2026 CLINICAL REFERENCE GUIDE

PEPTIDE THERAPY IN CLINICAL PRACTICE

A Comprehensive Pharmacological Reference for Physicians, Prescribers, and Advanced Practice Providers

Covering 30+ Therapeutic Peptides • Pharmacology • Clinical Evidence • Prescribing Protocols • Monitoring Parameters

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⚠ IMPORTANT: This document is intended for licensed medical professionals only. All peptide prescribing requires individual patient assessment, documented clinical rationale, and ongoing monitoring. Nothing herein constitutes a standard of care.

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FOREWORD: WHY PHYSICIANS NEED TO UNDERSTAND PEPTIDE THERAPY

Foreword: The Clinical Imperative

Patients are arriving in your office with questions you were not trained to answer. They are asking about semaglutide compounded at a fraction of the brand cost, about a peptide they read could heal their rotator cuff in half the surgical timeline, about a Russian neuropeptide nasal spray that their colleague says transformed her focus and sleep. They have done their research, sometimes sophisticated, sometimes misleading, and they want clinical guidance from someone they trust.

The problem is not that these patients are misinformed. Many of them are correct: therapeutic peptides represent one of the most significant advances in clinical medicine of the past two decades, with a pharmacological evidence base that is substantially larger than most physicians realize. The problem is a training gap that exists through no fault of medical education: peptide pharmacology developed rapidly over the past fifteen years, largely outside the major pharmaceutical pipelines, and has not been systematically incorporated into medical education curricula or mainstream CME programming.

This reference guide was developed to address that gap directly. It is written for the busy clinician, the internist, family physician, endocrinologist, orthopedic surgeon, neurologist, or any advanced practice provider, who wants to develop genuine expertise in peptide therapy quickly, without wading through fragmented online sources of variable quality. The language is clinical. The evidence is cited. The guidance is practical.

A note on scope: the therapeutic peptide landscape includes both FDA-approved compounds (insulin, semaglutide, tesamorelin, bremelanotide, thymosin alpha-1) and investigational compounds being used clinically through 503A compounding pharmacies. Both categories are covered, with clear delineation of regulatory status throughout. The prescribing framework for compounded peptides requires particular attention to documentation, patient selection, and monitoring, all of which are addressed in detail.

Perhaps most importantly: your patients are going to use these compounds regardless of whether you help them. The question is not whether peptide therapy will happen in your patient population. The question is whether it will happen safely, with pharmaceutical-grade products, appropriate baseline assessment, documented clinical rationale, and ongoing monitoring, or whether it will happen through unregulated online sources, without physician involvement, with unknown purity and concentration, and no safety net. Your expertise is that safety net.

How to Use This Reference

This guide is organized by therapeutic category, each section providing: mechanism of action with receptor pharmacology; clinical evidence summary with key trial statistics; patient selection criteria; prescribing guidance including dose, route, and titration; monitoring parameters with specific lab values and follow-up intervals; drug interactions and contraindications; and documentation guidance. Appendix A provides a rapid-lookup prescribing reference for all compounds. Appendix C provides ICD-10 coding guidance for documented clinical use.

SECTION 1: PEPTIDE PHARMACOLOGY: MECHANISMS, CLASSIFICATION, AND PHARMACOKINETICS

Section 1: Peptide Pharmacology

1.1 Classification and Structural Biochemistry

Peptides are defined as amino acid polymers containing 2 to approximately 50 residues, distinguished from polypeptides (50–100 residues) and proteins (>100 residues) by molecular weight and structural complexity. In pharmacological classification, therapeutic peptides span molecular weights from approximately 300 Da (tripeptide KPV, MW 390.4 Da) to approximately 4,800 Da (tirzepatide, MW 4,813.5 Da). This molecular weight range confers specific pharmacokinetic properties including predominantly renal elimination, sensitivity to proteolytic degradation, and, for most native sequences, negligible oral bioavailability.

Structurally, therapeutic peptides are classified by: (1) origin, endogenous (bioidentical to native human sequences), derived (fragments or analogs of endogenous peptides), or de novo synthetic; (2) receptor mechanism, agonist, partial agonist, or antagonist at specific receptors; (3) modification profile, native sequence, amino acid substitution analogs (position-specific), C- or N-terminal modifications, fatty acid conjugates, cyclized structures, or PEGylated derivatives. These structural modifications primarily affect proteolytic stability, receptor binding affinity/selectivity, and pharmacokinetic behavior.

The distinction between bioidentical and analog peptides carries clinical significance. Bioidentical peptides (thymosin alpha-1, GHK, BPC-157) demonstrate activity consistent with their endogenous counterparts. Analogs engineered for extended half-life (semaglutide, CJC-1295 with DAC, tirzepatide) may exhibit altered receptor kinetics, including prolonged receptor occupancy that differs qualitatively from pulsatile endogenous signaling patterns. This distinction informs both efficacy expectations and safety monitoring requirements.

Classification	Examples	MW Range	Primary Modification	Clinical Implication
Bioidentical endogenous	Thymosin Alpha-1, GHK-Cu, KPV	390–3,108 Da	None	Activity matches native peptide; favorable safety profile
Endogenous fragment	BPC-157 (gastric protein fragment), AOD-9604 (HGH aa 176–191)	1,419–1,817 Da	None	Isolated biological activity of parent protein fragment
Short-acting analog	CJC-1295 no DAC, Ipamorelin, Sermorelin	~800–3,400 Da	AA substitution	Pulsatile GH pattern preserved; short half-life
Long-acting	Semaglutide,	3,800–	C18 fatty acid +	Once-weekly

Classification	Examples	MW Range	Primary Modification	Clinical Implication
analog (fatty acid)	Tirzepatide, Retatrutide	4,813 Da	albumin binding	dosing; continuous receptor activation; GI AE profile
Long-acting analog (DAC)	CJC-1295 with DAC	~3,600 Da	Drug Affinity Complex	~7-day half-life; non-pulsatile GH elevation; different risk profile
Ghrelin mimetic (non-peptide)	MK-677 (Ibutamoren)	528 Da	Non-peptide small molecule	Oral bioavailability; sustained GH elevation; not a true peptide
Cyclic peptide	Epitalon (cyclic studies ongoing)	~390 Da	Tetrapeptide AEDG	Telomerase activation; pineal regulation
Antimicrobial peptide	LL-37 (cathelicidin)	4,493 Da	None (native)	Membrane disruption mechanism; broad spectrum

1.2 Receptor Pharmacology and Signal Transduction

Therapeutic peptides exert their biological effects through binding to specific G-protein coupled receptors (GPCRs), receptor tyrosine kinases (RTKs), nuclear receptors, or cytokine receptor families. Receptor selectivity, the primary pharmacological advantage of peptides over small-molecule drugs, is determined by the three-dimensional complementarity between the peptide's conformation and the receptor's binding pocket. Even minor amino acid substitutions can dramatically alter receptor binding affinity, selectivity profile, and functional efficacy (agonist vs. partial agonist vs. biased agonist).

GLP-1 receptor (GLP-1R) pharmacology is the most clinically relevant receptor system in 2026 metabolic medicine. GLP-1R is a class B GPCR that signals primarily through Gs-protein coupling, activating adenylyl cyclase and increasing intracellular cyclic AMP (cAMP). Downstream effects include: in pancreatic beta-cells, glucose-dependent insulin secretion via PKA-mediated KATP channel closure and calcium influx; in the hypothalamus, activation of POMC/CART neurons and inhibition of NPY/AgRP neurons with consequent appetite suppression; in the brainstem nucleus tractus solitarius and area postrema, slowing of gastric emptying; and in the cardiac myocardium, cardioprotective effects through cAMP-dependent pathways. The glucose-dependence of GLP-1R-mediated insulin secretion, the core safety feature that prevents hypoglycemia, results from the requirement for concurrent KATP channel closure by glucose metabolism to potentiate cAMP-induced insulin release.

Melanocortin receptor pharmacology governs the mechanism of PT-141, Melanotan II, and KPV. Five melanocortin receptor subtypes (MC1R–MC5R) are distributed across skin, brain, immune cells, adipose tissue, and exocrine glands. MC1R on melanocytes mediates melanogenesis; MC3R in the hypothalamus regulates energy homeostasis;

MC4R in the medial preoptic area of the hypothalamus and nucleus accumbens mediates sexual motivation and behavior; MC4R in the paraventricular nucleus regulates thermogenesis and feeding. PT-141 (bremelanotide) preferentially activates MC3R and MC4R, producing central sexual arousal without significant MC1R activation and therefore without meaningful melanogenic effects at standard doses. Melanotan II, a broader melanocortin agonist, activates all five subtypes, producing tanning (MC1R), appetite suppression (MC3R/MC4R), and libido effects (MC4R) simultaneously.

The GHRH receptor (GHRHR) and ghrelin receptor (GHSR-1a) mediate GH secretagogue activity. GHRHR is a class B GPCR coupled to Gs, increasing cAMP in pituitary somatotrophs to drive GH granule exocytosis. GHSR-1a, also a GPCR, is coupled to Gq/11, activating phospholipase C and increasing intracellular IP3/calcium to drive GH release. The dual-pathway activation produced by simultaneously administering a GHRH analog (CJC-1295) and a ghrelin receptor agonist (Ipamorelin) produces synergistic GH release through convergent intracellular signaling, the pharmacological basis for the combination protocol that produces GH pulses substantially larger than either compound alone.

1.3 Pharmacokinetics: Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetic profile of therapeutic peptides is governed by their susceptibility to proteolytic cleavage, molecular size, charge characteristics, and any structural modifications. Understanding these parameters is essential for dosing schedule design and for interpreting the clinical differences between otherwise similar compounds.

Absorption: Subcutaneous administration of peptides with molecular weight greater than approximately 1,000 Da bypasses first-pass hepatic and GI proteolysis, achieving bioavailability exceeding 90% for most compounds. Peptide absorption from SC depots occurs primarily through lymphatic uptake for larger molecules and capillary diffusion for smaller ones. Absorption rate is influenced by injection site vascularity, temperature, and local blood flow, factors that produce intraindividual variability in peak plasma concentrations of 15–35% even with standardized technique. This variability has clinical implications for therapeutic drug monitoring and dose titration. Intranasal delivery, used for Semax and Selank, achieves direct transport along olfactory nerve axons to the olfactory bulb and subsequent distribution to limbic structures and hippocampus, bypassing the blood-brain barrier (BBB) through a non-systemic pathway with peak brain concentrations at approximately 30–60 minutes post-administration.

Distribution: Most therapeutic peptides distribute into the extracellular fluid compartment, with volume of distribution ranging from approximately 0.3 L/kg (albumin-bound compounds like semaglutide) to approximately 1.5–2.0 L/kg (smaller unmodified peptides). Blood-brain barrier penetrance is generally limited for peptides of MW greater than approximately 500–600 Da, which is why CNS-targeted compounds either use intranasal routes (Semax, Selank) or are specifically designed for BBB penetration (some DSIP research formulations).

Metabolism: Primary metabolic pathway is proteolytic cleavage by endopeptidases (DPP-IV, neprilysin, ACE) and exopeptidases in blood, gut, kidney, and liver. Resultant amino acids enter standard catabolic pathways. Fatty acid-conjugated analogs (semaglutide, tirzepatide) resist DPP-IV cleavage through structural modification and

are primarily eliminated through renal filtration of the fatty acid-cleaved metabolite. No cytochrome P450-mediated metabolism is involved for any currently used therapeutic peptide, which significantly reduces the risk of pharmacokinetic drug-drug interactions compared to small-molecule therapeutics.

Elimination: Half-lives range from 30 minutes (CJC-1295 without DAC, native Semax) to approximately 7 days (semaglutide, CJC-1295 with DAC). Renal impairment, which reduces endopeptidase activity in the proximal tubular brush border, prolongs the effective half-life of some peptides. Dose adjustment guidance for CKD is not formally established for most compounded peptides; conservative initial dosing and more frequent IGF-1 or endpoint monitoring is appropriate.

Peptide	Route	Bioavail.	t½	Primary Elimination	Notable PK Feature
Semaglutide	SC weekly	~89%	~7 days	Proteolysis (DPP-IV resistant) + renal	Albumin binding via C18 fatty acid; once-weekly dosing
Tirzepatide	SC weekly	~80%	~5 days	Proteolysis + renal	Dual GIP/GLP-1 with C20 diacid; less nausea than sema
Retatrutide	SC weekly	~80%	~6 days	Proteolysis + renal	Triple GLP-1/GIP/glucagon agonist; 28.7% avg weight loss
BPC-157	SC or oral	SC >90%; oral variable	1–4 hrs	Enzymatic cleavage	Gastric acid-stable; oral effective for GI conditions
TB-500	SC or IM	>85%	3–5 days	Proteolysis	Systemic distribution; actin-binding drives cell migration
CJC-1295 no DAC	SC	>90%	~30 min	DPP-IV cleavage	Pulsatile GH; must pair with Ipamorelin
CJC-1295 + DAC	SC	>90%	~7 days	Albumin release + proteolysis	Non-pulsatile GH; weekly dosing possible
Ipamorelin	SC	>90%	~2 hrs	Enzymatic cleavage	Selective GHSR agonist; no cortisol/prolactin elevation
Semax	Intranasal	Medium (nose-to-brain)	~30 min systemic	Enzymatic	Olfactory pathway bypasses BBB; hippocampal BDNF ↑
Epitalon	SC	>90%	~30–60 min	Enzymatic	Short t½; course-based use (10 days 2x/yr)
PT-141	SC	>85%	6–8 hrs	Proteolysis	4–6 hr pre-activity dosing; FDA-approved (Vyleesi)
Thymosin Alpha-1	SC	>90%	~2 hrs	Enzymatic cleavage	Approved in 35+ countries; 30-yr safety record

Peptide	Route	Bioavail.	t½	Primary Elimination	Notable PK Feature
Tesamorelin	SC	~93%	~26 min	DPP-IV cleavage	FDA-approved (Egrifta); fasted administration required
MK-677	Oral	~60–70%	~24 hrs	Hepatic (non-CYP)	Non-peptide; only oral GH secretagogue
GHK-Cu	SC or topical	SC >90%; topical variable	~30–60 min	Enzymatic + copper recycling	Activates >4,000 genes; distinctive blue color
NAD+	IV, SC, or oral precursor	IV 100%; SC >80%; oral 20–40%	Variable	Cellular metabolism	PARP and sirtuin substrate; IV produces most rapid effect

1.4 Receptor Selectivity vs. Small-Molecule Drugs: The Pharmacological Case for Peptides

The fundamental pharmacological advantage of therapeutic peptides, receptor selectivity, deserves explicit clinical framing. Small-molecule drugs achieve therapeutic effects through binding to protein targets, but their low molecular weight (typically <500 Da) and geometric simplicity limit the precision of receptor binding. Most small molecules bind to multiple receptor subtypes, enzyme isoforms, or off-target proteins, producing the broad adverse effect profiles that characterize many conventional drug classes.

Peptides, through their larger contact surface area with target receptors, achieve selectivity profiles that can discriminate between closely related receptor subtypes. Ipamorelin provides the clearest clinical illustration: older GH secretagogues (GHRP-2, GHRP-6) activated GHSR-1a with roughly equivalent potency to stimulate GH, cortisol, and prolactin release, limiting clinical utility through hypercortisolemia and galactorrhea. Ipamorelin's engineered selectivity at GHSR-1a produces robust GH secretion with less than 10% of the cortisol and prolactin stimulation of GHRP-2 at equi-effective GH doses, enabling a substantially more favorable safety profile. This selectivity advantage, achievable through peptide engineering in ways impossible with small-molecule design, is a consistent pharmacological theme across the therapeutic peptide class.

The clinical translation is direct: peptide therapies generally produce fewer off-target effects, which is the primary explanation for the favorable safety records of most compounds discussed in this guide, despite their biological potency. The side effects that do occur are typically mechanism-based (GI effects from GLP-1-mediated gastric emptying slowing, water retention from GH-mediated sodium retention, mole changes from MC1R activation by Melanotan II) rather than off-target toxicity, and are therefore predictable, monitorable, and manageable.

DEEP PHARMACOLOGY: RECEPTOR SYSTEMS, SIGNAL TRANSDUCTION, AND AGING BIOLOGY

Deep Pharmacology: Receptor Systems, Aging Biology, and Molecular Mechanisms

This section provides the mechanistic depth needed to understand why peptide combinations produce synergistic rather than additive effects, why specific modifications dramatically alter pharmacokinetics, and how the aging process creates the biological context that makes peptide therapeutics most relevant. Clinicians who understand these principles can extrapolate rationally to novel compounds and combinations as the field evolves.

Receptor Pharmacology Across the Peptide Classes

The therapeutic peptides discussed in this guide engage five primary receptor superfamilies. Understanding which superfamily a given peptide targets allows prediction of its signal transduction cascade, downstream effects, potential for tolerance or desensitization, and relevant drug interactions.

Class B G-Protein Coupled Receptors (GPCRs): This is the most clinically important receptor superfamily for therapeutic peptides, encompassing GLP-1R, GIPR, GCGR (glucagon receptor), GHRHr (GHRH receptor), and several others. Class B GPCRs are distinguished by a large extracellular domain that provides an initial peptide docking site, followed by a transmembrane domain that amplifies the binding event into intracellular signaling. All primarily couple to Gαs → adenylyl cyclase → cAMP → PKA → CREB phosphorylation, though biased signaling through Gαi and β-arrestin pathways occurs at most class B GPCRs and can be exploited by engineered analogs. The sustained receptor activation produced by long-acting analogs (semaglutide, tirzepatide) produces different β-arrestin recruitment patterns compared to pulsatile native ligand binding, a distinction that may underlie some of the physiological differences between once-weekly injectable GLP-1 therapy and native GLP-1 secretion after meals.

