.
- **Myostatin inhibition:** Via CK2-PTEN-AKT-FOXO1 cascade, promoting muscle growth and preventing atrophy.
- **Thermogenic effects:** Promotes brown adipose tissue activation.

3. Physiological Effects (Animal Models)

Effect	Outcome
Weight Management	Prevents lipid accumulation despite high-fat diet
Muscle	Exercise mimetic; prevents atrophy via myostatin

Effect	Outcome
	suppression
Bone	Dual anabolic effects on osteoblasts and osteoclasts
Cardiovascular	Repairs mitochondrial dysfunction in diabetic cardiomyopathy
Neuroprotection	Reduces traumatic brain injury via MIF downregulation

4. Human Clinical Evidence

CB4211 Trial (Phase 1a/1b): A stabilized MOTS-c analog in obese subjects with NAFLD demonstrated:

- ALT reduction: 21%
- AST reduction: 28%
- Fasting glucose reduction: 6%
- Tolerability: Well-tolerated with mild injection site reactions

5. Administration Reference

Parameter	Details
Route	Subcutaneous injection
Anecdotal Protocol	5–10 mg weekly or pre-exercise
Reported Effects	Enhanced aerobic capacity, visceral fat loss, thermogenic sensation
Adverse (Anecdotal)	Injection site irritation ("MOTS-c burn"), insomnia, jitteriness

6. Safety Profile

6.1 Contraindications

- Active malignancy (oncogenic paradox—tumor-suppressive in some cancers, risk in others)
- Pregnancy or lactation
- Insulin-dependent diabetes (hypoglycemia risk)

6.2 Key Safety Concerns

- **Immunogenicity risk:** Anti-drug antibodies could neutralize endogenous MOTS-c, potentially causing permanent metabolic deficiency.
- **Oncology paradox:** Tumor-suppressive in ovarian cancer (LARS1 targeting) but potential risk in certain other malignancies.

7. Investigational Future Applications

- Sarcopenic obesity treatment (dual fat-loss, muscle-sparing potential)
- Exercise mimetic for immobilized or elderly patients
- Adjunct to GLP-1 agonists for preserved lean mass during weight loss

8. Reference Sources

1. Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; PMID: 25738459.

2. Reynolds JC, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator. Nat Commun. 2021; PMID: 34301943.

CLINICAL REFERENCE MONOGRAPH

Glutathione

(GSH — Reduced)

The Body's Master Antioxidant — Injectable Reference

Redox Balance · Detoxification · IV/IM Administration · Skin · Safety Profile

1. Overview

Glutathione (GSH) is a tripeptide (L-glutamate + L-cysteine + glycine) and the most abundant endogenous antioxidant in mammalian cells, with intracellular concentrations of 1–10 mM. Injectable glutathione bypasses the near-zero oral bioavailability caused by GI degradation, achieving direct systemic delivery. Standard oral GSH achieves <1% systemic absorption; IV/IM formulations provide clinically meaningful plasma elevation. This reference guide covers the injectable formulation used in clinical settings.

Parameter	Details
Name	Glutathione (Reduced GSH)
Reference Code	GSH
Composition	L-glutamate + L-cysteine + glycine (tripeptide)
Injectable Strength	1,500 mg vial (manufacturer-dependent)
Reference Range	600–2,000 mg per injection, 1–3x weekly
Route	IV push or IM injection
Plasma Half-Life	~10 minutes (rapid cellular uptake)
Key Warning	Unstable after reconstitution; use within 24 hours; caution in oncology settings

2. Mechanism of Action

2.1 Direct Antioxidant Action

The cysteine thiol (-SH) group directly neutralizes reactive oxygen species (ROS) and reactive nitrogen species (RNS) through electron donation. The GSH/GSSG ratio (reduced:oxidized) serves as a sensitive barometer of cellular oxidative stress status; healthy cells maintain a ratio >100:1.

2.2 Phase II Liver Detoxification

Glutathione S-transferases (GSTs) conjugate GSH to electrophilic compounds, xenobiotics, and drug metabolites, facilitating their excretion. This is the primary mechanism supporting injectable GSH in detoxification protocols.

2.3 Mitochondrial Function

10–15% of cellular GSH resides in mitochondria (imported from cytosol; mitochondria cannot synthesize their own). Mitochondrial GSH depletion is an early event in many degenerative conditions and is the target of injectable GSH in mitochondrial support frameworks.

2.4 Immune Modulation

GSH is required for optimal lymphocyte proliferation and NK cell cytotoxicity. Immune cells have among the highest GSH requirements of any tissue, supporting injectable GSH use in immune support protocols.