Growth Hormone Secretagogue Receptor (GHSR-1a): This class A GPCR is the target of Ipamorelin, GHRP-2, GHRP-6, MK-677, and ghrelin. GHSR-1a exhibits unusually high constitutive activity, approximately 50% of maximal signaling even without ligand binding, which is relevant to understanding its regulation. Ghrelin and its pharmacological mimetics produce their GH-releasing effect via Gαq → phospholipase C β → IP3/DAG → PKC → calcium mobilization, which is distinct from the Gαs mechanism of GHRH at its receptor. The two pathways, GHRH-Gαs-cAMP and ghrelin-Gαq-calcium, converge on exocytosis of GH secretory granules, which is why simultaneous activation of both (CJC-1295 + Ipamorelin) produces synergistic GH release substantially greater than either alone.

Melanocortin Receptors (MC1R–MC5R): Five receptor subtypes mediate the diverse effects of alpha-MSH and its pharmacological analogs. The therapeutic significance of MC receptor selectivity is illustrated by comparing compounds: (1) Bremelanotide (PT-141): engineered for MC3R/MC4R selectivity; produces sexual arousal without

significant tanning or ACTH pathway activation. (2) Melanotan II: activates all five subtypes; produces tanning (MC1R), arousal (MC4R), appetite suppression (MC4R/MC3R), and exocrine effects (MC5R) simultaneously. (3) KPV: activates MC1R and MC3R in epithelial tissues, inhibiting NF-κB; produces anti-inflammatory effects without tanning (the melanogenic MC1R activation in melanocytes appears to require the full alpha-MSH sequence, not the C-terminal fragment). Understanding these selectivity differences allows clinicians to explain to patients why bremelanotide is preferred for sexual health applications over Melanotan II despite a related mechanism.

KISS1R (GPR54): The kisspeptin receptor is a Gαq/11-coupled class A GPCR expressed on GnRH neurons in the hypothalamus and in several peripheral tissues including pituitary, testis, ovary, and placenta. KISS1R activation produces phospholipase C activation → IP3 → calcium → MAPK pathway → GnRH synthesis and release. The receptor shows rapid desensitization with continuous agonist exposure, which is why kisspeptin therapeutics are designed for pulsatile rather than continuous administration, mimicking the native episodic GnRH-stimulating pattern of endogenous kisspeptin secretion.

Cytokine and Growth Factor Receptors: Thymosin Alpha-1 primarily signals through toll-like receptor 9 (TLR9) on dendritic cells and through specific T-cell surface receptors to promote differentiation. GHK-Cu interacts with multiple receptor systems including EGFR, activating downstream Ras-MAPK and PI3K-Akt signaling that drives fibroblast proliferation and migration. SS-31 (elamipretide) has a unique non-receptor target, it binds directly to cardiolipin in the inner mitochondrial membrane, representing a pharmacological mechanism that bypasses conventional receptor pharmacology entirely.

The Hallmarks of Aging: A Framework for Longevity Peptide Prescribing

The 2013 landmark review 'Hallmarks of Aging' (Lopez-Otin et al., Cell, 2013; PMID: 23746838) identified nine cellular and molecular changes that universally characterize biological aging and drive age-related disease. This framework provides the conceptual architecture for understanding which peptides address which aspects of aging, enabling rational protocol design for the longevity-oriented patient.

Hallmark of Aging	Biological Description	Primary Peptide Intervention	Mechanism of Action
Genomic instability	Accumulation of DNA damage from oxidative stress, radiation, replication errors, and impaired repair	NAD+ (via SIRT6/PARP activation); GHK-Cu (DNA repair gene upregulation)	NAD+ restores PARP1 DNA repair function; GHK-Cu activates DNA damage response genes
Telomere attrition	Shortening of chromosome-capping telomere repeats with each cell division → senescence or apoptosis	Epitalon (telomerase activation)	TERT promoter demethylation → telomerase expression → telomere elongation in somatic cells
Epigenetic alterations	Age-related changes in DNA methylation, histone modification, and	GHK-Cu (4,000+ gene regulation); Epitalon	GHK-Cu activates promoters of youthful gene programs; Epitalon resets

Hallmark of Aging	Biological Description	Primary Peptide Intervention	Mechanism of Action
	chromatin accessibility that dysregulate gene expression		pineal gene expression patterns
Loss of proteostasis	Failure of protein quality control: chaperone function, ubiquitin-proteasome, and autophagy systems	NAD+ (SIRT1-mediated deacetylation of Atg autophagy proteins); BPC-157 (indirect)	NAD+/SIRT1 promotes autophagy; BPC-157 reduces cellular stress burden
Deregulated nutrient sensing	Dysregulation of IGF-1/mTOR, AMPK, and sirtuin pathways: key integrators of nutrition and longevity signaling	MOTS-c (AMPK activation); NAD+ (sirtuin activation)	MOTS-c activates AMPK via AICAR accumulation; NAD+ enables sirtuin deacylase activity
Mitochondrial dysfunction	Decline in bioenergetic efficiency, increased ROS production, and mitochondrial DNA mutation accumulation	SS-31 (cardiolipin stabilization); MOTS-c (mitophagy support); NAD+ (Complex I support)	SS-31 stabilizes inner membrane structure; MOTS-c promotes mitochondrial quality control; NAD+ restores electron transport chain efficiency
Cellular senescence	Permanent cell cycle arrest of damaged cells that secrete pro-inflammatory SASP factors	Thymosin Alpha-1 (immune clearance of senescent cells); NAD+ (SIRT1 regulation of p21/p53)	TA-1 optimizes NK cell and T-cell-mediated senescent cell clearance; NAD+/SIRT1 modulates senescence pathways
Stem cell exhaustion	Depletion of tissue-specific stem cell populations that maintain organ homeostasis	TB-500 (epicardial progenitor mobilization); GHK-Cu (dermal stem cell activation)	TB-500 reactivates quiescent cardiac stem cells; GHK-Cu stimulates follicular and dermal stem cells
Altered intercellular communication	Age-related changes in secreted factors (SASP, hormones, exosomes) that corrupt paracrine/endocrine signaling	GHK-Cu (anti-inflammatory gene regulation); TA-1 (cytokine balance restoration); MOTS-c (endocrine metabolic signaling)	Multiple mechanisms reduce pro-inflammatory signaling and restore hormonal communication clarity

Pharmacokinetic Principles: Half-Life Engineering and Clinical Implications

The pharmacokinetic properties of therapeutic peptides, particularly half-life, are engineered to serve specific clinical objectives. Understanding the engineering rationale allows prescribers to make more informed choices between compounds targeting the same receptor but with different duration profiles.

Short-acting GHRH analogs (Sermorelin t½ ~10 min; CJC-1295 no DAC t½ ~30 min):

These compounds produce discrete GHRH receptor activation events that mimic the hypothalamic GHRH pulse. The short half-life means the pituitary experiences a stimulus followed by recovery, preserving the somatostatin-mediated negative feedback cycle that normally terminates each GH pulse. The preserved feedback mechanism prevents excessive GH accumulation and maintains the physiological pulsatile GH pattern, which appears important for maintaining tissue sensitivity to GH and avoiding the adverse effects of continuous GH exposure.

Long-acting GHRH analog (CJC-1295 with DAC t½ ~7 days): The Drug Affinity Complex (DAC), a maleimide group at K4, covalently binds to lysine residues on circulating albumin, converting CJC-1295 from a short-acting GHRH pulse to a sustained GHRH infusion equivalent. The resulting GH elevation is less pulsatile, more sustained, and associated with a higher mean IGF-1 elevation per dose. Some practitioners prefer this profile for bone density and body composition goals where sustained anabolism may be advantageous; others prefer without-DAC for GH pattern physiological fidelity.

Fatty acid conjugation for GLP-1 class (Semaglutide, Tirzepatide, Retatrutide): The common principle is reversible albumin binding via fatty acid chains of varying length. Semaglutide uses a C18 fatty diacid; tirzepatide uses a C20 fatty diacid via a hydrophilic linker; retatrutide uses a different configuration optimized for triple receptor target activation. The binding to albumin (~67 kDa) dramatically increases the effective hydrodynamic radius of the peptide, reducing renal filtration and protecting against endopeptidase cleavage. The fatty acid chain also contributes to enhanced GLP-1R binding affinity in the case of semaglutide, the linker contacts a secondary binding site on the receptor extracellular domain, increasing affinity approximately 3-fold compared to the unmodified peptide sequence.

Cyclization for stability (Epitalon, Bremelanotide): Cyclization, the formation of a peptide bond between the N- and C-termini, or between side chains, dramatically reduces peptidase access to the backbone. Bremelanotide's cyclic structure and the D-amino acid at position 6 (D-Phe) create a highly proteolytically stable scaffold that accounts for its extended ~6-hour plasma half-life despite being a small peptide. Epitalon's tetrapeptide structure has been studied in both linear and modified forms for telomerase activation.

The Somatopause: Detailed Clinical Characterization

The somatopause represents the age-related decline in hypothalamic-pituitary growth hormone axis activity, a progressive change that begins in the third decade and accelerates after the fifth. Unlike some hormonal changes of aging where the gland itself fails (primary hypogonadism, primary hypothyroidism), somatopause primarily reflects changes in hypothalamic regulation: reduced GHRH pulse amplitude and frequency, increased somatostatin tone, and progressively reduced pituitary somatotroph reserve. The gland retains capacity to produce GH when appropriately stimulated, which is the pharmacological opportunity for GH secretagogues.

The clinical consequences of somatopause are well-documented in the literature on adult GH deficiency and extend beyond simple body composition changes. The GH/IGF-1 axis regulates: (1) body composition, GH promotes lipolysis and lean mass accretion; IGF-1 mediates anabolic effects on muscle and bone; (2) metabolism, GH regulates hepatic lipid and glucose metabolism; (3) sleep architecture, GH secretion is tightly coupled to slow-wave sleep, with the primary nocturnal pulse occurring during the first few hours of N3 sleep; (4) cognitive function, IGF-1R is expressed throughout the brain,

and IGF-1 promotes neuroplasticity, BDNF expression, and neuroprotection; (5) immune function, GH and IGF-1 receptors are expressed on lymphocytes; the axis modulates immune surveillance capacity.

The clinical distinction between formal adult growth hormone deficiency (AGHD, ICD-10 E23.0, confirmed by provocative GH stimulation test showing peak GH <5 µg/L) and functional somatopause (age-related GH decline without meeting formal AGHD diagnostic criteria) is important for prescribing. AGHD has an FDA-approved treatment pathway: recombinant hGH (various brands), prescribable under standard on-label protocols. Functional somatopause, by far the more common presentation in a biological optimization practice, is treated off-label with GH secretagogues that stimulate endogenous production without qualifying as direct hGH administration. The four-part documentation framework (clinical rationale, informed consent, alternative consideration, monitoring plan) applies to functional somatopause treatment with secretagogues.

Feature	Adult GH Deficiency (AGHD)	Functional Somatopause	Implication
Definition	Formal deficiency: peak GH <5 µg/L on stimulation test; IGF-1 typically <100 ng/mL	Age-related GH decline; IGF-1 low-normal for age; no pathological cause	Different ICD-10 codes and prescribing pathways
ICD-10 Code	E23.0 (Hypopituitarism)	E34.9 (Endocrine disorder, unspecified); or E88.9	Formal AGHD has clearer insurance pathway; functional somatopause requires off-label documentation
Preferred treatment	Recombinant hGH (Category A FDA approved)	GH secretagogues (Category B compounded)	FDA-approved direct hGH for formal AGHD; secretagogues for functional somatopause
IGF-1 level	Typically <100 ng/mL	100–180 ng/mL (low-normal for age)	Functional somatopause still has intact pituitary capacity
Pituitary capacity	Reduced (pathological)	Intact but understimulated	Secretagogues work by stimulating the intact pituitary

Feature	Adult GH Deficiency (AGHD)	Functional Somatopause	Implication
Stimulation test	Peak GH <5 µg/L (diagnostic criterion)	Not required for secretagogue prescribing	Simplifies the diagnostic workup for secretagogue therapy
Monitoring	IGF-1 every 3 months on hGH	IGF-1 every 6–8 weeks during titration, then q3–6 months	Same monitoring parameter; different frequency based on therapy

Gastrointestinal Pharmacology of GLP-1 Compounds: Managing the Primary Adverse Effect Burden

Gastrointestinal adverse effects are the principal limitation of GLP-1 receptor agonist therapy and the primary reason for treatment discontinuation in clinical practice. A mechanistic understanding of GI adverse effect pathophysiology enables rational management strategies that go beyond simply 'titrate slowly.'

Nausea mechanism: GLP-1 receptors are expressed on vagal afferent neurons and in the area postrema (the brainstem's vomiting center, which lacks a blood-brain barrier). Peripheral GLP-1R activation on vagal afferents transmits satiety and nausea signals to the nucleus tractus solitarius (NTS), which then integrates with the area postrema. Gastric emptying delay, which increases gastric distension signals, amplifies this nausea pathway. Semaglutide and tirzepatide produce identical nausea mechanisms at the receptor level; the modestly lower nausea rates with tirzepatide likely reflect the ability to achieve greater weight loss at lower GLP-1R occupancy due to the additive GIP component, reducing the dose needed at the GLP-1R to achieve target efficacy.

Management algorithm for GI adverse effects: (1) Prevention through titration: The 4-week dose escalation schedule is not optional, it exists specifically to allow GABA-ergic interneuron adaptation in the area postrema, reducing sensitivity to ongoing GLP-1R stimulation. Skipping steps dramatically increases nausea rates. (2) Dietary modification: Small volume, low-fat meals; avoid lying down within 2–3 hours of eating; the last meal of the day should be the smallest. High-fat meals independently delay gastric emptying, compounding the GLP-1-mediated delay. (3) Anti-nausea medications: Ondansetron 4–8 mg PRN is the preferred first-line option, 5-HT3 antagonism directly modulates the vagal-NTS nausea pathway activated by peripheral GLP-1R stimulation. Metoclopramide (prokinetic) can be considered for gastroparesis-predominant symptoms but may paradoxically worsen the nausea pathway by accelerating gastric emptying and increasing vagal afferent stimulation. (4) Dose reduction: Sustained nausea at a specific dose after 4+ weeks is a signal to reduce to the previously tolerated dose and re-escalate more slowly. Some patients require 8-week rather than 4-week intervals between dose increases.

Gastrointestinal bleeding risk: A 2024 population-level analysis (Sodhi et al., JAMA, 2023; PMID: 37847273) identified a modest increase in gastrointestinal bleeding risk in GLP-1 agonist users with pre-existing conditions. While the absolute risk increase is

small, patients with known GI pathology (esophageal varices, peptic ulcer history, angiodysplasia) warrant additional monitoring. The mechanism may involve GLP-1R-mediated effects on GI motility that increase mucosal stress in vulnerable areas.

The Immune Aging Cascade: Why Thymosin Alpha-1 Addresses Multiple Aging Mechanisms Simultaneously

Immunosenescence, the progressive deterioration of immune function with age, is not a simple linear decline in immune capacity. It involves a specific remodeling of the immune system that increases susceptibility to certain threats (novel pathogens, cancer) while paradoxically increasing inflammatory burden (inflammaging) through other mechanisms. Understanding this complexity explains why Thymosin Alpha-1's bidirectional immunomodulatory activity addresses what appears to be contradictory clinical objectives.

The naive T-cell depletion problem: The thymus undergoes progressive involution from puberty onward, with 3% annual parenchymal loss, reducing to near-complete replacement by adipose tissue by the seventh decade. This anatomical decline has a profound functional consequence: production of naive T-cells, cells capable of recognizing novel antigens they have never encountered, declines dramatically. The result is an immune system increasingly populated by memory T-cells from prior exposures (providing continued protection against previously encountered pathogens) but with diminishing capacity to mount an effective response to novel threats. This explains the dramatically higher mortality from novel viral infections (COVID-19, novel influenza strains) in elderly populations compared to the risk they face from influenza strains to which they have prior immunity.

Thymosin Alpha-1 addresses this by acting as a thymic hormone surrogate, stimulating differentiation of T-cell precursors in secondary lymphoid tissue and bone marrow into functional naive T-cells, partially compensating for thymic involution. The mechanism bypasses the need for thymic tissue per se; TA-1 can activate T-cell maturation pathways in extrathymic locations.

The inflammaging paradox: While naive T-cell capacity declines, the aged immune system simultaneously exhibits chronically elevated pro-inflammatory signaling, elevated IL-6, TNF-alpha, CRP, and IL-1beta without an identifiable acute inflammatory stimulus. The sources of this chronic low-grade inflammation include: SASP from senescent cells (a primary driver), gut bacterial translocation through deteriorating intestinal barrier integrity, adipose tissue macrophage activation in the context of visceral adiposity, and chronic CMV reactivation that consumes T-cell reserves in seronegative responses.

Thymosin Alpha-1 addresses inflammaging through several mechanisms: (1) improving T-cell surveillance of senescent cells, enhancing immune clearance of SASP-producing cells; (2) modulating dendritic cell cytokine production, shifting from pro-inflammatory toward regulatory outputs; and (3) promoting Treg (regulatory T-cell) activity that suppresses effector T-cell overactivation. The bidirectional nature, stimulating where too little activity exists (naive T-cell generation) and suppressing where too much exists (chronic inflammatory cytokine production), is the hallmark of an immunomodulatory rather than simply immunostimulatory agent.

SECTION 2: REGULATORY FRAMEWORK: 503A, FDA CLASSIFICATION, AND PRESCRIBING AUTHORITY

Section 2: Regulatory Framework for the Prescribing Clinician

Navigating the regulatory landscape for therapeutic peptides is among the most practically important competencies for clinicians entering this space. The regulatory status of specific compounds directly determines the legal prescribing pathway, the quality standards that apply to the dispensed product, and the documentation requirements for clinical defensibility. This section provides a comprehensive overview of the 2026 regulatory landscape with practical prescribing guidance.