3. Clinical Indications (Investigational / Off-Label)

Indication	Evidence Level
Antioxidant and redox support	Pharmacologically supported; clinical data variable
Hepatic detoxification support	Mechanistically sound; formal RCT data limited
Parkinson's disease (intranasal/IV)	Phase 2 signal; strong placebo response confounds interpretation
Peripheral neuropathy (cisplatin)	Most robust indication; reduces chemotherapy neurotoxicity
Skin brightening / melanin reduction	Phase 2 data; IV carries serious risks (anaphylaxis, SJS)

4. Administration Protocol

Parameter	Details
Route	IV push (primary) or IM injection
Rate	Slow IV push over 5–10 minutes (never rapid bolus)
Frequency	1–3 times weekly
Dose Range	600–2,000 mg per session
Loading	600–1,500 mg, 2–3x weekly for weeks 1–2
Maintenance	600–1,500 mg, 1–3x weekly
Setting	Clinical IV setting; vital sign monitoring recommended

5. Reconstitution & Stability

Diluent: Sterile water or normal saline. Typical concentration: ~200 mg/mL. Stability: use within 24 hours when refrigerated (protect from light). Unlike stable peptides, GSH oxidizes rapidly after reconstitution.

Volume (at 200 mg/mL)	Dose
1 mL	200 mg
3 mL	600 mg
6 mL	1,200 mg
10 mL	2,000 mg

6. Safety Profile

6.1 Contraindications

- Known hypersensitivity to glutathione
- Pregnancy or breastfeeding (limited safety data)

6.2 Adverse Events

- Injection site reactions (IV site phlebitis; IM soreness)
- Bloating and abdominal cramping (uncommon)
- Zinc deficiency with prolonged high-dose use (GSH chelates zinc)
- Allergic reactions (rare)

6.3 Serious Risks (IV for Skin Lightening)

FDA issued a 2019 alert documenting seven cases of severe adverse reactions linked to potentially contaminated compounded injectable glutathione products, including anaphylaxis, acute kidney injury, hepatotoxicity, and Stevens-Johnson Syndrome. IV glutathione for cosmetic skin lightening is explicitly not FDA-approved.

6.4 Oncology Caution

Glutathione is a substrate for GSTs involved in chemotherapy drug detoxification. High-dose GSH may theoretically reduce the efficacy of certain chemotherapy regimens. Oncologist consultation is essential before any injectable GSH use in cancer patients.

7. Reference Sources

1. Pompella A, et al. The changing faces of glutathione, a cellular protagonist. Biochem Pharmacol. 2003; PMID: 14505762.

2. Townsend DM, et al. The importance of glutathione in human disease. Biomed Pharmacother. 2003; PMID: 14652165.

3. Perricone C, et al. Glutathione: a key player in autoimmunity. Autoimmun Rev. 2009; PMID: 19095071.

DISCLAIMER: *Injectable glutathione is not FDA-approved for skin lightening, anti-aging, or detoxification claims. The 2019 FDA alert documented severe adverse reactions with compounded injectable forms. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

VIP

(Vasoactive Intestinal Peptide)

The Pleiotropic Neuro-Immune-Endocrine Peptide

PAH · ARDS · Immunomodulation · Circadian · CIRS · Safety Profile

1. Overview

VIP (Vasoactive Intestinal Peptide) is a 28-amino acid neuropeptide belonging to the secretin/glucagon superfamily, remarkably conserved across mammals. It functions as a master neuro-immune-endocrine mediator with roles spanning pulmonary vasodilation, gastrointestinal regulation, circadian rhythm synchronization, immune Th1/Th2 balance, and neuroprotection. Synthetic VIP (Aviptadil) is in clinical development for pulmonary arterial hypertension (PAH) and ARDS.

Parameter	Details
Name	VIP (Vasoactive Intestinal Peptide)
Synthetic Form	Aviptadil (inhaled or IV)
Molecular Weight	~3,326 Daltons (28 amino acids)
Plasma Half-Life	1–2 minutes (rapid hepatic/pulmonary metabolism)
Receptors	VPAC1 (constitutive) and VPAC2 (inducible)
Primary Signal	cAMP-PKA pathway; NF-κB inhibition
Key Warning	Hypotension in ~25% ICU patients; migraine trigger; not for self-administration

2. Receptor Pharmacology

Receptor	Expression Pattern	Key Functions
VPAC1	Constitutive; resting immune cells; GI	Basal homeostasis; anti-inflammatory; GI regulation
VPAC2	Inducible; SCN; activated immune cells	Circadian synchronization; T-cell modulation; inflammation resolution

3. Mechanisms of Action

3.1 Pulmonary & Cardiovascular

- Potent pulmonary and systemic vasodilator via cAMP-mediated smooth muscle relaxation
- Reduces pulmonary vascular resistance; maintains low pulmonary artery pressure
- Antiproliferative effects on vascular smooth muscle cells, preventing vascular remodeling

3.2 Immune Modulation

- Promotes Th2 (anti-inflammatory) phenotype shift; suppresses Th1 (pro-inflammatory) responses

- Induces regulatory T cells (Tregs) producing IL-10 and TGF-β
- Inhibits TNF-α, IL-6, and NF-κB signaling

3.3 Neuroprotection & Circadian

- Upregulates Ikaros transcription factor; promotes CNS grey matter restoration
- Acts as primary synchronizing agent for SCN neuronal oscillators (circadian output)

4. Clinical Applications

Indication	Formulation	Phase	Key Finding
Pulmonary Arterial Hypertension	Inhaled Aviptadil	Phase 2	Reduced mPAP/PVR; improved cardiac output
COVID-19 ARDS	IV Aviptadil	Phase 2/3	Rapid PaO_2/FiO_2 improvement; radiographic clearance
COVID-19 ARDS	Inhaled Aviptadil	Phase 2	Shortened recovery; well-tolerated
Sarcoidosis	Inhaled Aviptadil	Phase 2	Reduced BAL TNF-α; increased Tregs

5. CIRS Protocol Role

In Chronic Inflammatory Response Syndrome (CIRS) treatment frameworks, VIP is the final restorative step after environmental removal, binder therapy, MARCoNS eradication, and biomarker normalization. Effects include transcriptomic reset addressing mitochondrial/ribosomal dysfunction, reversal of multinuclear grey matter atrophy, and immune system restoration.

6. Safety Profile

6.1 Contraindications

- Pregnancy and breastfeeding (safety not established)
- Active intracellular infections
- Uncontrolled hypotension or severe arrhythmias
- History of migraine or cluster headache (VIP is a potent migraine trigger)

6.2 Adverse Events

- **Hypotension:** ~25% in ICU settings; 10–15% in stable outpatients; rate-dependent.
- **Transient cutaneous flushing:** ~33.9% incidence.
- **Watery diarrhea:** ~30% from intestinal secretagogue effects.
- Tachycardia (possible with hypotensive response)

- **Migraine induction:** 71% of susceptible subjects in one provocation study.
- **Serum lipase elevation:** Often asymptomatic chemical pancreatitis without clinical inflammation.

7. Reference Sources

1. Said SI, Mutt V. Polypeptide with broad biological activity: isolation from small intestine. Science. 1970; PMID: 5477401.

2. Olschewski H, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002; PMID: 12440092.

3. Dickson RP, et al. Aviptadil in COVID-19 ARDS. Chest. 2023.

CLINICAL REFERENCE MONOGRAPH

PT-141

(Bremelanotide)

The Centrally-Acting Sexual Health Peptide

HSDD · Erectile Dysfunction · MC4R Agonism · Neurobiological Pathways · Safety Profile

1. Overview

PT-141 (Bremelanotide) is a cyclic heptapeptide melanocortin receptor agonist approved by the FDA as Vyleesi® for hypoactive sexual desire disorder (HSDD) in premenopausal women. It is the first centrally-acting pharmacological treatment for sexual dysfunction, operating via hypothalamic dopaminergic and oxytocinergic pathways rather than vascular mechanisms.

Parameter	Details
Brand Name	Vyleesi® (FDA-approved)
Molecular Weight	1,025.2 g/mol
Primary Mechanism	MC4R agonism in the hypothalamus
Route	Subcutaneous injection (FDA-approved)
Half-Life	~2.7 hours
Bioavailability	~100% (subcutaneous)
FDA-Approved Indication	HSDD in premenopausal women

2. Pharmacokinetics

- ~100% bioavailability following subcutaneous administration
- Peak plasma concentrations achieved within 0.5–1.0 hours post-injection
- Undergoes peptide hydrolysis rather than CYP450 metabolism (minimal drug-drug interactions)
- Half-life approximately 2.7 hours; duration of effect up to 12 hours reported

3. Neurobiological Mechanisms

CNS Region	Effect
Medial Preoptic Area (mPOA)	Stimulates dopamine release; governs sexual motivation and arousal
Paraventricular Nucleus (PVN)	Triggers oxytocin release for consummatory phase and partner bonding
Spinal Output	Initiates pro-erectile signals via pelvic nerves (males)

4. Clinical Efficacy

4.1 Female HSDD (FDA-Approved Indication)

The RECONNECT Phase 3 trials demonstrated statistically significant improvements in both desire and distress endpoints, leading to FDA approval in June 2019:

Endpoint	Result
FSFI-D Desire Domain Score	Mean increase of +0.35
FSDS-DAO Distress Score	Mean reduction of -0.33
Population	Premenopausal women with HSDD

4.2 Male Erectile Dysfunction (Investigational)

In sildenafil non-responders, 33.5% of the bremelanotide group reported positive clinical results versus 8.5% placebo. Evidence supports combination therapy with PDE5 inhibitors for treatment-refractory cases.