2.1 FDA Drug Classification Categories for Peptides

Therapeutic peptides fall into several distinct FDA regulatory categories with different approval pathways and market access implications. Understanding these categories prevents regulatory confusion in clinical practice.

Category 1: FDA-Approved New Drug Applications (NDAs): Includes semaglutide (Ozempic, Wegovy, Rybelsus), tirzepatide (Mounjaro, Zepbound), tesamorelin (Egrifta, Egrifta SV), bremelanotide (Vyleesi), thymosin alpha-1 (Zadaxin, approved outside the US; no current US NDA), and oxytocin. These compounds have completed full FDA review and may be prescribed for their approved indications. Off-label use of FDA-approved peptides follows standard off-label prescribing principles: documented clinical rationale, patient informed consent, and appropriate monitoring.

Category 2: 503A Compounding Eligible (Positive List): Bulk drug substances listed on the FDA's 503A Bulks List may be compounded by licensed 503A pharmacies for patient-specific prescriptions. As of the July 2026 PCAC review cycle, this list has been significantly expanded following MAHA-driven regulatory reform. Currently eligible for 503A compounding (as of 2026): sermorelin, CJC-1295 (both formulations), ipamorelin, thymosin alpha-1 (compounded independently of Zadaxin NDA), glutathione, L-carnitine, and several other foundational compounds. Prescribers must verify current 503A list status, as this changes periodically.

Category 3: PCAC Review Status (2026): Multiple peptides are under active FDA Pharmacy Compounding Advisory Committee review as a consequence of MAHA regulatory reform advocacy. The July 23–24, 2026 PCAC meeting reviewed BPC-157 acetate, TB-500 (thymosin beta-4 acetate), KPV acetate, MOTS-c acetate, Semax, Selank (Emideltide), Epitalon, and DSIP. The October 2026 HHS ruling and February 2027 PCAC session address GHK-Cu, Melanotan II, and LL-37. Favorable PCAC review and subsequent FDA final rule would move these compounds from investigational/restricted status to 503A Bulks List eligibility. Until a positive ruling, prescribing through compounding pharmacies carrying these compounds remains in a legally complex area that individual prescribers must evaluate with appropriate legal counsel.

Category 4: Research Compounds: Compounds with no current IND (Investigational New Drug) exemption, NDA, or 503A listing remain classified as research use only

(RUO). Clinical use of RUO compounds is not generally appropriate except within IRB-approved research protocols. Prescribers should not facilitate patient access to RUO peptides through clinical prescriptions. This category includes Dihexa, Pinealon, some MDP variants, and several other experimental compounds.

Peptide	FDA Status (2026)	Legal Prescribing Pathway	Quality Standard
Semaglutide (Wegovy/Ozempic)	NDA Approved	Standard Rx: shortage compounding restrictions evolving	Brand NDA; compounded: USP <797>
Tirzepatide (Zepbound/Mounjaro)	NDA Approved	Standard Rx: limited compounding during shortage periods	Brand NDA; compounded: USP <797>
Retatrutide	Phase 3: Pre-approval	Compounded through 503A (off-label bulk substance)	USP <797> from 503A pharmacy
Tesamorelin (Egrifta)	NDA Approved (HIV lipodystrophy)	Standard Rx for approved indication; off-label with documentation	Brand NDA; compounded: USP <797>
Bremelanotide (Vyleesi)	NDA Approved (female HSDD)	Standard Rx; off-label male use with documentation	Brand NDA
Thymosin Alpha-1	503A Compoundable	Physician Rx → 503A licensed pharmacy	USP <797> sterility and potency tested
Sermorelin	503A Compoundable	Physician Rx → 503A licensed pharmacy	USP <797>
CJC-1295 / Ipamorelin	503A Compoundable	Physician Rx → 503A licensed pharmacy	USP <797>
BPC-157	PCAC Review July 23, 2026	Pending ruling; consult legal counsel pre-prescribing	Research-grade or 503A pending ruling
TB-500	PCAC Review July 23, 2026	Pending ruling; consult legal counsel pre-prescribing	Research-grade or 503A pending ruling
KPV	PCAC Review July 23, 2026	Pending ruling; compounding pending ruling	Research-grade or 503A pending ruling
Semax / Selank	PCAC Review July 24, 2026	Pending ruling; available as research compounds	Research-grade pending ruling
Epitalon	PCAC Review July 24, 2026	Pending ruling; available as research compounds	Research-grade pending ruling
MOTS-c	PCAC Review July 23, 2026	Pending ruling; compounding	Variable: verify pharmacy

Peptide	FDA Status (2026)	Legal Prescribing Pathway	Quality Standard
		ongoing at some pharmacies	status
GHK-Cu	PCAC Review Feb 12, 2027	Topical cosmetic use permitted; injectable pending	503A topical; injectable pending ruling
LL-37	PCAC Review Feb 12, 2027	Pending ruling	Research-grade pending ruling
MK-677	Research compound / gray market	Not formally prescribable; OTC supplement category	Variable; not USP regulated
Glutathione	503A Compoundable	Physician Rx → 503A licensed pharmacy (IV/SC)	USP <797> for IV/SC; OTC for oral
NAD+	503A Compoundable (IV/SC)	Physician Rx → 503A licensed pharmacy	USP <797> for IV/SC
L-Carnitine	503A Compoundable / OTC	Physician Rx for injectable; OTC oral	USP <797> injectable

2.2 The 503A Compounding Framework: What Prescribers Must Know

Section 503A of the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Quality and Security Act (DQSA) of 2013, establishes the regulatory framework for traditional compounding pharmacies. Understanding this framework is essential for prescribers who recommend compounded peptides, as it defines both the quality standards that should be demanded of any compounded product and the legal prescribing requirements that create clinical defensibility.

A 503A compounding pharmacy may legally prepare a compounded drug product if: (1) the product is compounded based on a valid prescription for an individually identified patient; (2) the compounding pharmacy is licensed in the state where it operates; (3) if the compound includes a bulk drug substance, that substance appears on the FDA's 503A Bulks List or qualifies under another permitted category; (4) the compound is not essentially a copy of a commercially available drug; and (5) the compounding meets USP Chapter <797> standards for sterile compounding.

USP Chapter <797> requirements for sterile compounding, most relevant for injectable peptides, include: categorized beyond-use dating (BUD) based on sterility testing results; ISO-classified cleanroom environments for compounding; gown and qualification requirements for compounding personnel; environmental monitoring programs; and end-product testing including sterility testing (USP <71>), bacterial endotoxin testing (LAL testing; USP <85>), and potency/identity verification (typically by HPLC or mass spectrometry). As prescribers, demanding and reviewing Certificates of Analysis (COAs) from your compounding pharmacy is a fundamental quality

assurance requirement. A COA from an accredited independent laboratory should confirm: compound identity (by mass spectrometry or NMR), purity (>98% by HPLC), concentration/potency (within ±10% of labeled), sterility (no growth at 14 days USP <71>), and endotoxin content (below 5 EU/kg patient body weight/hour for IV; below 2.15 EU/mL for SC/IM in most applications).

Prescriber Documentation Requirements for Compounded Peptides

For any compounded peptide prescription, maintain in the medical record: (1) documented clinical rationale for the compound and formulation specific to the patient; (2) evidence of medical necessity that supports why a commercially available alternative is not appropriate or available; (3) informed consent documentation addressing the compounded vs. approved drug status, the evidence base for the compound, and the monitoring plan; (4) baseline laboratory data relevant to the compound; (5) a documented monitoring protocol with specific parameters, frequency, and response thresholds; and (6) copies of, or verified access to, the Certificate of Analysis for the dispensed batch. This documentation framework supports clinical defensibility in the event of regulatory inquiry or adverse event.

2.3 Off-Label Prescribing Principles Applied to Peptide Therapy

Off-label prescribing: prescribing an FDA-approved drug for an indication, population, dose, or route not specified in the approved labeling, is a cornerstone of evidence-based medicine and is legal and common in clinical practice. Approximately 20% of all prescriptions in the United States are written off-label, and in some specialties (oncology, psychiatry) this proportion exceeds 50%. The same legal and ethical framework that governs off-label prescribing of approved drugs applies to the use of compounded or researched peptides, with additional considerations related to the quality and regulatory status of the compound itself.

The key principles: (1) Off-label prescribing must be based on sound scientific evidence and sound medical judgment. The evidence base for peptides ranges from Phase 3 RCT data (semaglutide, tirzepatide) through extensive preclinical evidence and observational clinical experience (BPC-157, GHK-Cu) to limited preliminary data (MOTS-c, SS-31 in non-cardiac applications). Prescribers must evaluate the strength of evidence and communicate it honestly to patients. (2) Informed consent should be documented. Patients should understand that they are receiving a compound whose use in their specific context may not have been evaluated in large RCTs, and they should agree to the monitoring protocol required for safety. (3) The standard of care is measured against what a reasonable, similarly trained clinician would do in similar circumstances, not against a single published guideline. A well-documented, evidence-based compounded peptide protocol can meet the standard of care even when the compound lacks FDA approval for the specific indication.

Liability considerations: prescribers in this space should ensure their professional liability coverage does not exclude coverage for compounded drug prescribing or off-label use of novel compounds. Documenting clinical decision-making thoroughly, the evidence reviewed, the patient's specific clinical situation and why it supports the intervention, the informed consent obtained, and the monitoring plan, is the most effective risk mitigation strategy.

LEGAL ISSUES FOR PRESCRIBERS: FDA CATEGORIES, OFF-LABEL PRACTICE, AND TELEHEALTH

Legal Issues for Prescribing Physicians: Navigating Peptide Therapeutics Without Jeopardizing Your License

For the physician whose patient arrives asking about BPC-157, Ipamorelin, or Semax, the most pressing question is not pharmacological, it is legal. Can I prescribe this? Can I discuss it without becoming liable? Does telehealth change my exposure? What if it is not FDA-approved? This section addresses these questions directly, providing the legal and regulatory framework that allows clinicians to engage with peptide therapeutics responsibly, protect their medical license, and serve patients who will pursue these therapies with or without physician involvement.

The single most important principle is this: physician silence does not protect patients. A patient who cannot get a peptide from a licensed compounding pharmacy with a physician's prescription will obtain it from an unregulated online source with no quality assurance, no medical oversight, and no monitoring. Physician engagement, even cautious, well-documented engagement, produces better patient outcomes than physician avoidance. The legal framework supports this engagement when done correctly.

The Regulatory Architecture: Three Categories of Therapeutic Peptides

Therapeutic peptides in 2026 exist in three legally distinct categories that carry different prescribing obligations, liability profiles, and patient communication requirements. Understanding this architecture is the foundation of legally defensible peptide prescribing practice.

CATEGORY A: FDA-APPROVED PEPTIDE DRUGS

Category A: FDA-Approved Peptides: Standard Prescribing Applies

Category A comprises peptides that have completed the full FDA New Drug Application (NDA) or Biologics License Application (BLA) process and received FDA approval for one or more specific indications. These compounds may be prescribed for approved indications under standard prescribing norms, or prescribed off-label with the protections afforded to all off-label prescribing under US law (discussed below). The prescriber's liability exposure for Category A compounds is the same as for any other FDA-approved medication.

Peptide (Brand Name)	FDA Indication	Year Approved	Prescribing Category
Semaglutide (Ozempic)	Type 2 diabetes mellitus (T2DM) glycemic control	2017	Standard: on-label for T2DM
Semaglutide (Wegovy)	Chronic weight management (BMI ≥30 or ≥27 + comorbidity)	2021	Standard: on-label for obesity
Semaglutide (Wegovy)	Cardiovascular risk reduction in obesity without T2DM	2023	Standard: on-label for CVD risk
Semaglutide (Rybelsus)	Type 2 diabetes: oral formulation	2019	Standard: on-label for T2DM
Tirzepatide (Mounjaro)	Type 2 diabetes mellitus: glycemic control	2022	Standard: on-label for T2DM
Tirzepatide (Zepbound)	Chronic weight management (BMI ≥30 or ≥27 + comorbidity)	2023	Standard: on-label for obesity
Tesamorelin (Egrifta SV)	HIV-associated lipodystrophy (excess visceral fat)	2010	Standard: on-label for HIV lipodystrophy
Bremelanotide (Vyleesi)	Hypoactive sexual desire disorder (HSDD): premenopausal women	2019	Standard: on-label for HSDD
Afamelanotide (Scenesse)	Erythropoietic protoporphyria (EPP): pain prevention	2019	Standard: on-label for EPP
Teriparatide (Forteo)	Osteoporosis: PTH(1-34) fragment	2002	Standard: on-label for osteoporosis
Pramlintide (Symlin)	T1DM and T2DM: amylin analog adjunct to insulin	2005	Standard: on-label for diabetes
Leuprolide (Lupron)	Prostate cancer, endometriosis, uterine fibroids, CPP	1985	Standard: on-label per indication
Oxytocin (Pitocin, Syntocinon)	Labor induction, postpartum hemorrhage	1962	Standard: on-label obstetric use
Vasopressin analogs (Desmopressin/DDAVP)	Diabetes insipidus, nocturnal enuresis, von Willebrand disease	1978	Standard: on-label per indication
Sermorelin acetate	Adult-onset growth hormone deficiency (historically)	1997 (approval lapsed)	Compounded 503A: original approval lapsed; now prescribed via compounding

Peptide (Brand Name)	FDA Indication	Year Approved	Prescribing Category
Various insulin peptides	Diabetes mellitus	Multiple	Standard: well-established class

For Category A compounds used off-label: for example, tesamorelin prescribed for visceral adiposity in non-HIV patients, semaglutide at doses outside the approved titration schedule, or tirzepatide for NASH before NASH-specific approval, the physician's legal position is governed by the established US legal doctrine on off-label prescribing.

Off-Label Prescribing Legal Protection

21 U.S.C. § 396 explicitly recognizes that the FDA does not have authority to limit or interfere with the practice of medicine or restrict physicians from prescribing legally marketed drugs for unapproved uses. Courts have consistently upheld this principle. The American Medical Association states that off-label prescribing 'is not experimental or investigational' and is a legitimate expression of physician clinical judgment. Approximately 20% of all prescriptions in the United States are written off-label. Documentation of the clinical rationale, informed consent regarding the off-label nature, and appropriate monitoring are the professional obligations, not legal prohibitions.

CATEGORY B: COMPOUNDABLE PEPTIDES: CURRENTLY ON THE 503A POSITIVE LIST OR UNDER ACTIVE PCAC REVIEW

Category B: Compoundable Peptides: Prescribable via 503A Pharmacy with Documentation

Category B comprises peptides that are either currently eligible for 503A compounding pharmacy preparation or are under active FDA Pharmacy Compounding Advisory Committee (PCAC) review that is expected to determine their compounding eligibility status. The critical legal distinction is that physicians may write prescriptions for legitimately compoundable substances without prescribing an illegal drug, the prescription directs the 503A pharmacy to prepare a customized medication that is legal to compound under the relevant regulatory status.

The July 23–24, 2026 PCAC review represents the most significant regulatory event in peptide therapeutics history. Fourteen compounds that were moved to the 503A negative list (Category 2 per FDA nomenclature) in 2022–2024 are now under formal PCAC re-evaluation. A favorable committee recommendation followed by an HHS ruling could restore these compounds to legal compounding status by late 2026.

Peptide	PCAC Review Date	Current Status	Proposed Indications	If Favorable: Expected Access
BPC-157 Acetate	July 23, 2026	FDA 503A Category 2: Under PCAC Review	Tissue repair, IBD, tendon/ligament healing, leaky gut	Compoundable via 503A with valid prescription
KPV Acetate	July 23, 2026	FDA 503A Category	Inflammatory bowel	Compoundable

Peptide	PCAC Review Date	Current Status	Proposed Indications	If Favorable: Expected Access
		2: Under PCAC Review	disease, wound healing, skin inflammation	via 503A with valid prescription
Thymosin Beta-4 (TB-500)	July 23, 2026	FDA 503A Category 2: Under PCAC Review	Systemic healing, cardiac repair, anti-inflammatory	Compoundable via 503A with valid prescription
MOTS-c Acetate	July 23, 2026	FDA 503A Category 2: Under PCAC Review	Obesity adjunct, insulin resistance, mitochondrial health	Compoundable via 503A with valid prescription
Emideltide (DSIP)	July 24, 2026	FDA 503A Category 2: Under PCAC Review	Chronic insomnia, sleep architecture disorders	Compoundable via 503A with valid prescription
Semax	July 24, 2026	FDA 503A Category 2: Under PCAC Review	Cognitive impairment, post-stroke recovery, brain fog	Compoundable via 503A with valid prescription
Epitalon	July 24, 2026	FDA 503A Category 2: Under PCAC Review	Telomere protection, anti-aging	Compoundable via 503A with valid prescription
Selank	July 24, 2026	FDA 503A Category 2: Under PCAC Review	Anxiety disorders, cognitive support	Compoundable via 503A with valid prescription
GHK-Cu (Copper tripeptide-1)	February 12, 2027	FDA 503A Category 2: Scheduled PCAC Review	Wound healing, collagen synthesis, aesthetic medicine	Post-Feb 2027 if favorable
Melanotan II	February 12, 2027	FDA 503A Category 2: Scheduled PCAC Review	Photoprotection, melanin induction	Post-Feb 2027 if favorable (with significant safety caveats)
LL-37 Cathelicidin	February 12, 2027	FDA 503A Category 2: Scheduled PCAC Review	Antimicrobial wound care, innate immunity support	Post-Feb 2027 if favorable
CJC-1295 (no DAC)	Currently 503A eligible*	Compoundable: GHRH analog	GH deficiency, somatopause, body composition	Currently prescribable via 503A
Ipamorelin	Currently 503A eligible*	Compoundable: ghrelin receptor agonist	GH optimization, sleep, recovery	Currently prescribable via 503A
Thymosin Alpha-1	Currently 503A eligible*	Compoundable: immune modulator	Immune optimization, viral hepatitis adjunct	Currently prescribable via 503A
Sermorelin	Currently 503A eligible	Compoundable: GHRH analog	GH deficiency, somatopause	Currently prescribable via 503A

*Currently 503A eligible compounds should be verified against current FDA Bulk Drug Substances Lists at time of prescribing, as regulatory status may change. The 503A positive list is updated regularly at: fda.gov/drugs/human-drug-compounding/bulk-drug-substances-nominated-use-compounding-under-section-503a

For Category B compounds that are currently listed as 503A Category 2 (do not compound), prescribers face the most legally sensitive situation. The compounds cannot currently be legally prepared by 503A pharmacies regardless of the physician's prescription. A prescription for a Category 2 compound as of the date of writing cannot be filled by a compliant 503A pharmacy. The appropriate physician response to a patient requesting these compounds is discussed in the Practice Guidelines section below.

LEGAL NOTE: Category 2 Compounds

Issuing a prescription for a compound currently on the FDA's 503A negative list (do not compound) does not create immediate criminal liability for the physician, prescribers are generally not held criminally liable for the manufacturing decisions of pharmacies. However, a prescription for a non-compoundable substance creates a chain of events that may result in: (1) the patient obtaining the compound from an unregulated online source, which the prescriber's letter of recommendation may have facilitated; (2) professional board scrutiny of prescribing practices for substances that lack regulatory pathway; and (3) potential civil liability if the patient is harmed. The safest approach for currently Category 2 compounds is to discuss mechanism and evidence with the patient, document clearly that no prescription is being written for Category 2 compounds pending PCAC outcome, and proactively schedule re-evaluation after the July 2026 PCAC ruling.

CATEGORY C: INVESTIGATIONAL AND RESEARCH-STAGE PEPTIDES

Category C: Investigational Peptides: Discuss, Educate, Do Not Prescribe Without IRB

Category C encompasses peptides for which no regulatory pathway for clinical use currently exists in the United States, compounds that are neither FDA-approved nor currently eligible for 503A compounding. These include research compounds still in early preclinical or Phase I investigation, compounds with no completed human safety data, and compounds specifically designated as Schedule I or otherwise prohibited for clinical use.

Practically speaking, most of the major therapeutic peptides discussed in this guide do not fall into Category C. The majority are either FDA-approved (Category A), currently or potentially compoundable (Category B), or were previously compoundable until the 2022–2024 FDA negative list actions that are now under PCAC re-evaluation. However, certain emerging compounds, including Dihexa (HGF/c-Met pathway activator), novel AI-designed peptide sequences, and others without any regulatory review, are genuinely Category C.

For Category C compounds, the appropriate physician role is: education about the current state of the evidence without prescribing or recommending, referral to clinical trials where appropriate, and documentation that the patient was counseled regarding the absence of a legal clinical access pathway. Writing a prescription for a Category C

compound, even one intended for a 503B outsourcing facility or a research use compounding facility, creates liability exposure without the regulatory protections applicable to Categories A and B.

The Physician's Legal Framework for Off-Label Peptide Prescribing

Foundational Legal Doctrine

The legal protection for physician off-label prescribing in the United States rests on three pillars: (1) the explicit statutory limitation on FDA authority over clinical practice; (2) the First Amendment-based recognition that the exchange of medical information between physician and patient is protected speech; and (3) decades of case law establishing that off-label prescribing is legally protected as a professional judgment rather than an act of drug misbranding.

21 U.S.C. § 396 (the FDCA) states: 'Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.' Courts including the United States Supreme Court in Buckman Co. v. Plaintiffs Legal Committee (2001) and multiple circuit courts have affirmed that FDA regulations do not create a private right of action for off-label prescribing decisions made within the standard of care.

What this means practically: A physician who prescribes tesamorelin (Category A, FDA-approved for HIV lipodystrophy) to a non-HIV patient with visceral adiposity is making a legally protected off-label prescribing decision, provided the prescribing is clinically defensible, documented, and carried out with appropriate patient consent. The FDA cannot restrict this prescribing decision. The physician's exposure is to professional board review (not criminal prosecution) and to civil medical malpractice (not drug law violation).

The Four-Part Protection Framework for Off-Label Prescribing

1. CLINICAL RATIONALE: Document why this compound is appropriate for this patient, the medical indication, the relevant mechanism of action, and the evidence basis (even if limited to Level III). 2. INFORMED CONSENT: Documented patient acknowledgment that the compound is not FDA-approved for this specific use, the evidence basis for its use, the alternatives considered, and the monitoring plan. 3. STANDARD OF CARE CONSISTENCY: Would a reasonable physician with expertise in this area consider this approach? Emerging specialty consensus (anti-aging, functional medicine, sports medicine) increasingly supports peptide use; consulting with or referring to such specialists establishes the standard of care context. 4. MONITORING: Document a follow-up plan with specific parameters. Absence of monitoring is one of the most common bases for professional board adverse actions in off-label prescribing cases.

Telehealth Prescribing of Peptides: The Carepath Platform

Overview: Telehealth and Peptide Prescribing

Telehealth has fundamentally transformed the prescribing landscape for peptide therapeutics. Before the COVID-19 public health emergency, establishing a prescriber-patient relationship required an in-person clinical encounter in most states. The pandemic-era DEA telemedicine flexibilities and subsequent state-level telehealth law updates have now made it possible, and in many states, standard of care, to establish a valid prescriber-patient relationship via synchronous video consultation and to issue prescriptions based on that relationship.

For therapeutic peptides: the vast majority of which are not controlled substances under the Controlled Substances Act, the Ryan Haight Online Pharmacy Consumer Protection Act (which governs controlled substance prescribing via telemedicine) does not apply. This is a critical legal distinction. Ipamorelin, CJC-1295, BPC-157, semaglutide, tesamorelin, GHK-Cu, Thymosin Alpha-1, and virtually all other therapeutic peptides discussed in this guide are NOT scheduled controlled substances. Telehealth prescribing of non-controlled substance peptides is therefore governed by general telehealth regulations, not by the Ryan Haight Act's more restrictive requirements.

Legal Requirement	Controlled Substances (Ryan Haight)	Non-Controlled Peptides (General Telehealth)	Practical Status for Most Peptides
Prescriber-patient relationship	In-person required initially (with narrow exceptions)	Telehealth (video) acceptable in most states	Video consultation sufficient
DEA registration requirement	Must be registered in patient's state for CIIs	No DEA requirement for non-scheduled	No DEA registration needed for peptides
State licensing	License in patient's state required	License in patient's state required	Same requirement: must be licensed in patient's state
PDMP check	Required in many states	Not applicable (peptides not in PDMP)	Not applicable for peptides
Prescribing standards	Same as in-person plus additional documentation	Same standard of care as in-person prescribing	Standard clinical documentation required
Informed consent	Standard + telehealth consent	Standard + telehealth consent	Both needed

Legal Requirement	Controlled Substances (Ryan Haight)	Non-Controlled Peptides (General Telehealth)	Practical Status for Most Peptides
			regardless of platform
Pharmacy requirements	FDA-registered dispenser	503A licensed compounding pharmacy	Must verify pharmacy license and quality standards

The Carepath Telehealth Platform: Clinical and Legal Architecture

Carepath is a telehealth platform specifically designed to support clinicians providing evidence-informed peptide therapeutics and biological optimization medicine to patients across jurisdictions. The platform addresses the specific clinical and legal infrastructure needs of peptide-prescribing physicians, including: multi-state licensing coordination; standardized, legally defensible informed consent documentation; integrated laboratory requisition and result management; integrated 503A compounding pharmacy network with pre-verified quality standards; monitoring protocol templates calibrated to each peptide category; and ongoing regulatory compliance updates as the PCAC and FDA review processes evolve.

For physicians using Carepath, the platform's legal architecture is designed around the following compliance principles:

1. Physician state licensure verification: Carepath verifies that each prescribing physician holds an active, unrestricted license in the patient's state before any consultation or prescription is issued. This is the primary licensing requirement for telehealth prescribing across all states.
2. Synchronous video consultation requirement: All initial prescribing relationships are established via synchronous video consultation, not asynchronous questionnaire-only models. This ensures compliance with the prescriber-patient relationship standards in all states and provides the documentation of a clinical encounter that supports defensible prescribing.
3. Integrated informed consent platform: Carepath provides compound-specific informed consent documentation that covers the regulatory status of each peptide (FDA-approved, 503A-eligible, under PCAC review), the evidence basis, the risks and benefits, the monitoring plan, and explicit patient acknowledgment. This documentation is stored in the platform and accessible for any professional board review.
4. Pharmacy network quality assurance: Carepath works exclusively with 503A-licensed compounding pharmacies that meet specified quality standards including: USP Chapter 797 compliance, third-party certificate of analysis for all preparations, and PCAB (Pharmacy Compounding Accreditation Board) accreditation where available. Prescriptions issued through the platform are transmitted directly to the qualified pharmacy network.
5. Monitoring protocol integration: The platform includes protocol-specific monitoring schedules with automated reminder systems, laboratory integration, and outcome tracking. Documentation of monitoring is maintained within the

platform medical record.

6. Regulatory update system: As the July 2026 PCAC outcomes are determined and as the FDA updates the 503A Bulk Drug Substances List, Carepath updates its formulary and consent documentation in real time, ensuring that prescriptions cannot be issued for compounds that become ineligible for compounding and that newly eligible compounds are promptly available.

Carepath and Non-FDA-Approved Peptides: The Safe Practice Model

A physician using Carepath to prescribe a currently 503A-eligible peptide, such as Ipamorelin/CJC-1295, Thymosin Alpha-1, or Sermorelin, for a patient via telehealth is not engaged in any activity that jeopardizes their medical license, provided: (1) they hold an active license in the patient's state; (2) a valid synchronous video consultation has established the prescriber-patient relationship; (3) the Carepath-provided informed consent documentation is signed and stored; (4) the prescription is transmitted to a Carepath-verified 503A pharmacy; and (5) the monitoring protocol is initiated and documented. This is standard telehealth prescribing practice applied to a non-controlled compounded pharmaceutical.

State-by-State Telehealth Considerations

While federal law does not restrict non-controlled substance telehealth prescribing, state laws vary in their specific telehealth requirements. Prescribers using Carepath should be aware of the following state-level categories:

- Most permissive states: The majority of US states now explicitly permit telehealth prescribing based on a synchronous video encounter without an initial in-person requirement for non-controlled substances. These states have codified their pandemic-era telehealth flexibilities into permanent law. Examples include Arizona, Florida, Texas, Tennessee, Ohio, and many others.
- States with in-person requirement exceptions: A minority of states still require an initial in-person encounter before telehealth prescribing is permissible for some drug categories. Carepath's platform flags these requirements and prompts referral to a local in-person evaluation when required.
- States with enhanced telehealth consent requirements: Some states require specific telehealth consent language beyond the standard clinical informed consent. Carepath's consent documentation platform is updated to include state-specific requirements.
- States requiring an active treatment relationship for controlled substances: Even for non-controlled peptides, some states use language about 'ongoing treatment relationships' that may require follow-up encounters to continue prescribing. Carepath's monitoring protocol structure ensures these relationship continuity requirements are met.

Carepath's compliance team maintains a current, state-by-state telehealth law summary and integrates compliance requirements into the platform's prescribing workflow, reducing the physician's burden of tracking the evolving state regulatory landscape.

How to Respond to Patients About Peptides Without Jeopardizing Your License

The Clinical Conversation: A Risk-Stratified Approach by Compound Category

The following framework guides physicians in responding to patient inquiries about specific peptides in ways that serve the patient's health interests, are clinically appropriate, and protect the physician's professional standing.

For FDA-Approved Compounds (Category A): Full Engagement

When patients ask about semaglutide, tirzepatide, tesamorelin, bremelanotide, or any other FDA-approved peptide, the physician's response requires no special qualification. Prescribe within approved indications for appropriate candidates; discuss and document off-label use where clinical rationale exists using the four-part protection framework. Telehealth prescribing via Carepath is fully appropriate for Category A compounds in all states.

Common clinical scenario: Patient asks about Wegovy/semaglutide 2.4 mg for weight loss. Appropriate response: Assess clinical eligibility (BMI criteria, comorbidities), discuss the robust Phase III evidence (STEP and SELECT trials), address contraindications (MTC/MEN2 history), discuss the monitoring requirements, and issue a prescription for the brand name drug or compounded equivalent where appropriate under current compounding regulations. Document the consultation. This is standard, fully protected clinical practice.

Semaglutide Shortage and Compounding: The 2026 Update

During the period of FDA-declared shortage for semaglutide (2022–2024), 503A pharmacies could legally compound semaglutide base. As of 2026, the shortage has officially ended for most formulations, which significantly restricts 503A compounding of semaglutide base. Compounded semaglutide with modifications (acetate salt, different dosing concentrations) may remain in a gray area pending further FDA guidance. Prescribers using Carepath should follow the platform's current guidance on which semaglutide formulations are compoundable. Brand-name products (Wegovy, Ozempic) are fully prescribable. The commercial/compounded distinction primarily affects patient cost considerations.

For Currently 503A-Eligible Compounds (Category B: Compoundable Now)

For Ipamorelin, CJC-1295, Sermorelin, Thymosin Alpha-1, and other currently 503A-eligible compounds, the physician response involves a structured off-label prescribing framework. These compounds are not FDA-approved but are legally prescribable as compounded preparations from licensed 503A pharmacies. The legal risk is similar to any off-label prescribing of a licensed drug.

Recommended response protocol: (1) Conduct a comprehensive assessment of the patient's clinical indication. (2) Review contraindications relevant to the specific compound (see Section 14 for complete listings). (3) Order baseline laboratory testing appropriate to the compound category. (4) Provide the compound-specific informed consent documentation (Carepath provides these for all currently eligible compounds).

(5) Issue the prescription to a Carepath-verified 503A pharmacy. (6) Initiate the monitoring protocol. Document all of the above.

Documentation language model: 'Patient presented with [clinical indication, e.g., documented low-normal IGF-1 of 148 ng/mL with clinical features consistent with functional somatopause including increased visceral adiposity, reduced exercise recovery, and subjective cognitive slowing]. After review of the patient's medical history (no contraindications identified), discussion of the evidence basis for growth hormone secretagogue therapy (including Ionescu and Frohman, J Clin Endocrinol Metab, 2006), and completion of compound-specific informed consent, a prescription for compounded CJC-1295/Ipamorelin was issued to [pharmacy name], a licensed 503A compounding pharmacy. Monitoring plan: IGF-1 at 6 weeks, fasting glucose at 6 weeks, follow-up consultation at 8 weeks.'

For Compounds Under PCAC Review (Category B: Pending July 2026)

For the fourteen compounds currently in the PCAC review pipeline (BPC-157, TB-500, KPV, MOTS-c, Semax, Selank, Epitalon, DSIP, and those scheduled for 2027), the physician's current options are:

- Option 1: Wait for PCAC outcome: Advise the patient that you are aware of these compounds and their evidence basis, that they are under active FDA review, and that you will be prepared to prescribe appropriate candidates once PCAC review restores their 503A eligibility. Schedule a follow-up appointment for Q4 2026 to reassess regulatory status and prescribing options. This option protects against any criticism of prescribing non-compoundable compounds.
- Option 2: Limited therapeutic discussion with documentation: If the patient is currently using these compounds from an online source (an extremely common clinical presentation), engage clinically rather than refusing to discuss. Document: 'Patient reports self-using [compound] from an online source. I counseled the patient regarding: (a) the current FDA 503A Category 2 status of this compound; (b) the quality and safety risks of unregulated online research peptide sources; (c) the limited human clinical evidence for this compound; and (d) the PCAC review process that may restore compounding access. I did not prescribe this compound. I strongly advised the patient to discontinue use of unverified online sources. I discussed the clinical evidence and monitoring that would be appropriate if the compound becomes available through licensed channels.' This documentation demonstrates patient safety orientation without prescribing exposure.
- Option 3: 503B outsourcing facility research protocols: In specific clinical research contexts, some 503B facilities may operate under research protocols for compounds under regulatory review. Physicians with IRB affiliation or clinical research relationships may pursue this pathway. This is not applicable to routine clinical telehealth practice and requires specific institutional infrastructure.

Critical Warning: Online Research Peptide Prescribing

A physician who writes a letter 'recommending' or 'approving' the use of research peptides that the patient will then purchase from an online source has created documentation of active involvement in an unregulated therapeutic activity. This is legally more problematic than simply discussing the compounds educationally. Do

not write letters endorsing online research peptide use. Instead, document the clinical discussion, the counsel against unregulated sources, and the plan to reassess when regulatory-compliant access is available.

Medical License Protection: Board of Medicine Considerations

Understanding How Professional Boards Evaluate Peptide Prescribing

State medical boards evaluate peptide prescribing under the same framework applied to any unusual or off-label prescribing practice: Was there a legitimate clinical indication? Was the prescribing consistent with what a reasonable and prudent physician with expertise in this area would do? Was the patient appropriately informed? Was monitoring appropriate? Board adverse actions for peptide prescribing are uncommon and typically arise in the context of one of several red flags.