5. Dosing

Parameter	Details
FDA Label Dose	1.75 mg SC; max 1 dose per 24 hours; max 8 doses/month
Timing	45 minutes before anticipated sexual activity
Anecdotal Titration	0.5–2.0 mg; delayed peak effects 1–5 hours post-injection
Nausea Management	Consider sleep-dosing, hydration, or antihistamine co-administration

6. Safety Profile

6.1 Adverse Effects

Effect	Incidence	Notes
Nausea	~40%	Centrally mediated; often transient
Flushing	~20%	Related to sympathetic activation
Headache	~11%	Mild and typically self-limiting
Hyperpigmentation	~1%	Dose-dependent; potentially irreversible
Blood Pressure Increase	2–4 mmHg systolic	Peaks 2–4 hours post-injection

6.2 Contraindications

- Uncontrolled hypertension or cardiovascular disease
- Pregnancy

6.3 Critical Drug Interaction

Bremelanotide significantly slows gastric emptying, reducing naltrexone absorption. This is a clinically significant concern for patients on opioid-dependence treatment programs using naltrexone.

7. Reference Sources

1. Clayton AH, et al. Bremelanotide for female sexual dysfunctions: RECONNECT Phase 3 trials. Obstet Gynecol. 2016; PMID: 27741198.

2. Safarinejad MR. Evaluation of the safety and efficacy of bremelanotide in erectile dysfunction. J Urol. 2008; PMID: 18207179.

3. King SH, et al. Melanocortin receptors, melanotropic peptides and penile erection. Curr Top Med Chem. 2007; PMID: 17266596.

DISCLAIMER: *PT-141 (Bremelanotide / Vyleesi®) is FDA-approved only for HSDD in premenopausal women. Male use is investigational and off-label. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

Kisspeptin

(KISS1 / Metastin)

The HPG Axis Master Regulator

GnRH Stimulation · LH/FSH · Fertility · Hypogonadism · Safety Profile

1. Overview

Kisspeptin is an endogenous neuropeptide produced by KISS1 neurons in the hypothalamus that functions as the master upstream regulator of the hypothalamic-pituitary-gonadal (HPG) axis. It stimulates GnRH (gonadotropin-releasing hormone) release from the hypothalamus, which in turn triggers LH and FSH secretion from the pituitary—initiating the reproductive hormone cascade. Kisspeptin deficiency is established as a cause of hypogonadotropic hypogonadism. Multiple synthetic isoforms are under investigation for fertility and reproductive endocrinology applications.

Parameter	Details
Name	Kisspeptin (KISS1 / Metastin)
Reference Code	KISS
Endogenous Isoforms	Kisspeptin-54 (full length), -14, -13, -10 (active fragments)
Category	Reproductive Axis Peptide / GnRH Secretagogue
Half-Life	~27 minutes (kisspeptin-54); ~4 minutes (kisspeptin-10)
Route	Subcutaneous or intravenous
Response Time	LH/FSH response within hours
Key Warning	Research peptide; non-standardized dosing; contraindicated in hormone-sensitive cancers

2. Mechanism of Action

2.1 HPG Axis Activation

Kisspeptin binds KISS1R (GPR54) receptors on hypothalamic GnRH neurons, triggering GnRH pulse generation and release into the pituitary portal system. This stimulates LH and FSH secretion from anterior pituitary gonadotrophs, which in turn drives gonadal steroidogenesis (testosterone in men, estradiol in women) and gametogenesis.

2.2 Pulsatile vs. Continuous Signaling

Kisspeptin normally acts in a pulsatile pattern, coordinating GnRH pulse frequency with the ovarian cycle in women and maintaining tonic testosterone production in men. Continuous kisspeptin exposure causes receptor desensitization and paradoxical gonadotropin suppression—the same principle underlying GnRH agonist therapy for chemical castration.

2.3 Negative Feedback Integration

Kisspeptin neurons in the arcuate nucleus are direct targets of estrogen and testosterone negative feedback, making kisspeptin the critical integration point for gonadal steroid sensing in the brain.