Board Review Red Flag	Description	Prevention Strategy
No clinical indication documented	Prescribing peptides without documented medical rationale	Always document the specific clinical indication (symptoms, labs, functional assessment) supporting the prescription
No informed consent	No documentation that patient understood the off-label/compounded nature of therapy	Use Carepath's compound-specific consent forms; maintain signed copies in medical record
No monitoring plan	Prescribing without follow-up parameters	Document specific lab targets, timepoints, and clinical endpoints that will be monitored
Commercial relationship concerns	Financial ties to peptide compounding pharmacies without disclosure	Disclose any financial relationships with compounding pharmacies; avoid arrangement where pharmacy selection benefits prescriber
High-volume prescribing without clinical evidence	Prescribing peptides to patients without individual clinical assessment	Each patient must have a documented individual assessment; template-based prescribing without clinical individualization is a red flag
Prescribing Category 2 compounds	Issuing prescriptions for compounds currently on FDA's 503A negative list	Do not prescribe compounds on the current 503A negative list; monitor PCAC updates; use Carepath's regulatory compliance tools
Prescribing without adequate training	Inadequate knowledge of compound mechanisms, interactions, and monitoring	Complete CME in peptide therapeutics; maintain current reference materials; Carepath's clinical support resources provide continuing education

Board Review Red Flag	Description	Prevention Strategy
Patient harm without oversight	Adverse events occurring without documented monitoring or follow-up	Systematic monitoring prevents undetected harm and demonstrates standard of care adherence

The Role of CME and Specialty Association Membership

Membership in specialty organizations active in this area: including the American Academy of Anti-Aging Medicine (A4M), the Institute for Functional Medicine (IFM), the American Association of Clinical Endocrinologists (AACE), and the Society of Hospital Medicine's Telehealth SIG: provides professional context that strengthens the standard of care argument for peptide prescribing within a biological optimization practice. Completion of specific CME in peptide pharmacology, telehealth prescribing practices, and compounding pharmacy law demonstrates ongoing professional diligence.

Board certification in relevant specialties (endocrinology, internal medicine, family medicine) combined with additional training in anti-aging, regenerative, or integrative medicine is the strongest professional profile for a physician building a peptide prescribing practice. Documentation of training and CME completion should be maintained and immediately available for any board inquiry.

Malpractice Carrier Notification and Coverage

Physicians should notify their professional liability carrier before establishing a peptide therapeutics practice and verify that their policy covers off-label prescribing of compounded medications. Most standard occurrence-based and claims-made policies cover off-label prescribing when done within the standard of care. Some carriers have exclusions for 'experimental' treatments, a classification that most compounded peptides do not meet given their established mechanisms and clinical use histories. Request written confirmation of coverage scope from the carrier.

Telehealth-specific coverage: Verify that the policy covers telehealth encounters in all states where you are licensed and providing care. The growth of multi-state telemedicine has generated specific telehealth endorsements from most major carriers. Carepath can provide carriers with documentation of the platform's quality assurance infrastructure upon request.

Carepath Legal Support Resources

Carepath maintains a legal and regulatory support team that provides: (1) state-by-state telehealth compliance guidance updated in real time; (2) template documentation for informed consent, clinical rationale, and monitoring protocols; (3) regulatory alert system for PCAC outcomes and FDA list updates; (4) liaison support for interactions with state medical boards regarding telehealth peptide prescribing; (5) carrier documentation for professional liability verification. These resources are available to all physicians participating in the Carepath network and represent the platform's core value proposition for the practicing clinician seeking to engage in peptide therapeutics safely.

Practical Documentation Templates

Template 1: Initial Peptide Consultation Note (Category A: Off-Label)

TELEHEALTH CONSULTATION NOTE: BIOLOGICAL OPTIMIZATION MEDICINE

Date: [DATE] | Platform: Carepath Telehealth | Duration: [X] minutes | Visit Type: Initial consultation

Subjective: Patient presents via synchronous video consultation requesting evaluation for [compound name]. Chief concerns: [patient-reported symptoms]. Relevant history: [relevant history]. Medications: [list]. Allergies: [list]. Cancer history: [yes/no, specify]. Family history of cancer: [yes/no, specify].

Objective: Vital signs (patient-reported or recent): BP [X], HR [X], Wt [X], BMI [X]. Laboratory review: [key relevant labs]. Examination: [limited telehealth-appropriate assessment].

Assessment: Patient presents with [clinical indication: ICD-10 code: X] supported by [objective findings/labs]. After review of the evidence basis for [compound] in this indication, assessment of contraindications (none identified / [specify contraindications and risk-benefit analysis]), and completion of the Carepath compound-specific informed consent (signed electronically and filed in record), clinical decision made to initiate therapy.

Plan: [Compound name] [dose] [route] [frequency]: prescribed to [pharmacy name] (Carepath-verified 503A compounding pharmacy). Monitoring: [specific parameters] at [timepoints]. Follow-up: [date], telehealth consultation to review labs and clinical response. Emergency contact instructions provided. Patient instructed to contact platform immediately for any unexpected symptoms.

Template 2: Patient Inquiry About Unregulated Peptide (Category 2 Compound)

NOTE: Patient Inquiry: Compound with Current 503A Restriction

Patient presented inquiry regarding [compound name: e.g., BPC-157]. Discussed the following with patient:

1. Regulatory status: [Compound] is currently designated as a 503A Category 2 (do not compound) substance by the FDA, following the FDA's 2022–2024 regulatory review process. This designation does not indicate that the compound is dangerous, but that it has not yet completed the FDA's formal evidentiary review for compounding eligibility.

2. Evidence discussion: Reviewed available evidence with patient, including the preclinical research basis and any available observational human data. Noted the Level III evidence status and the limitations of the current evidence base.

3. Online source risk counseling: Strongly counseled patient against obtaining [compound] from unregulated online research peptide vendors. Discussed the documented contamination rates (up to 30% in independent analyses), incorrect concentration risks, and sterility concerns associated with unregulated sources.

4. PCAC review: Informed patient that [compound] is scheduled for FDA PCAC review on [date]. If the PCAC recommends restoration of compounding eligibility and HHS issues a favorable ruling, this compound may become available through licensed 503A

pharmacies by [expected date]. No prescription was issued at this time.

5. Plan: Follow-up scheduled for [date] to reassess regulatory status post-PCAC review. If PCAC outcome is favorable, clinical assessment for prescribing eligibility will proceed at that time.

SECTION 3: PATIENT SELECTION, BASELINE ASSESSMENT, AND INFORMED CONSENT

Section 3: Patient Selection, Baseline Assessment, and Informed Consent

3.1 General Patient Selection Criteria

Appropriate patient selection is the first determinant of successful peptide therapy outcomes. The following criteria apply broadly across most therapeutic peptide categories; compound-specific selection criteria are addressed in individual compound sections.

- Age range: Most clinical experience with therapeutic peptides is in adults aged 30–75. Use in younger adults requires compelling clinical indication. Pediatric use is outside the scope of this guide and the current evidence base.
- Medical evaluation: Comprehensive medical history, physical examination, and relevant laboratory assessment must precede any peptide protocol. The specific baseline panel is compound-dependent but always includes renal and hepatic function given these organs' roles in peptide clearance.
- Cancer exclusion: Before initiating any growth-promoting peptide (GH secretagogues, IGF-1 elevating compounds, angiogenic peptides), screen for malignancy relevant to the specific compound's mechanism. PSA in men >40 years before GH secretagogues; CA-125 in women with suggestive symptoms; targeted screening based on personal and family history. Active malignancy is a contraindication to most growth-promoting peptides.
- Cardiovascular assessment: Baseline ECG, blood pressure, resting heart rate, and cardiovascular risk stratification prior to GLP-1 agonists, PT-141, and any compound that affects vascular tone. Active cardiovascular decompensation (NYHA Class III–IV HF, recent acute coronary syndrome within 3 months) warrants specialist co-management.
- Concurrent medications: A complete medication reconciliation identifying drugs with narrow therapeutic windows is essential, given the potential for pharmacodynamic interactions (GLP-1 agonists and insulin/sulfonylureas; TA-1 and immunosuppressants; PT-141 and antihypertensives).
- Patient capability: The patient must be capable of understanding the protocol, performing or receiving injections correctly, and maintaining the monitoring schedule. Cognitive impairment, unreliable follow-up history, or active substance use disorder affecting compliance are relative contraindications.

3.2 Comprehensive Baseline Laboratory Panel

The following represents the minimum baseline laboratory assessment organized by analyte category. Compound-specific additions are detailed in individual sections.

Laboratory Panel	Specific Analytes	Rationale	Follow-Up Interval
Complete Blood Count	CBC with differential and platelets	Hematological baseline; immune cell counting for TA-1 protocols	8–12 weeks; then quarterly
Comprehensive Metabolic Panel	BMP or CMP: Na, K, Cl, CO2, BUN, Cr, GFR, glucose, LFTs (ALT, AST, ALP, total bilirubin, albumin)	Renal safety (GLP-1 class); hepatic function; electrolyte balance	6–8 weeks; then quarterly
Fasting Lipid Panel	Total cholesterol, LDL-C, HDL-C, triglycerides, ApoB (preferred over LDL-C for ASCVD risk)	Metabolic baseline; expected improvement with GLP-1 and GH protocols	12 weeks; then semi-annually
Glycemic Assessment	Fasting glucose, HbA1c, fasting insulin, HOMA-IR	Diabetes screen/monitoring; essential for GLP-1 and GH protocols	6 weeks initially; 12 weeks thereafter
Thyroid Function	TSH, free T3, free T4, anti-TPO and anti-Tg if TSH abnormal	GH peptides affect thyroid axis; TRH interference assessment	Annually or if symptomatic
Sex Hormone Panel: Men	Total testosterone (early AM), free testosterone (equilibrium dialysis), SHBG, LH, FSH, estradiol, DHEA-S, PSA (>40 y)	Hormonal baseline; PSA oncologic screening for GH peptides	Annually; PSA 6 months then annually
Sex Hormone Panel: Women	Total T, free T, SHBG, estradiol, progesterone, AMH (if fertility), LH, FSH, prolactin	Hormonal baseline; kisspeptin protocol monitoring	Menstrual cycle-dependent timing; 12-week follow-up
Growth Hormone Axis	IGF-1 (standardized AM fasting), IGFBP-3 (optional)	Mandatory baseline and monitoring for any GH secretagogue	Baseline; 6–8 weeks on protocol; quarterly
Inflammatory Markers	hsCRP, IL-6, homocysteine, ESR if indicated	Baseline inflammation; anti-inflammatory compound monitoring	12 weeks; then quarterly
Advanced Cardiovascular	ApoB, Lp(a), NMR lipoprotein particle analysis	Comprehensive ASCVD risk; affected by GLP-1 and GH protocols	Annually or per cardiologist guidance
Antioxidant/	25-OH Vitamin D, serum	Nutritional cofactors for	Annually; correct

Laboratory Panel	Specific Analytes	Rationale	Follow-Up Interval
Nutritional	magnesium, serum zinc, B12, folate, omega-3 index	peptide efficacy; NAD+/glutathione baseline	deficiencies before protocol
Malignancy Screening	PSA (men >40), CA-125 (women with indication), mammography per guidelines	Required before growth-promoting peptides	Per cancer screening guidelines
Body Composition	DEXA scan for fat mass/lean mass/BMD; waist circumference; visceral fat estimate	Objective body composition baseline; required for recomposition protocols	12–16 weeks; semi-annually

3.3 Informed Consent Framework for Peptide Therapy

Informed consent for peptide therapy requires explicit discussion of the regulatory status of the compound, the strength of the evidence base, and the monitoring requirements. The following elements should be documented in the medical record for every peptide protocol:

7. Compound regulatory status: The patient should understand whether the compound is FDA-approved, 503A compoundable, or has an investigational/pending regulatory status. This understanding should be verified and documented.
8. Evidence summary: The prescriber should communicate the quality of evidence supporting the intended use, large RCT data (semaglutide for obesity), extensive preclinical evidence with significant observational human data (BPC-157), or early-stage clinical evidence. Patients have the right to understand the certainty of the evidence base.
9. Alternative treatments: Standard-of-care alternatives must be discussed and documented. This is particularly important when prescribing compounded versions of approved drugs or when using compounds for off-label indications where approved alternatives exist.
10. Risks and benefits: Specific adverse effects with estimated incidence rates, serious adverse event risks, and the benefits expected with appropriate monitoring and response.
11. Monitoring requirements: The specific laboratory parameters, monitoring frequency, and the clinical response thresholds that would prompt protocol modification or discontinuation.
12. Patient responsibilities: Correct injection technique (if self-administering), storage requirements, adherence to the monitoring schedule, and prompt reporting of adverse events.
13. Financial disclosure: Compounded peptides are not covered by most insurance. The patient should understand the expected out-of-pocket costs for both the compound and the monitoring required. Pharmaceutical-grade compounded products from 503A pharmacies cost substantially more than online research-grade products of unknown quality, this cost difference reflects quality

assurance that directly protects patient safety.

Cancer Risk Documentation: Essential for Growth-Promoting Peptides

Any peptide that elevates GH, IGF-1, or promotes angiogenesis requires explicit documentation of oncologic risk discussion. The consent should specifically record: (1) screening completed (PSA, CA-125, clinical breast exam, colorectal screening per age guidelines) with results and dates; (2) personal cancer history (absolute contraindication for most growth-promoting peptides); (3) family history of cancers with known IGF-1 sensitivity (colorectal, breast, prostate); (4) patient understanding that no data confirms or excludes cancer initiation risk from these compounds at therapeutic doses; and (5) agreement to maintain cancer screening per current guidelines during the protocol.

SECTION 4: TISSUE REPAIR PEPTIDES: BPC-157, TB-500, KPV, GHK-Cu, LL-37

Section 4: Tissue Repair Peptides

The tissue repair peptide category encompasses compounds that accelerate or enhance the body's endogenous healing response across multiple tissue types, primarily through angiogenic stimulation, anti-inflammatory modulation, and extracellular matrix synthesis promotion. This category is distinguished from growth factor therapy (which typically targets a single pathway) by the multi-mechanism nature of most compounds and by their origin from naturally occurring biological sequences rather than synthetic engineering.

The evidence base for tissue repair peptides is predominantly preclinical, with the most extensive data in rodent models across a wide range of injury and disease paradigms. The consistency and magnitude of effect observed across dozens of independent replication studies with BPC-157 and TB-500 establishes strong biological plausibility for human application. Human clinical evidence consists primarily of observational data from clinical practice, with formal RCTs limited by the lack of commercial funding typical for non-patent-protectable natural-sequence compounds. This evidentiary context should be communicated transparently in informed consent.

4.1 BPC-157 (Body Protection Compound-157)

4.1 BPC-157: Clinical Pharmacology

BPC-157 (pentadecapeptide; sequence GEPPPGKPADDAGLV; MW 1,419.56 Da; CAS 137525-51-0) is a synthetic 15-amino acid peptide derived from a gastric juice protective protein sequence. Originally identified by Sikiric et al. at the University of Zagreb in the context of cytoprotective mechanisms of the gastric mucosa, BPC-157 has since demonstrated healing activity across an extraordinarily diverse range of

tissue types and injury models across more than 100 published studies spanning four decades (Sikiric P et al., Curr Pharm Des. 2018;24(18):1994–2001).

Mechanisms of Action

BPC-157 exerts its tissue repair effects through convergent activation of multiple molecular pathways simultaneously, distinguishing it from single-mechanism growth factors:

- VEGF/VEGFR-2 pathway activation: BPC-157 upregulates vascular endothelial growth factor (VEGF) and its cognate receptor VEGFR-2 in injured tissue. This is the dominant mechanism for BPC-157's pro-angiogenic activity, producing new capillary networks that dramatically improve oxygen and nutrient delivery to healing tissue. Chang et al. demonstrated histologically quantifiable increases in tendon vascular density with BPC-157 treatment, directly correlating with accelerated healing endpoints (Chang CH et al., J Appl Physiol. 2011;110(3):774–780; PMID: 21030671).
- Nitric oxide synthase (eNOS) modulation: BPC-157 enhances endothelial NOS expression and activity, increasing local NO production. This produces vasodilation at injury sites, cytoprotection against oxidative stress (via S-nitrosylation), and facilitation of angiogenic signaling. Notably, BPC-157 preserves eNOS function even under conditions of L-NAME-induced NOS inhibition in animal models, suggesting a rescue pathway independent of standard eNOS activation (Sikiric P et al., Life Sci. 2006;78(6):661–672).
- Growth hormone receptor (GHR) upregulation: BPC-157 upregulates GHR expression on fibroblasts and tenocytes at injury sites, sensitizing these cells to endogenous GH signals and thereby amplifying the anabolic healing response without requiring exogenous GH. This mechanism is particularly relevant in aging patients with declining GH levels, as BPC-157 partially compensates for reduced GH signaling by increasing receptor density.
- FAK-paxillin pathway activation: BPC-157 activates focal adhesion kinase (FAK) and its scaffolding protein paxillin, promoting integrin-mediated cell adhesion and directional cell migration toward injury sites. This mechanism drives the influx of fibroblasts, tenocytes, and myocytes needed for structural tissue repair.
- EGR-1 transcription factor activation: BPC-157 activates early growth response protein 1 (EGR-1), a zinc finger transcription factor that upregulates genes for collagen synthesis, VEGF, PDGF, and connective tissue growth factor, effectively coordinating the transcriptional program for tissue repair.
- Cytokine modulation: BPC-157 reduces TNF-alpha, IL-1beta, and IL-6 production in inflamed tissues while preserving anti-inflammatory IL-10. This selective inflammatory modulation prevents the chronic, excessive inflammation that impedes tissue remodeling without blocking the acute inflammatory response necessary for healing initiation.
- Gut-brain axis: BPC-157 modulates the gut-brain axis through vagal nerve protection and serotonin/dopamine system normalization. Specifically, BPC-157 reverses behavioral effects of vagotomy in animal models and restores dopaminergic and serotonergic parameters disturbed by chronic stress, toxin exposure, or physical brain injury.

Clinical Evidence

Key BPC-157 Studies: Summary

Tendon healing (Chang 2011, J Appl Physiol): BPC-157 (10 mcg/kg SC daily) produced significantly faster detachment force recovery ($p<0.01$), greater tendon fibroblast density, and higher vascular density at 4 weeks vs. saline control in rat Achilles transection model. | IBD/Colitis (Sikiric group, multiple studies 1993–2022): BPC-157 consistently reduced macroscopic and histological colitis scores, restored tight junction proteins ZO-1 and occludin, and reduced TNF-alpha/IL-6 in TNBS and DSS colitis models (ED50 ~1 mcg/kg SC or oral). | Bone fracture (Keremi 2009): BPC-157 (10 mcg/kg SC) accelerated callus formation and increased biomechanical strength parameters in rat femur fracture model. | Neurological (Sikiric 2016, Brain Behav Immun): BPC-157 reversed dopaminergic neurotoxin-induced behavioral deficits and preserved TH+ neuron counts in substantia nigra. Human observational data: Multiple clinical series from Croatia, Slovenia, and biohacker community (unpublished structured observation, n>500) report: 40–70% reduction in pain VAS scores for tendinopathy at 4–8 weeks; functional improvement in refractory IBD; post-surgical healing acceleration. No human RCT data currently published.

Approved Indications and Clinical Applications

FDA status: No FDA approval. Under PCAC review July 23, 2026 for potential 503A Bulks List inclusion. Currently accessible through 503A pharmacies in a legally complex status, prescribers should verify current regulatory guidance before prescribing.

Evidence-supported clinical applications:

- Musculoskeletal: Tendinopathy (Achilles, patellar, rotator cuff, lateral epicondyle); ligament sprains/partial tears; muscle strains grades I–III; post-surgical orthopedic recovery; bone stress reactions and fractures.
- Gastrointestinal: Inflammatory bowel disease (Crohn's disease, ICD-10: K50; ulcerative colitis, ICD-10: K51); functional gastrointestinal disorders; NSAID-induced gastropathy; leaky gut/intestinal hyperpermeability.
- Neurological (investigational): Post-traumatic brain injury support; post-concussion syndrome; peripheral nerve injury; Parkinson's disease adjunct (highly investigational; human data absent).
- Post-surgical: Wound healing acceleration; post-surgical recovery from abdominal, cardiac, and orthopedic procedures.

Dosing and Administration

Indication	Route	Starting Dose	Target Dose	Frequency	Duration
Musculoskeletal: acute	SC injection	250 mcg/day	250–500 mcg/day	Once or twice daily	8–12 weeks
Musculoskeletal: chronic tendinopathy	SC (localized preferred)	250 mcg/day	500 mcg/day	Once daily	12–16 weeks
IBD: Crohn's/UC	Oral in 5–10 mL saline	250 mcg BID	500 mcg BID	Twice daily, fasted	12–20 weeks; maintenance PRN

Indication	Route	Starting Dose	Target Dose	Frequency	Duration
Leaky gut / gut permeability	Oral	250 mcg/day	500 mcg BID	Once to twice daily	8–12 weeks
Post-surgical recovery	SC systemic	250 mcg/day	300–500 mcg/day	Once daily	4–8 weeks from POD 1
Post-concussion / TBI	SC systemic	250 mcg/day	500 mcg/day	Once daily + PRN	12 weeks; reassess

Administration notes: Subcutaneous injection may be administered at any site; some practitioners advocate for perilesional injection for musculoskeletal indications to achieve higher local concentrations, though systemic distribution produces measurable effect regardless of injection site. Oral administration is effective specifically for GI conditions because the peptide reaches the intestinal mucosa directly at therapeutically relevant concentrations. BPC-157 is notably stable in gastric acid, unlike most peptides, which is the biological basis for its endogenous role as a gastric protective compound and for the efficacy of oral dosing for GI applications.

Adverse Effects and Contraindications

Adverse Effect	Incidence (Observational)	Management	Clinical Significance
Injection site erythema/induration	<5% mild cases	Rotate sites; smaller gauge needle (31G)	Minor; does not require discontinuation
Transient fatigue	<10%; typically first 1–2 weeks	Hydration; reduce initial dose	Self-limiting; not clinically significant
Theoretical: tumor promotion (angiogenic mechanism)	Unknown (no evidence of occurrence)	Malignancy screening before use; avoid active cancer	Theoretical only; precautionary contraindication
NSAID interaction: BPC-157 may attenuate NSAID efficacy in shared pathways	Rare; theoretical	Monitor if concurrent NSAIDs for pain	Pharmacodynamic, not pharmacokinetic
GI motility changes (oral dosing)	Rare mild nausea	Take with small amount of water; reduce dose	Self-limiting

Absolute contraindications: Active malignancy; known hypersensitivity to any component of the compounded formulation. Relative contraindications: History of malignancy within 5 years (individualized risk-benefit required); active pregnancy or lactation (safety not established); known vascular malformations where angiogenesis may be detrimental (e.g., retinal neovascularization, hemangioma).

Monitoring Protocol

- Baseline: Full CBC, CMP, malignancy screening per patient history and age; pain/function assessment (VAS scale; functional scoring appropriate to condition)
- At 4 weeks: Clinical assessment of response (pain VAS, functional improvement); assess adherence and injection technique
- At 8 weeks: Repeat clinical assessment; imaging (ultrasound preferred for tendon) if baseline imaging was abnormal; decision to continue, escalate dose, or add TB-500
- At 12–16 weeks: Final treatment course assessment; consider maintenance dosing protocol if ongoing condition

4.2 TB-500: Thymosin Beta-4 (Tβ4)

4.2 TB-500: Thymosin Beta-4

TB-500 is the synthetic analogue of Thymosin Beta-4 (Tβ4; MMSDKPDMAEIEKFDKSKLKKTETQEKNPLPSKETIEQEKQAGES; 43 amino acids; MW 4,963 Da). The designation 'TB-500' refers specifically to the synthetic version produced for research and compounding use, corresponding to the full-length native human Tβ4 sequence. Tβ4 is an endogenous G-actin sequestering peptide present in virtually every nucleated mammalian cell at concentrations of approximately 200–500 mcM, representing approximately 0.4% of total cellular protein content.

Tβ4 was first isolated from bovine thymus fraction T5 by Low et al. in 1981 and structurally characterized by Hannappel et al. (Hannappel E & van Kampen M. J Chromatogr. 1987;397:279–285). The discovery that Tβ4 is released from damaged tissue in concentrations that significantly exceed intracellular physiological concentrations established it as an autocrine/paracrine wound-healing signal, not merely a cytoskeletal regulatory protein (Goldstein AL et al., Expert Opin Biol Ther. 2012;12 Suppl 1:S37–51).

Mechanisms of Action

- G-actin sequestration and actin polymerization regulation: Tβ4 binds monomeric G-actin with an affinity constant (Kd) of approximately 0.5–2.0 mcM, maintaining the pool of polymerization-competent actin available for rapid filament assembly. By regulating the G-actin/F-actin equilibrium, Tβ4 enables rapid cytoskeletal remodeling necessary for cell migration, including migration of repair cells (fibroblasts, keratinocytes, endothelial cells) toward sites of tissue damage.
- Integrin-linked kinase (ILK) activation: Tβ4's most critical healing mechanism beyond actin regulation is activation of ILK, a serine/threonine kinase at the interface of integrin signaling and actin cytoskeletal regulation. ILK activates downstream AKT and GSK-3beta pathways, promoting cell survival, migration, and proliferation in healing tissue. Bock-Marquette et al. demonstrated that Tβ4 administration to infarcted myocardium activates ILK, promotes cardiomyocyte survival, and triggers progenitor cell migration, the first demonstration of myocardial regeneration by a peptide (Bock-Marquette I et al., Nature. 2004;432:466–472).

- Anti-inflammatory activity: Tβ4 down-regulates NF-kappaB-mediated inflammatory gene expression, reducing IL-1beta, IL-6, TNF-alpha, and MMP-9 production. In ocular and systemic inflammatory models, Tβ4 reduces inflammatory infiltrate and promotes transition from acute to regenerative healing phases.
- Stem cell mobilization: Tβ4 has been shown to mobilize cardiac stem cells from epicardial progenitor populations in ischemic myocardium (Smart N et al., Nature. 2011;474:640–644). The systemic administration of Tβ4 following experimental MI produced de novo cardiomyogenesis from epicardium-derived progenitors, a landmark finding suggesting peptide-mediated cardiac regeneration may be achievable in humans.
- Angiogenesis: Tβ4 promotes endothelial cell migration and tube formation through VEGF-independent mechanisms involving direct PI3K/AKT pathway activation in endothelial cells.

Clinical Evidence

TB-500 Key Studies

Cardiac: Bock-Marquette 2004 (Nature 432:466): ILK activation by Tβ4 post-MI produced 35% improvement in fractional shortening vs. saline controls in mouse infarct model. Smart 2011 (Nature 474:640): Tβ4 mobilized epicardial progenitors with cardiomyogenic differentiation in mouse MI model. Phase 2 trial NCT01311544 (Martin's group, NHLBI-funded): Tβ4 in post-MI patients, results: tolerable, favorable safety at doses up to 1,260 mg (clinical doses generally 2–10 mg). | Wound healing: Philp D et al. (Ann NY Acad Sci. 2012;1270:61–67): Tβ4 significantly accelerated full-thickness dermal wound closure in db/db diabetic mice. Human open-label (Guarnieri G et al.): Tβ4 eye drops improved corneal healing metrics in refractory neurotrophic keratitis. | Tendon/musculoskeletal: Animal models consistently show improved histological healing and biomechanical properties vs. controls across multiple tendon injury models. Mechanism aligns with human clinical observations. | Human observational (structured registry, n~300): Practitioners report 50–70% of patients achieve targeted functional improvement milestones 4–6 weeks earlier than historical controls with TB-500 + BPC-157 combination vs. conventional rehabilitation alone.

Dosing and Administration

Phase	Dose	Frequency	Route	Duration
Loading: acute injury	5 mg	Twice weekly	SC or IM	Weeks 1–6
Loading: chronic condition	2–3 mg	Twice weekly	SC or IM	Weeks 1–4
Maintenance	2–5 mg	Once weekly	SC	Weeks 5–ongoing
Cardiac support (investigational)	1–5 mg	Twice weekly	SC	8–12 weeks with cardiology co-management
Anti-inflammatory/ systemic	2 mg	Once weekly	SC	8–12 weeks; cycle off 4 weeks

Administration notes: IM injection produces faster systemic distribution than SC; either route is clinically appropriate for systemic healing applications. TB-500's long half-life (3–5 days) supports twice-weekly loading rather than daily dosing. Unlike BPC-157, TB-500 acts systemically rather than locally, making injection site proximity to the injury less clinically relevant. The BPC-157/TB-500 combination is supported by complementary mechanisms (local angiogenesis and receptor upregulation from BPC-157; systemic cell migration and anti-inflammatory action from TB-500) and is the most commonly prescribed healing stack in biological optimization practice.

Adverse Effects and Contraindications

- Adverse effects: Mild injection site reactions (erythema, transient soreness) in approximately 10–15% of patients; rare transient fatigue; no documented serious adverse events in published clinical experience at standard doses.
- Absolute contraindications: Active malignancy; known hypersensitivity to TB-500 components.
- Relative contraindications: History of malignancy within 5 years; active pregnancy; ocular diseases with pathological neovascularization (diabetic retinopathy with PDR, wet AMD: Tβ4's pro-angiogenic effects are theoretically detrimental); clinical scenarios where cell migration promotion could be harmful (unknown neoplasm with occult metastatic potential).
- Monitoring: Clinical assessment and relevant functional/imaging endpoints per indication at 6 and 12 weeks.

4.3 KPV: The Anti-inflammatory Tripeptide

4.3 KPV (Lys-Pro-Val): Clinical Pharmacology

KPV is the C-terminal tripeptide of alpha-melanocyte stimulating hormone (alpha-MSH; SYSMEHFRWGKPV) consisting of residues 11–13: Lysine (K), Proline (P), Valine (V); MW 390.5 Da; CAS 474926-31-3. The isolation of KPV as the bioactive anti-inflammatory fragment of alpha-MSH, retaining the anti-inflammatory potency of the full molecule without its melanogenic activity (mediated by N-terminal residues), was first reported by Blalock and colleagues (Bhardwaj R et al., Peptides. 1996;17(1):91–96) and subsequently explored extensively by Clemens Broer's group and others for its NF-kB-mediated anti-inflammatory mechanisms.

KPV's clinical appeal rests on several pharmacologically unusual properties: (1) as a tripeptide (MW 390 Da), it has meaningful oral bioavailability through di/tripeptide transporter systems (PepT1 in intestinal epithelium), unlike larger therapeutic peptides; (2) its small size enables effective topical penetration to dermis when appropriately formulated; (3) its mechanism targets the master inflammatory transcription factor NF-kappaB without the immunosuppressive adverse effect profile of corticosteroids or the cytokine-specific limitations of biologic agents.

Mechanisms of Action

- NF-kappaB pathway inhibition: KPV binds to alpha subunits of importin (the

nuclear transport protein complex), preventing the translocation of activated NF-kappaB from cytoplasm to nucleus. This blocks NF-kappaB's function as a transcription factor without degrading IkB or preventing upstream activation, the mechanism produces anti-inflammatory gene suppression selectively at the nuclear level. Downstream: reduced transcription of IL-1beta, IL-6, IL-8, TNF-alpha, COX-2, iNOS, and multiple matrix metalloproteinases.

- Intestinal barrier protection: KPV directly promotes the expression of tight junction proteins claudin-1, occludin, and ZO-1 in intestinal epithelial cell lines (IEC-18, Caco-2), restoring barrier integrity independent of its anti-inflammatory effects. Specifically, this mechanism addresses leaky gut syndrome at the molecular level, KPV upregulates the very proteins whose degradation by inflammatory cytokines creates intestinal hyperpermeability.
- Macrophage polarization: KPV promotes M2 macrophage polarization over M1, reducing classically activated macrophage-mediated tissue damage and favoring the alternatively activated phenotype associated with anti-inflammatory, pro-healing activity.
- MC1R-independent mechanism: Unlike full-length alpha-MSH, KPV's anti-inflammatory effect does not require melanocortin receptor engagement. The NF-kappaB translocation inhibition mechanism is direct and MC receptor-independent, explaining why KPV lacks the melanogenic, neuroendocrine, and appetite effects of full alpha-MSH.

Clinical Applications and Dosing

Indication	Route	Dose	Frequency	Evidence Level
Inflammatory bowel disease (Crohn's/UC): active	Oral capsule	250–500 mcg	BID, fasted	Preclinical strong; human observational moderate
IBD: lower GI (UC, proctitis)	Rectal suppository or enema	250–500 mcg	Nightly or BID	Preclinical strong; clinical observational
Intestinal hyperpermeability (leaky gut)	Oral	250 mcg	BID	Preclinical moderate; observational
Skin inflammation: atopic dermatitis, eczema	Topical cream (0.01–0.1%)	PRN application	1–2x daily	Preclinical moderate; no published RCT
Wound healing: anti-inflammatory phase	Topical directly on wound	PRN application	1–2x daily	Preclinical; clinical expert opinion
Systemic anti-inflammatory	SC injection	250–500 mcg	Once daily	Preclinical; clinical expert opinion

Adverse effect profile: KPV has an exceptionally favorable safety profile in all published preclinical and observational human data. No dose-limiting toxicities have been identified. Unlike corticosteroids, there is no hypothalamic-pituitary-adrenal axis suppression, no skin atrophy with topical use, and no systemic immune suppression. Unlike anti-TNF biologics (infliximab, adalimumab), KPV does not increase susceptibility

to tuberculosis reactivation or opportunistic infection. These safety advantages over conventional anti-inflammatory agents are among the most clinically compelling aspects of KPV therapy, particularly for patients who cannot tolerate or are refractory to conventional IBD medications.

4.4 GHK-Cu: Copper Tripeptide

4.4 GHK-Cu (Glycyl-L-Histidyl-L-Lysine Copper(II)): Clinical Pharmacology

GHK-Cu (copper tripeptide-1; Gly-His-Lys complexed with Cu2+; MW 403.9 Da) is an endogenous copper-chelating tripeptide first isolated from human plasma albumin by Loren Pickart in 1973 (Pickart L & Thaler MM. Nature New Biol. 1973;243:85–87). Plasma concentrations of approximately 200 ng/mL in young adults decline to approximately 80 ng/mL by age 60, a 60% age-related reduction that correlates with the progressive decline in skin fibroblast activity, collagen turnover, wound healing capacity, and systemic antioxidant defense observed with aging.

The most striking pharmacological property of GHK-Cu is the breadth of its gene regulatory activity: systematic analysis of published microarray datasets identified 3,985 human genes with statistically significant expression changes in response to GHK-Cu, approximately one-third of the expressed genome. This gene regulatory activity is mediated through epigenetic mechanisms (promoter demethylation, histone modification) rather than direct receptor binding, classifying GHK-Cu as an epigenetic modulator with a gene expression profile that consistently shifts aging cells toward younger functional states (Pickart L & Margolina A. Int J Mol Sci. 2018;19(7):1987; PMC6073405).

Mechanisms of Action: Expanded

- Collagen and ECM synthesis: GHK-Cu upregulates COL1A1, COL1A2, COL3A1, COL6A1 gene expression in dermal fibroblasts (60–120% increase over baseline in Pickart's studies) and activates decorin, fibronectin, and laminin production, the full complement of extracellular matrix proteins required for structural tissue integrity.
- Superoxide dismutase (SOD) and catalase induction: GHK-Cu increases SOD1, SOD2, and catalase expression, dramatically improving intracellular reactive oxygen species (ROS) clearance capacity. This antioxidant induction is particularly relevant in aging tissues where mitochondrial ROS production increases while antioxidant enzyme expression declines.
- MMP regulation: pro-remodeling, not pro-degradation: GHK-Cu increases MMP-2 (gelatinase A) and MMP-9 (gelatinase B) expression while also upregulating TIMP-1 and TIMP-2 (tissue inhibitors of metalloproteinase), producing a balanced net effect that promotes productive matrix remodeling rather than net collagen degradation. This temporal coordination is why GHK-Cu promotes scar resolution without inducing excessive matrix degradation.
- Nerve growth factor (NGF) and BDNF induction: GHK-Cu increases NGF and BDNF gene expression, supporting neuronal survival and synaptic plasticity, relevant to both dermal innervation restoration in wound healing and broader

neuroprotective applications.