3. Clinical Applications (Investigational)

Indication	Evidence Level	Notes
Hypogonadotropic hypogonadism	Phase 1/2 clinical trials	Effective LH/FSH stimulation; fertility restoration
Ovulation induction (IVF)	Phase 2 trials	Safer alternative to hCG trigger; reduced OHSS risk
Male hypogonadism	Phase 1/2 data	Testosterone and sperm production stimulation
Infertility (both sexes)	Clinical trials	LH/FSH surge induction for ART protocols
Hormonal optimization	Investigational	Off-label; research context only

4. Kisspeptin Isoforms

Isoform	Length	Half-Life	Relative Potency
Kisspeptin-54	54 amino acids	~27 minutes	Standard (full-length)
Kisspeptin-14	14 amino acids	Shorter	Active; used in research
Kisspeptin-10	10 amino acids	~4 minutes	Most studied; high receptor affinity
TAK-683 (analog)	Synthetic	Extended	Investigational long-acting analog

5. Administration Details

Parameter	Details
Route	Subcutaneous or intravenous (protocol-dependent)
Frequency	Protocol-dependent; pulsatile administration mirrors physiology
Injection Sites	Abdomen or thigh (subcutaneous)
Response	LH and FSH measurable within hours
Reconstitution	10 mg + 2 mL BW = 5 mg/mL; stable 28 days refrigerated

6. Safety Profile

6.1 Contraindications

- Hormone-sensitive cancers (breast, prostate, ovarian, uterine)

- Pregnancy (exogenous gonadotropin stimulation is contraindicated)
- Pituitary tumors or disorders affecting GnRH/LH/FSH secretion

6.2 Adverse Events

- Flushing (common; related to LH surge)
- Abdominal discomfort
- Headache (transient)
- **Ovarian Hyperstimulation Syndrome (OHSS):** Risk in women undergoing ovarian stimulation; lower risk vs. hCG trigger (key advantage).

6.3 Monitoring Parameters

- LH and FSH levels (baseline and post-dose)
- Testosterone (men) or estradiol (women)
- Ovarian response monitoring (women; ultrasound in ART protocols)

7. Reference Sources

1. Dhillo WS, et al. Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. J Clin Endocrinol Metab. 2005; PMID: 16174730.

2. Jayasena CN, et al. Kisspeptin-54 triggers egg maturation in women undergoing IVF. J Clin Invest. 2014; PMID: 24642468.

3. Skorupskaite K, et al. The kisspeptin-GnRH pathway in human reproductive health and disease. Hum Reprod Update. 2014; PMID: 25012245.

CLINICAL REFERENCE MONOGRAPH

Oxytocin
(OXT)

The Hypothalamic Bonding & Social Hormone

Labor Induction · Social Bonding · Sexual Health · Intranasal · Safety Profile

1. Overview

Oxytocin is a nine-amino acid neuropeptide synthesized in the hypothalamic paraventricular and supraoptic nuclei and released by the posterior pituitary. It functions both as a peripheral hormone (uterine contractions, milk ejection) and as a central neurotransmitter modulating social attachment, trust, emotional processing, and sexual arousal. It is FDA-approved for obstetric indications; off-label intranasal and subcutaneous use is investigational.

Parameter	Details
Name	Oxytocin (OXT)
Reference Code	OXT
Category	Neurohormone / Social Bonding Peptide
FDA-Approved Indications	Labor induction; postpartum hemorrhage management
Intranasal Reference Range	10–40 IU as needed
Subcutaneous Reference Range	10–40 mcg as needed
IV Half-Life	~3–5 minutes
Onset (Intranasal)	15–30 minutes
Key Warning	Labor induction outside hospital is dangerous; high doses risk uterine hyperstimulation and hyponatremia

2. Mechanism of Action

2.1 Peripheral Actions

- **Uterine contractions:** Binds myometrial oxytocin receptors; triggers and augments labor contractions.
- **Milk ejection:** Stimulates mammary gland myoepithelial cell contraction for let-down reflex.
- **Postpartum hemorrhage:** Uterine tone promotion reduces blood loss after delivery.

2.2 Central Nervous System Actions

- **Social attachment:** Modulates amygdala activity; reduces social fear; promotes prosocial behavior and trust.
- **Emotional processing:** Influences perception of social cues, facial recognition, and empathic responses.
- **Sexual arousal:** Facilitates consummatory phase of sexual behavior; promotes partner bonding post-coitus.
- **Anxiety modulation:** Context-dependent anxiolytic effects via amygdala dampening.