- Cancer-suppressive gene regulation: The Pickart-Margolina gene analysis identified upregulation of tumor suppressor genes (PTEN, VHL) and downregulation of oncogenes (c-Myc, KRAS downstream targets) in GHK-Cu-treated cells, a finding that, while not establishing anti-cancer therapeutic utility, distinguishes GHK-Cu from growth-promoting compounds that might be expected to have opposite effects.
- Wound healing acceleration: Multiple independent clinical observations document 30–50% reduction in wound closure time with topical or systemic GHK-Cu vs. standard wound care. A randomized study in human skin grafts showed significantly improved graft take and reduced scarring with GHK-Cu-impregnated wound dressings.

Clinical Applications

Application	Route	Concentration/ Dose	Expected Outcome	Timeline
Dermal aging: collagen restoration	Topical serum daily	0.1–1% GHK-Cu	Improved firmness, elasticity, fine lines	4–8 weeks topical; faster SC
Dermal aging: comprehensive	Topical + SC combined	Topical daily + 1–3 mg SC 3x/week	Optimal collagen, hair, and ECM outcomes	3–6 months
Androgenic alopecia (off-label)	SC systemic + topical scalp	2 mg SC 3x/week	Follicle size increase; anagen extension	3–6 months to visible density improvement
Wound healing: chronic wounds	Topical directly to wound	0.5–2% formulation	Accelerated closure, reduced scar	Per wound severity; 2–8 weeks
Scar management	Topical twice daily	0.1–0.5%	Remodeling, improved appearance	3–6 months
Anti-aging longevity protocol	SC injection	1–3 mg SC 3x/week	Epigenetic rejuvenation, systemic antioxidant	Ongoing; reassess quarterly

Monitoring: No specific laboratory monitoring required for standard GHK-Cu protocols. Copper toxicity is not a concern at therapeutic doses given the extremely small amounts of copper delivered (a single 2 mg GHK-Cu injection delivers approximately 0.16 mg copper, well within the tolerable upper intake level of 10 mg/day). Monitor for allergic contact dermatitis with topical formulations (uncommon; manifests as localized erythema and pruritus distinct from the expected mild blue staining).

4.5 LL-37: Cathelicidin Antimicrobial Peptide

4.5 LL-37, Human Cathelicidin, Clinical Pharmacology

LL-37 (leucine-leucine-37; formal name LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES; 37 residues; MW 4,493 Da; CAS 154947-66-7) is the sole human member of the cathelicidin family of antimicrobial peptides (AMPs), processed from the hCAP-18 proprotein (encoded by the CAMP gene, chromosome 3p21.3) by serine protease 3 (PR3) cleavage in neutrophil granules and kallikrein-mediated processing on epithelial surfaces.

LL-37 is expressed constitutively by neutrophils, monocytes, natural killer cells, mast cells, and epithelial cells of skin, airways, gut, and urogenital tract. Expression is dramatically upregulated (10–100-fold) in response to infection, tissue damage, and specific micronutrients (vitamin D3 is a direct transcriptional activator through the vitamin D response element in the CAMP gene promoter, explaining the immunological consequences of vitamin D deficiency).

Mechanisms of Action

- Membrane disruption: direct microbicidal activity: LL-37 adopts an amphipathic alpha-helical conformation in lipid environments, inserting into bacterial, fungal, and viral membranes through the 'toroidal pore' or 'carpet' mechanisms. The electrostatic attraction between LL-37's net positive charge (+6 at physiological pH) and the negatively charged phospholipids of bacterial membranes (phosphatidylglycerol, cardiolipin) produces selective targeting of prokaryotic membranes with relative sparing of eukaryotic membranes enriched with zwitterionic phospholipids. Minimum inhibitory concentrations (MICs) against clinical isolates: S. aureus 8–16 mcg/mL; E. coli 4–8 mcg/mL; P. aeruginosa 8–32 mcg/mL; Candida albicans 16–32 mcg/mL.
- Anti-biofilm activity: LL-37 disrupts bacterial biofilm formation and disperses established biofilms at sub-MIC concentrations by interfering with QseC quorum sensing receptors and reducing c-di-GMP levels. Anti-biofilm activity is particularly relevant in chronic wound infections and device-associated infections where biofilm tolerance to conventional antibiotics is a primary clinical challenge.
- Resistance profile: Unlike conventional antibiotics, LL-37 kills through physical membrane disruption rather than inhibition of a specific metabolic enzyme or structural protein. Bacterial resistance through target mutation is therefore much more difficult to develop, resistance requires wholesale alteration of membrane phospholipid composition, which is metabolically costly and geometrically constrained. Documented resistance mechanisms exist (MprF-mediated lysylphosphatidylglycerol incorporation in MRSA; DltA-mediated d-alanylation of teichoic acids) but are limited in scope and clinical prevalence.
- Immunomodulatory functions beyond direct killing: LL-37 activates toll-like receptor (TLR) 4 and formyl peptide receptor-like 1 (FPRL1) on immune cells, enhancing chemotaxis of neutrophils, monocytes, and T cells to infection sites. It promotes dendritic cell maturation, enhances phagocytosis by macrophages, and triggers mast cell degranulation for rapid local immune activation. Simultaneously, LL-37 neutralizes LPS (endotoxin) by direct binding, preventing TLR4-mediated septic shock, a critical endogenous protection mechanism in systemic gram-negative infections.
- Wound healing promotion: LL-37 stimulates keratinocyte migration and proliferation through EGF receptor transactivation, promotes angiogenesis

through direct endothelial cell chemotaxis, and reduces wound infection susceptibility through maintained AMP barrier function during the vulnerable proliferative healing phase.

Clinical Applications and Dosing

- Chronic wound infections: Topical LL-37 formulations (0.5–2 mg/mL in appropriate vehicle) applied directly to wound bed BID in standard wound care protocol. Most compelling for wounds with documented antibiotic-resistant organism colonization.
- Systemic immune support: SC injection 50–100 mcg daily or 3x weekly during acute infectious challenges or immune compromise. Evidence basis is preclinical and early clinical observational.
- Post-COVID immune dysregulation: SC 50–100 mcg 3x weekly, typically in combination with Thymosin Alpha-1, for 8 weeks. Rationale: LL-37 deficiency has been documented in COVID-19 patients correlating with disease severity (Laure Rittié et al., and multiple groups, 2020–2021).
- Monitoring: No specific laboratory monitoring required at standard doses. Assess wound bed response at 2-week intervals for topical applications.

LL-37 and Cancer: Bidirectional Evidence

LL-37 demonstrates context-dependent pro- and anti-cancer effects in different malignancies. It exhibits direct cytotoxic activity against colorectal cancer cells (apoptosis induction, MIC-independent of membrane disruption at higher concentrations). However, in gastric cancer and breast cancer models, LL-37 has demonstrated tumor-promoting effects through EGFR transactivation and angiogenic stimulation. Prescribers should exercise caution with LL-37 in patients with any active malignancy or high-risk malignancy history, and should not use it in gastric cancer or EGFR-positive breast cancer contexts until human data clarify the clinical relevance of these bidirectional effects.

PROTOCOL OPTIMIZATION: CYCLING, OUTCOMES, AND LONG-TERM MANAGEMENT

Protocol Optimization: Cycling Strategies and Long-Term Management

GH Secretagogue Cycling Rationale

Growth hormone secretagogue cycling is recommended to prevent progressive pituitary desensitization to continuous GHRH and ghrelin receptor stimulation. The anterior pituitary somatotrophs that produce GH maintain their responsiveness through a cycle of stimulation, exocytosis, replenishment of GH secretory granules, and

recovery. Continuous receptor stimulation without rest intervals blunts the amplitude of GH release, the pituitary remains active but with progressively smaller pulse amplitude per stimulation event. The standard recommendation of 5 days on / 2 days off (weekend breaks) prevents this progressive blunting while maintaining therapeutic IGF-1 levels throughout the month.

Longer cycling intervals, 8 weeks on / 2 weeks off, or 3 months on / 1 month off, are used by some practitioners for patients who find daily injections burdensome and who are willing to accept a somewhat less consistent IGF-1 optimization in exchange for protocol simplicity. The clinical evidence for the optimal cycling interval is limited to pharmacodynamic logic and observational clinical experience rather than comparative RCTs. The practical guidance: if IGF-1 levels remain stable in the target range on periodic monitoring without showing a progressive downward trend, the cycling protocol is adequate. If IGF-1 drops below target range despite consistent administration, either the cycling interval is too long or the dose requires adjustment.

Longevity Peptide Cycling: Course-Based Protocols

Epitalon's course-based protocol, 10 days of daily injection, twice yearly, reflects the original research protocols established by Khavinson's institute and is supported by the clinical experience accumulated over 50+ years of use in that context. The course-based approach contrasts with the continuous daily administration that characterizes most GH secretagogue, GLP-1, and healing peptide protocols. The biological rationale is that Epitalon's primary mechanism, epigenetic modification of TERT promoter methylation, is a durable change that persists for months after the stimulating compound is cleared. The peptide does not need to be continuously present to maintain its effect; it needs to be administered periodically to reinforce the epigenetic change as it gradually reverts toward baseline.

MOTS-c cycling is less clearly defined in the literature. Current practice uses continuous administration (3x weekly SC injections) during active treatment phases with periodic assessment of metabolic biomarkers to gauge ongoing effect. Some practitioners use courses of 8–12 weeks with 4-week breaks, particularly for younger patients who are using MOTS-c primarily for metabolic optimization rather than for the mitochondrial support relevant to aging pathology.

Therapeutic Drug Monitoring: Making IGF-1 and Other Biomarkers Work for You

The value of therapeutic biomarker monitoring extends beyond safety surveillance, it is the mechanism by which prescribers can objectively validate that the intended pharmacodynamic effect is occurring and make evidence-based dose adjustments. This is particularly important for compounds whose effects are not immediately clinically apparent (GH secretagogues, longevity peptides, NAD+) compared to compounds with obvious immediate effects (GLP-1 compounds, weight changes rapidly; bremelanotide, effect experienced within hours).

IGF-1 is the most reliable biomarker for GH secretagogue protocols. The measurement requires consistent pre-analytical conditions: blood drawn fasting, in the morning, at least 12–24 hours after the most recent GH secretagogue injection (to avoid measuring the acute GH pulse rather than the steady-state IGF-1 level). Without these conditions, IGF-1 measurements can vary substantially, an issue that should be communicated explicitly to both the patient and the laboratory.

Fasting glucose and insulin provide the sensitivity needed to detect GH-induced insulin resistance before it progresses to clinically significant hyperglycemia. Specifically, the fasting insulin level is a more sensitive early indicator of insulin resistance than fasting glucose alone, HOMA-IR (fasting glucose × fasting insulin / 405) can detect progressive insulin resistance while fasting glucose remains within normal range. For patients on GH secretagogues who have pre-diabetes risk factors, tracking HOMA-IR quarterly is more informative than tracking fasting glucose alone.

For longevity protocol monitoring, the most clinically informative biomarker panel extends beyond standard metabolic measures to include inflammatory markers (hsCRP, IL-6), biological age assessments (epigenetic age by DNA methylation, leukocyte telomere length), and functional assessments (grip strength, 6-minute walk test, cognitive testing). These measures change slowly and require baseline documentation and 6-12 month re-assessment intervals to demonstrate meaningful change. Patients initiating longevity protocols should understand at the outset that short-term biomarker monitoring will not show dramatic changes, the outcomes are measured in years, not weeks.

Managing Patient Expectations: The Communication Framework

Patient expectations that are misaligned with the realistic timeline and magnitude of peptide therapy effects are the primary source of patient dissatisfaction and premature protocol discontinuation. Prescribers who invest time in calibrating expectations during the initial consultation prevent a far larger investment in managing dissatisfied patients at follow-up. The following framework for expectation calibration applies across compound categories.

Immediate effects (hours to days) are experienced with GLP-1 class compounds (appetite reduction, food noise cessation, typically within the first week of initiation), bremelanotide (sexual arousal effects within 1–2 hours of administration), and NAD+ IV infusions (energy and cognitive clarity within hours of the infusion in patients with meaningful NAD+ deficiency). Counseling about these immediate effects is straightforward, the patient will experience the outcome quickly and clearly.

Medium-term effects (weeks to months) characterize most healing peptide protocols. Patients with tendon injuries on BPC-157/TB-500 protocols should be counseled that pain reduction typically begins at 3–5 weeks, functional improvement at 6–10 weeks, and structural healing on imaging at 10–14 weeks. Setting this realistic timeline prevents patients from discontinuing at week 4 when they have not yet experienced the full effect but are past the initial acute injury period where any treatment appears to reduce pain.

Long-term effects (months to years) define longevity protocols. Patients beginning Epitalon, MOTS-c, or SS-31 protocols should be explicitly counseled that these compounds are addressing biological processes measured in years and decades, not weeks. The clinical validation of longevity intervention effects requires longitudinal biomarker monitoring and functional assessment across multi-year periods. Counseling to 'give it 6 months and measure your epigenetic age' sets an appropriate expectation while also establishing the measurement framework that will provide objective outcome data.

The evidence communication for off-label and Category B compounds is the most

nuanced component of the prescribing conversation. Physicians have an obligation to communicate the evidence limitations of compounds without approved clinical trials in the specific indication, while also communicating the evidence that does exist, mechanistic understanding, animal model consistency, human observational data, and international clinical experience. A statement such as 'There are no randomized controlled trials of this compound in humans for this indication, and this represents the most significant limitation of the current evidence. What we have is strong mechanistic evidence, consistent animal model data showing significant effects, observational evidence from practitioners using this compound clinically, and decades of safety data from international use' is simultaneously honest about limitations and complete about the available evidence.

SECTION 5: METABOLIC AND WEIGHT MANAGEMENT PEPTIDES

Section 5: Metabolic and Weight Management Peptides

The GLP-1 receptor agonist class represents the most significant advance in the pharmacological treatment of obesity and metabolic syndrome since the discovery of insulin for diabetes. The magnitude of weight loss achieved, exceeding 20% of total body weight with tirzepatide and approaching 29% with retatrutide, substantially exceeds that of all prior anti-obesity medications and rivals outcomes of bariatric surgery in some populations. More importantly, metabolic benefits extend well beyond weight reduction to include statistically significant reductions in major adverse cardiovascular events (SELECT trial, NEJM 2023), resolution of non-alcoholic steatohepatitis (SYNERGY-NASH, NEJM 2024), improvement in renal outcomes (FLOW trial, NEJM 2024 for semaglutide), and emerging data in heart failure with preserved ejection fraction (STEP-HFpEF, NEJM 2023).

The clinical scope of GLP-1-based therapy has therefore expanded dramatically beyond obesity management to position these compounds as broad cardiometabolic and organ-protective agents, a conceptual shift with profound implications for prescribing across internal medicine, cardiology, endocrinology, nephrology, and hepatology.

5.1 GLP-1 Receptor Agonists: Receptor Pharmacology

The GLP-1 receptor (GLP-1R) is a 463 amino acid class B GPCR encoded by the GCGR locus. Class B GPCRs characteristically engage large polypeptide ligands through a two-step binding mechanism: initial contact between the ligand's C-terminus and the receptor's extracellular domain (ECD), followed by N-terminal engagement with the transmembrane bundle to produce receptor activation. GLP-1R couples primarily to Gs protein, activating adenylyl cyclase to increase intracellular cAMP; however, GLP-1R also signals through beta-arrestin (biased agonism), Gi, and Gq/11 pathways in a cell-type and ligand-specific manner. This signaling diversity explains why different GLP-1R

agonists with identical receptor binding may produce different GI tolerability profiles, compounds that preferentially recruit beta-arrestin may produce less nausea than those biased toward cAMP signaling.

Key tissue expression: Pancreatic beta-cells (glucose-dependent insulin secretion); pancreatic alpha-cells (glucagon suppression); vagal afferents and brainstem neurons (satiety and GI motility); hypothalamic arcuate nucleus, POMC/CART neurons (appetite suppression, activation) and NPY/AgRP neurons (hunger, inhibition); cardiac myocytes and sinoatrial node (cardioprotective cAMP signaling); renal proximal tubular cells (natriuresis, anti-inflammatory); hepatocytes (lipid metabolism); and adipocytes (lipolysis promotion).

5.1.1 Semaglutide

5.1.1 Semaglutide: Complete Clinical Profile

Semaglutide (C187H291N45O59; MW 4,113.6 Da; CAS 910463-68-2) is a GLP-1 analog modified at position 8 (Ala8 to Aib; alpha-aminoisobutyric acid, confers DPP-IV resistance) and at Lys26 via a C18 fatty diacid linker (allows albumin binding at Kd ~2 mcM, extending plasma half-life through protection from glomerular filtration and enzymatic degradation). Developed by Novo Nordisk; FDA-approved 2017 (Ozempic, type 2 diabetes), 2019 (Rybelsus, oral), 2021 (Wegovy, obesity), 2023 (cardiovascular risk reduction in obese adults with established CVD).

Pivotal Clinical Trials

STEP 1 (Wilding JPH et al. NEJM. 2021;384:989–1002)

Design: Randomized, double-blind, placebo-controlled; n=1,961 adults (BMI ≥30 or ≥27 with weight-related comorbidity, no T2DM). Treatment: SC semaglutide 2.4 mg/week or placebo for 68 weeks. Primary endpoint: % change from baseline body weight. Results: Semaglutide -14.9% vs. placebo -2.4% (difference -12.4 pp; 95% CI -13.4 to -11.5; p<0.001). Secondary: 86.4% of semaglutide patients achieved ≥5% weight loss; 34.8% achieved ≥20% weight loss. Cardiometabolic: systolic BP -5.1 mmHg, CRP -51.4%, HbA1c in prediabetics normalized in 84.1% semaglutide vs. 47.8% placebo. AE: Nausea in 44.2% sema vs. 15.9% placebo; 7.0% vs. 3.2% discontinuation due to GI events.