3. Clinical Indications

Indication	Status	Route
Labor induction	FDA-approved	IV infusion
Postpartum hemorrhage	FDA-approved	IV/IM
Sexual dysfunction enhancement	Off-label investigational	Intranasal/SC
Social anxiety modulation	Investigational	Intranasal
Autism spectrum (social cognition)	Clinical trials	Intranasal
Emotional bonding enhancement	Off-label	Intranasal

4. Administration Reference (Off-Label)

Route	Dose Range	Onset	Notes
Intranasal	10–40 IU PRN	15–30 min	Standard off-label route; direct CNS access
Subcutaneous	10–40 mcg PRN	15–25 min	Systemic; less direct CNS distribution
IV (Obstetric)	Titrated by clinical protocol	3–5 min	Hospital supervision only

5. Reconstitution Reference (Educational)

Standard: 2 mg vial + 2 mL bacteriostatic water = 1 mg/mL concentration.

Volume	Dose
0.01 mL	10 mcg
0.02 mL	20 mcg
0.04 mL	40 mcg

6. Safety Profile

6.1 Contraindications

- Labor induction in non-medical, unsupervised settings (life-threatening risk)
- Hypersensitivity to oxytocin or excipients

6.2 Adverse Events

- Nasal irritation (intranasal route; common)
- Headache and nausea (common)
- Flushing and dizziness (dose-related)
- Hyponatremia (water retention at excessive doses; potentially life-threatening)
- Uterine hyperstimulation (obstetric dosing; fetal distress risk)

6.3 Special Populations

Oxytocin should never be self-administered for labor induction outside a clinical setting. In pregnant individuals, unsupervised use carries risks of uterine rupture, fetal hypoxia, and maternal cardiovascular complications.

7. Reference Sources

1. Meyer-Lindenberg A, et al. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat Rev Neurosci. 2011; PMID: 21164525.

2. MacDonald K, MacDonald TM. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. Harv Rev Psychiatry. 2010; PMID: 20047458.

CLINICAL REFERENCE MONOGRAPH

HCG / HMG

(Human Gonadotropins)

FDA-Approved Fertility Gonadotropins

Spermatogenesis · Ovulation · Testosterone · Fertility Protocols · Safety Profile

1. Overview

Human Chorionic Gonadotropin (HCG) and Human Menopausal Gonadotropin (HMG) are gonadotropins with established FDA-approved fertility indications. HCG mimics luteinizing hormone (LH), triggering ovulation in women and stimulating testosterone/spermatogenesis in men. HMG is a purified urinary preparation containing both FSH and LH activity, used primarily for ovarian stimulation and male spermatogenesis induction.

Parameter	Details
HCG Activity	LH mimetic; stimulates Leydig cells (testosterone) and ovulation trigger
HMG Activity	FSH + LH; follicular development (women); spermatogenesis support (men)
Example Strength	HCG: 500–10,000 IU vials; HMG: 75 IU vials
HMG Reference Range	75–150 IU per injection, 3x weekly
HMG Half-Life	20–40 hours
Route	IM or Subcutaneous
Key Warning	FDA-approved for fertility; specialist supervision required; OHSS risk in women

2. Mechanism of Action

2.1 HCG (LH Mimetic)

- Binds LH/hCG receptors on Leydig cells; stimulates testosterone production in men
- Triggers final follicular maturation and ovulation in women (ovulation trigger)
- Used in men to maintain intratesticular testosterone during TRT or stimulate spermatogenesis
- Stimulates Sertoli cells in men when combined with FSH activity

2.2 HMG (FSH + LH Activity)

- In women: stimulates ovarian follicular development and recruitment of multiple follicles
- In men: promotes spermatogenesis by stimulating Sertoli cell function (FSH component)
- Sequentially combined with HCG in male fertility protocols for spermatogenesis induction

3. Clinical Indications

Indication	Agent	Population
Ovulation induction	HCG + HMG	Women: anovulatory infertility

Indication	Agent	Population
IVF egg retrieval trigger	HCG	Women: ART cycles
Male hypogonadotropic hypogonadism	HCG ± HMG	Men: LH/FSH deficiency
Spermatogenesis induction	HCG + HMG	Men: azoospermia with gonadotropin deficiency
TRT-concurrent testosterone maintenance	HCG	Men: preventing testicular atrophy on TRT

4. HMG Administration Protocol

Timeline	Dose	Frequency
Weeks 1–4	75 IU	3x weekly
Weeks 5+	75–150 IU	3x weekly (based on response)

5. Safety Profile

5.1 Contraindications

- Primary ovarian failure or primary testicular failure
- Hormone-sensitive tumors (ovarian, uterine, testicular, prostate)
- Pregnancy (HMG is contraindicated once pregnant)
- Uncontrolled thyroid or adrenal disorders

5.2 Adverse Events

- Injection site reactions (pain, erythema)
- Abdominal bloating and discomfort
- Headache

5.3 Serious Risks

- **Ovarian Hyperstimulation Syndrome (OHSS):** Potentially life-threatening; requires immediate medical attention if severe.
- **Multiple pregnancy:** Significantly increased risk with ovarian stimulation protocols.

6. Monitoring Framework

- FSH and LH levels (baseline and during therapy)
- Estradiol levels in women (ovarian response monitoring)

- Testosterone levels in men
- Semen analysis (men; at intervals during spermatogenesis protocols)
- Ultrasound follicular monitoring (women; ovarian stimulation protocols)

7. Reference Sources

1. Balasch J, Fabregues F. FSH treatment of male infertility. Reprod Biomed Online. 2004; PMID: 14759283.

2. Humaidan P, et al. Urinary FSH versus highly purified urinary FSH with or without recombinant FSH. Reprod Biomed Online. 2004; PMID: 15149580.

DISCLAIMER: *HCG and HMG are FDA-approved for specific fertility indications and require specialist supervision. Off-label uses should be discussed with a qualified reproductive endocrinologist or urologist. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*

CLINICAL REFERENCE MONOGRAPH

Melanotan I

(Afamelanotide / MT-I)

The Photoprotective Melanocortin Analog

Melanin Induction · EPP · Photoprotection · MC1R Agonism · Safety Profile

1. Overview

Melanotan I (Afamelanotide) is a synthetic analog of alpha-melanocyte-stimulating hormone (α-MSH) that primarily binds melanocortin-1 receptors (MC1R) on melanocytes, stimulating eumelanin production and skin pigmentation. In implant form (Scenesse®), it is FDA-approved for reducing phototoxicity in adults with erythropoietic protoporphyria (EPP). Compounded injectable forms are not FDA-approved.

Parameter	Details
Name	Melanotan I (Afamelanotide)
Reference Code	MT-I
FDA-Approved Form	Scenesse® subcutaneous implant (16 mg) for EPP
Category	Melanocortin Analog / Photoprotective Peptide
Receptor Target	MC1R (primary); minimal CNS/sexual receptor activity
Reconstitution	10 mg vial + 2 mL BW = 5 mg/mL; 0.1 mL = 0.5 mg
Key Warning	Absolute contraindication: melanoma or melanoma family history; regular dermatologic monitoring essential

2. Mechanism of Action

Melanotan I binds MC1R on melanocytes, activating adenylyl cyclase and increasing cAMP. This stimulates the conversion of L-DOPA to melanin (specifically eumelanin, the photoprotective dark pigment) via tyrosinase enzyme activation. Unlike Melanotan II, MT-I demonstrates minimal activity at MC3R, MC4R, and MC5R, avoiding the sexual, CNS, and appetite effects of broader melanocortin agonism.

- **Eumelanin induction:** Increases photoprotective dark pigmentation in melanocytes.
- **Partial photoprotection:** Provides UV radiation protection through enhanced melanin density.
- **MC1R selectivity:** Minimal effects on sexual or central nervous system melanocortin receptors.

3. Clinical Indications

Indication	Status
Erythropoietic Protoporphyria (EPP)	FDA-approved (Scenesse® implant form only)
Vitiligo	Off-label research; limited clinical data
Cosmetic tanning	Not FDA-approved; investigational only
Polymorphic Light Eruption	Investigational

4. Administration Protocol (Injectable Reference)

Parameter	Details
Route	Subcutaneous injection
Injection Site	Abdominal area
Loading Phase	Weeks 1–2: 0.5 mg daily; Weeks 3–4: 0.5–1 mg daily
Maintenance	Week 5+: 0.5 mg weekly
Visible Tanning	Typically within 1–2 weeks of loading
Onset	~30 minutes per dose

5. Reconstitution Reference

Standard: 10 mg vial + 2 mL bacteriostatic water = 5 mg/mL, stable up to 28 days refrigerated.

Volume	Insulin Units	Dose
0.10 mL	10 units	0.5 mg
0.20 mL	20 units	1.0 mg

6. Safety Profile

6.1 Absolute Contraindications

- Active melanoma or personal/family history of melanoma
- Multiple atypical nevi (dysplastic nevus syndrome)
- Pregnancy or breastfeeding

6.2 Adverse Events

- Nausea and gastrointestinal effects (common)
- Facial flushing (dose-dependent)
- Injection site reactions
- Mole darkening and potential new nevi formation (requires monitoring)

6.3 Monitoring Requirements

- Baseline and periodic dermatologic examination
- Documentation and tracking of existing and new moles

- Assessment of any rapidly changing lesions
- Evaluation of photosensitizing medications for compatibility

7. Reference Sources

1. Langendonk JG, et al. Afamelanotide for erythropoietic protoporphyria. N Engl J Med. 2015; PMID: 26488690.

2. Abdel-Malek ZA, et al. Melanocortin receptors, melanotropic peptides and melanogenesis. Cell Mol Life Sci. 2009; PMID: 19859664.

CLINICAL REFERENCE MONOGRAPH

Melanotan II

(MT-II)

The Broad-Spectrum Melanocortin Agonist

Skin Pigmentation · Sexual Function · Appetite · MC1R/MC3R/MC4R · Safety Profile

1. Overview

Melanotan II (MT-II) is a synthetic cyclic analog of alpha-melanocyte-stimulating hormone (α-MSH) with broad melanocortin receptor activity. Unlike Melanotan I (which is selective for MC1R), MT-II activates multiple melanocortin receptors including MC1R (pigmentation), MC3R (appetite/energy), and MC4R (sexual function/CNS). This broader receptor profile accounts for its more pronounced central nervous system effects compared to MT-I, including significant libido stimulation and appetite suppression.

Parameter	Details
Name	Melanotan II (MT-II)
Reference Code	MT-II
Category	Broad-Spectrum Melanocortin Receptor Agonist
Receptors Targeted	MC1R (pigmentation), MC3R (appetite), MC4R (sexual/CNS)
Example Strength	10 mg vial
Reference Range	0.25–1.0 mg (research contexts)
Key Warning	Not FDA-approved; absolute contraindication in melanoma history; broader CNS activity than MT-I

2. Mechanism of Action

2.1 MC1R — Melanocyte Stimulation

Binding MC1R on melanocytes activates adenylyl cyclase, increasing cAMP and stimulating tyrosinase to convert L-DOPA into eumelanin (protective dark pigment). This produces both skin tanning and some UV photoprotection.

2.2 MC4R — Central Sexual & Appetite Effects

MC4R activation in the hypothalamus and limbic system triggers dopamine release and neural pathways governing sexual arousal, erectile function, and appetite suppression. This is the primary mechanism differentiating MT-II from MT-I and accounts for its investigational interest in erectile dysfunction.

2.3 MC3R — Energy & Metabolic Modulation

MC3R activation influences energy homeostasis, adiposity signaling, and autonomic nervous system activity contributing to the appetite suppression and thermogenic effects reported by users.

3. Indications (Off-Label / Research)

Indication	Mechanism	Status
Skin pigmentation enhancement	MC1R — eumelanin production	Off-label; investigational
Photoprotection	MC1R — melanin density increase	Off-label; investigational
Erectile dysfunction	MC4R — central dopaminergic arousal	Investigational (non-responders)
Appetite modulation	MC3R/MC4R — hypothalamic signaling	Research only

4. Administration Protocol

Phase	Dose	Frequency
Week 1 (Test)	0.25 mg	Daily
Weeks 2–4	0.5 mg	Daily
Week 5+ (Maintenance)	0.5 mg	PRN before sun exposure

5. Reconstitution Reference

10 mg vial + 2 mL bacteriostatic water = 5 mg/mL. Stable up to 28 days refrigerated.

Volume	Insulin Units	Dose
0.05 mL	5 units	0.25 mg
0.10 mL	10 units	0.5 mg
0.20 mL	20 units	1.0 mg

6. Safety Profile

6.1 Absolute Contraindications

- Active melanoma or personal/family history of melanoma
- Multiple atypical nevi (dysplastic nevus syndrome)
- Pregnancy or breastfeeding
- Significant cardiovascular disease

6.2 Adverse Events

- **Nausea:** Common, especially early treatment; centrally mediated via MC3R/MC4R.
- Facial flushing and injection site reactions
- Increased libido and spontaneous erections (MC4R-mediated)
- Mole darkening and potential new nevi formation
- Appetite suppression
- Blood pressure changes
- Priapism (rare; painful erection >4 hours — medical emergency)

6.3 Drug Interactions

PDE5 inhibitors (sildenafil, tadalafil) warrant caution due to additive erectile effects and potential hemodynamic consequences.

7. Monitoring Requirements

- Dermatologic evaluation before initiation and periodic skin examinations
- Documentation and tracking of new or changing moles/lesions
- Blood pressure assessment if symptomatic cardiovascular effects occur

8. Reference Sources

1. Wessells H, et al. Effect of an alpha-melanocyte stimulating hormone analog on penile erection. J Urol. 1998; PMID: 9474162.

2. Abdel-Malek ZA. Melanocortin receptors: their functions and regulation by physiological agonists. Cell Mol Life Sci. 2001; PMID: 11577241.

DISCLAIMER: *Melanotan II is not FDA-approved for any indication. It carries significant dermatologic and cardiovascular safety concerns. This monograph provides educational content only and does not constitute medical advice or treatment recommendations.*