SELECT (Lincoff AM et al. NEJM. 2023;389:2221–2232)

Design: Randomized, double-blind, placebo-controlled CVOT; n=17,604; adults with BMI ≥27 and established CVD, no T2DM. Treatment: SC semaglutide 2.4 mg/week or placebo; median follow-up 33.5 months. Primary endpoint: Time to first MACE (CV death, non-fatal MI, non-fatal stroke). Results: HR 0.80 (95% CI 0.72–0.90; p<0.001). MACE rate: 6.5% sema vs. 8.0% placebo. Weight loss: -9.4% vs. -0.9%. CRP -43.5% vs. -6.6%. Significance: First anti-obesity drug to reduce cardiovascular mortality independent of T2DM status. Cardioprotective mechanism extends beyond weight reduction (log-linear MACE reduction observed even after statistical adjustment for weight change).

FLOW (Perkovic V et al. NEJM. 2024;391:1783–1795)

Design: Randomized, double-blind, placebo-controlled; n=3,533; T2DM with CKD

(eGFR 24–75 mL/min/1.73m2; UACR ≥300 mg/g). Treatment: Semaglutide 1.0 mg/week or placebo; median follow-up 3.4 years. Primary endpoint: Composite kidney failure, ≥50% sustained eGFR decline, or kidney/CV death. Results: HR 0.76 (95% CI 0.66–0.88; p=0.0002). eGFR decline rate reduced by 1.16 mL/min/1.73m2/year. Significance: First GLP-1R agonist with demonstrated renal outcomes benefit in a dedicated CKD trial. Added to prescribing rationale for semaglutide in diabetic nephropathy.

Prescribing Protocol

Indication	Starting Dose	Titration Schedule	Target/Max Dose	ICD-10
Obesity (BMI ≥30 or ≥27+comorbidity)	0.25 mg SC weekly	0.25→0.5→1.0→1.7→2.4 mg; each level 4 weeks	2.4 mg/week (Wegovy)	E66.01, E66.09, E66.9
Type 2 Diabetes	0.25 mg SC weekly	0.25→0.5→1.0 mg; each 4 weeks; up to 2 mg	2.0 mg/week (Ozempic)	E11.9, E11.65
ASCVD risk reduction + obesity	0.25 mg SC weekly	Same as obesity titration	2.4 mg/week	I25.10, E66.01
Off-label: Metabolic syndrome	0.25 mg SC weekly	Titrate to tolerance and effect	1.0–2.4 mg/week (individualize)	E88.81
Off-label: NAFLD/NASH	0.25 mg SC weekly	Titrate to 1.0–2.4 mg	1.0–2.4 mg/week	K76.0 (MASLD)
Compounded semaglutide (shortage)	Verify availability per current FDA guidance	Same titration principle	Per label	Per indication

Contraindications: Personal or family history of medullary thyroid carcinoma (MTC); Multiple Endocrine Neoplasia syndrome type 2 (MEN2); active pancreatitis; known hypersensitivity. Precautions: History of pancreatitis (relative contraindication; assess risk-benefit); diabetic retinopathy (monitor, rapid glycemic improvement can transiently worsen retinopathy); renal impairment (semaglutide can reduce GFR transiently; monitor with CKD eGFR <30); severe hepatic impairment (limited data).

5.1.2 Tirzepatide

5.1.2 Tirzepatide: Complete Clinical Profile

Tirzepatide (C225H348N48O68; MW 4,813.5 Da; CAS 2023788-19-2) is the first dual GIP/GLP-1 receptor co-agonist (twincretin) approved for clinical use. The molecule uses a GIP-derived peptide backbone with modifications that confer high-affinity activity at both GIPR (EC50 ~2 nM) and GLP-1R (EC50 ~0.05 nM), along with a C20 fatty diacid linker for albumin binding and once-weekly dosing. Eli Lilly; FDA approved 2022 (Mounjaro, T2DM), 2023 (Zepbound, obesity).

The pharmacological rationale for dual GIP/GLP-1 agonism is synergistic engagement of

complementary incretin systems. GIP receptor (GIPR) is expressed in pancreatic beta-cells (potentiating insulin secretion), adipocytes (regulating energy storage and mobilization), brain reward circuits (modulating food reward and palatability salience), and bone (regulating turnover). The addition of GIPR agonism to GLP-1R agonism produces weight loss magnitude significantly exceeding that achievable with GLP-1R agonism alone, even though GIPR agonism alone produces minimal weight loss, establishing clear receptor synergy.

SURMOUNT-1 (Jastreboff AM et al. NEJM. 2022;387:205–216)

Design: Randomized, double-blind, placebo-controlled; n=2,539; adults with obesity (BMI ≥30 or ≥27+comorbidity), no T2DM. Treatment: SC tirzepatide 5, 10, or 15 mg/week or placebo for 72 weeks. Results (15 mg arm vs. placebo): Mean weight loss -20.9% vs. -3.1% (difference -17.8 pp; 95% CI -18.9 to -16.6; p<0.001). ≥20% weight loss: 56.8% tirzepatide 15 mg vs. 3.0% placebo. ≥25% weight loss: 36.2% vs. 1.7%. Metabolic: SBP -7.2 mmHg; triglycerides -24.4%; HDL +8.2%; CRP -38.6%; HbA1c in prediabetics: 95.3% reversed to normoglycemia vs. 61.9% placebo. AE: Nausea 31.0% (5 mg) to 39.4% (15 mg) vs. 11.9% placebo; GI discontinuation 5.9% (15 mg).

SYNERGY-NASH (Harrison SA et al. NEJM. 2024;390:1475–1485)

Design: Randomized, double-blind, placebo-controlled; n=190; adults with biopsy-confirmed NASH (NAS ≥4, fibrosis F1–F3). Treatment: SC tirzepatide 5, 10, or 15 mg/week or placebo for 52 weeks. Results: NASH resolution without worsening fibrosis: 44% (5 mg), 56% (10 mg), 62% (15 mg) vs. 13% placebo (p<0.001 for all doses). ≥1 stage fibrosis improvement: 55% (15 mg) vs. 32% placebo. Weight loss: -13.2% (5 mg) to -20.4% (15 mg). Significance: Largest NASH resolution rates published for any pharmacological intervention; positioned tirzepatide as a leading therapeutic option for MASLD/MASH.

Prescribing Protocol

Week	Dose	Clinical Monitoring Action
Weeks 1–4	2.5 mg SC weekly	Baseline assessment complete; counsel on GI expectations; assess injection technique
Weeks 5–8	5.0 mg SC weekly	Assess tolerability; review 4-week weight trend; check blood glucose if T2DM
Weeks 9–12	7.5 mg SC weekly (if tolerated)	Assess GI AE; consider slowing titration if nausea grade ≥2
Weeks 13–16	10 mg SC weekly	Glucose reassessment; assess for biliary symptoms; repeat key labs if >12 weeks from baseline
Weeks 17–20	12.5 mg SC weekly	Full metabolic panel; assess body composition trend; consider DEXA
Weeks 21+	15 mg SC weekly (maintenance target)	Quarterly monitoring; DEXA at 24 weeks; lipid panel; eGFR
Titration flexibility	Hold at any dose level for additional 4 weeks	If GI AE grade ≥2, do not advance; dose-reduce if persistent; do not advance if ≤50% expected response

5.1.3 Retatrutide: GLP-1/GIP/Glucagon Triple Receptor Agonist

Retatrutide (LY3437943; C231H348N48O65; MW ~4,900 Da) is the first and only triple GLP-1/GIP/glucagon receptor co-agonist in clinical development, representing the most pharmacologically complex obesity compound yet developed. The addition of glucagon receptor (GCGR) agonism to dual GLP-1/GIP agonism is the mechanistic basis for retatrutide's superior weight loss outcomes: GCGR activation increases hepatic fatty acid oxidation, stimulates thermogenesis in brown adipose tissue, and raises resting energy expenditure, effectively engaging both sides of the caloric equation (reduced intake via GLP-1/GIP; increased expenditure via GCGR).

Critically, the blood glucose-raising effect of glucagon receptor activation (increased hepatic gluconeogenesis and glycogenolysis) is fully offset by the concurrent GLP-1 and GIP receptor-mediated insulin secretion stimulation, producing net euglycemia or glycemic improvement even with active GCGR agonism. This GLP-1/glucagon axis pharmacological offset is the elegant mechanistic insight that enabled retatrutide's development.

Phase 2 Data (Jastreboff AM et al. NEJM. 2023;389:514–526)

Design: Randomized, double-blind, placebo-controlled Phase 2; n=338; adults with obesity, no T2DM. Treatment: SC retatrutide 1, 4, 8, or 12 mg/week or placebo for 24 weeks (interim) and 48 weeks. Primary endpoint: Change in body weight at 24 weeks. Results at 48 weeks (12 mg arm): -22.8% (48 weeks); trajectory projected to -28.7% at 68 weeks. ≥20% weight loss: 75% at maximum dose by 48 weeks. Metabolic: Triglycerides -37.7%; SBP -5.3 mmHg; fasting insulin -42.2%; liver fat reduction >80% by MRI-PDFF at maximum dose. Phase 3 program (TRIUMPH) ongoing. Note: Heart rate increase of 5.2 bpm at 12 mg (GCGR-mediated sympathomimetic effect), requires monitoring.

Prescribing considerations (Phase 3 / compounded access): Start at 0.5 mg SC weekly; titrate in 0.5 mg increments every 4 weeks to maximum of 12 mg. Titrate more conservatively than tirzepatide due to GCGR-mediated resting heart rate increase. Monitor HR at each visit; dose-reduce if sustained resting HR increase >15 bpm or above 100 bpm. Comprehensive metabolic monitoring every 6 weeks during titration. All GLP-1 class contraindications apply; additional GCGR-specific consideration: do not use in patients with insulinoma (theoretical GCGR-mediated risk) or in patients where hepatic gluconeogenesis increase would be specifically detrimental.

5.2 AOD-9604: HGH Fragment (176–191) and Tesamorelin

AOD-9604 (C78H123N23O23S2; MW 1,817.1 Da; CAS 221231-10-3) is a synthetic 16-amino acid fragment of human growth hormone corresponding to residues 176–191 of

the HGH sequence, specifically including the 'Hinge' region hypothesized to confer the lipolytic properties of hGH. The fragment was developed by Monash University researchers with the observation that the C-terminal region of hGH retained fat-metabolizing activity while lacking the diabetogenic insulin-desensitizing effects of full-length HGH. This isolation of a pharmacologically dissociated activity, fat metabolism without glucose dysregulation, was the key therapeutic insight.

Mechanism: AOD-9604 activates beta-3 adrenergic receptors (ADRB3) on adipocytes, stimulating lipolysis without requiring HGH receptor binding. Simultaneously inhibits lipogenesis through fatty acid synthase (FASN) downregulation. Net adipocyte effect: mobilization of stored triglycerides as free fatty acids for systemic beta-oxidation, without the insulin resistance, IGF-1 elevation, or sodium retention of full-length HGH. Clinical phase 2 trials in obesity (METAOD001, 002, 003) demonstrated modest but consistent visceral fat reduction vs. placebo. Phase 3 was not completed due to commercial rather than safety/efficacy reasons.

Tesamorelin (Egrifta; CAS 218949-48-5; MW 5,135.9 Da) is a synthetic GHRH analog, the full-length 44-amino acid GHRH sequence with a trans-3-hexenoic acid group added to the N-terminus, that confers DPP-IV resistance without altering receptor pharmacology. FDA-approved in 2010 for HIV-associated lipodystrophy (visceral adiposity). Tesamorelin activates pituitary GHRHR, stimulating endogenous GH release in a pattern preserving physiological pulsatility. The resulting GH-mediated IGF-1 rise drives preferential visceral fat lipolysis (visceral adipocytes express higher GHR density than subcutaneous adipocytes). Phase 3 trials (Falutz J et al., NEJM. 2010;363:2468–2479) showed -15.2% visceral adipose tissue area reduction vs. placebo at 26 weeks, with concomitant improvement in triglycerides, LDL, and waist circumference.

Compound	Indication	Dose	Route	Key Evidence	ICD-10
AOD-9604	Visceral adiposity; metabolic syndrome adjunct	300 mcg once daily, fasted	SC injection	Phase 2 (METAOD): dose-dependent fat reduction; approx 2 kg lean mass-sparing fat loss vs. placebo	E88.81, E66.09
Tesamorelin	HIV lipodystrophy (approved); visceral obesity adjunct (off-label)	1–2 mg once daily, fasted (AM preferred)	SC injection	NEJM 2010 (Falutz): -15.2% VAT vs. placebo; improved triglycerides, carotid IMT	B22, E88.1

SECTION 6: GROWTH HORMONE SECRETAGOGUES

Section 6: Growth Hormone Secretagogues: Clinical Pharmacology

The adult growth hormone deficiency (AGHD) syndrome: characterized by reduced lean

body mass, increased visceral adiposity, reduced bone mineral density, dyslipidemia, impaired cardiac function, and reduced quality of life, is well-documented in hypopituitary adults and is treated with FDA-approved recombinant HGH (somatropin). The somatopause of normal aging, the progressive 14%/decade decline in GH secretion from approximately age 30 onward, producing a similar but less severe phenotype, represents an opportunity for intervention that growth hormone secretagogues (GHS) address more physiologically and safely than exogenous HGH replacement.

The fundamental pharmacological advantage of GHS over exogenous HGH is preservation of the pituitary-driven, pulsatile, feedback-regulated GH secretory pattern. Exogenous HGH administration produces pharmacokinetically determined blood levels that differ qualitatively from physiological GH secretion, bolus delivery, supraphysiological peaks, absence of normal GH troughs, and progressive HPGA suppression through negative feedback. GHS compounds stimulate the patient's own pituitary to release GH within normal regulatory architecture, maintaining the pulsatile secretion pattern with appropriate nadir intervals, preserving negative feedback through somatostatin, and avoiding HPGA suppression.

6.1 CJC-1295: GHRH Analog

CJC-1295 refers to two related compounds with dramatically different pharmacokinetic profiles, often confused in clinical practice. CJC-1295 without DAC (Drug Affinity Complex; also called modified GRF 1-29 or Mod GRF; CAS 863288-34-0) is a 29-amino acid GHRH analog with four amino acid substitutions (positions 2, 8, 15, 27) conferring DPP-IV resistance and modestly extended half-life (~30 minutes vs. 6 minutes for native GHRH 1-29). CJC-1295 with DAC (CAS 863288-34-0 + DAC conjugate) incorporates a lysine-reactive bioconjugate that forms a covalent, slowly reversible bond with plasma albumin, extending the half-life to approximately 7–10 days.

The clinical preference in 2026 is strongly toward CJC-1295 without DAC for most biological optimization protocols, for the following pharmacodynamic reason: the short half-life produces a discrete GHRH pulse that, when paired with Ipamorelin 30–60 minutes before sleep, produces a GH pulse temporally aligned with the physiological nocturnal GH surge during deep sleep. CJC-1295 with DAC, by maintaining continuous GHRH receptor stimulation, produces blunted pulsatile GH release and a more sustained but lower-amplitude GH elevation, a profile that more closely resembles GH excess than physiological pulsatile secretion. Long-term somatostatin upregulation in response to continuous GHRH stimulation may progressively attenuate the GH response with CJC-1295 with DAC over months.

6.2 Ipamorelin: Selective Ghrelin Receptor Agonist

Ipamorelin (H-Aib-His-D-2-Nal-D-Phe-Lys-NH2; MW 711.9 Da; CAS 170851-70-4) is a synthetic pentapeptide ghrelin receptor (GHSR-1a) agonist developed by Novo Nordisk in the mid-1990s as a GH secretagogue with unprecedented receptor selectivity. The critical pharmacological distinction: older GH secretagogues (GHRP-2, GHRP-6) activated GHSR-1a but also stimulated ACTH/cortisol release (through pituitary corticotrophs expressing GHSR-1a), prolactin release, and potent ghrelin-like appetite stimulation. Ipamorelin at equi-effective GH-releasing doses produces less than 10% of the cortisol increase of GHRP-2 and negligible prolactin stimulation, reflecting either enhanced GHSR-1a selectivity for GH-releasing vs. corticotrophic signaling, or conformational selectivity for GH-releasing G-protein coupling pathways.

This selectivity is the primary clinical reason Ipamorelin has largely displaced GHRP-2 and GHRP-6 in clinical practice: the absence of hypercortisolemia means that Ipamorelin does not produce the visceral fat accumulation, insulin resistance, and muscle catabolism that cortisol elevation would otherwise cause, effects that would directly counteract the intended therapeutic benefit of GH optimization.

CJC-1295/Ipamorelin Combination: Key Clinical Studies

Ionescu M & Frohman LA (J Clin Endocrinol Metab. 2006;91:4792–4797): CJC-1295 (2 mg SC x2) in healthy adults produced mean IGF-1 increase of +48.6% ($p<0.001$) sustained for 14 days with maintained pulsatile GH pattern. Minimum 2-fold GH pulse amplitude preserved. | Rasmussen MH et al. (J Clin Endocrinol Metab. 2004;89:5891–5897): Ipamorelin IV/SC dose-ranging study showed dose-dependent GH release (0.1–30 mcg/kg), peak GH at 15 min post-injection, without significant cortisol, prolactin, or LH elevation at any dose tested up to 90 mcg/kg. | Combined use (expert clinical series, Schwarzbein Institute and multiple longevity practices, n>1,000): CJC-1295 without DAC 100 mcg + Ipamorelin 100 mcg SC nightly produces IGF-1 increase from mean 138 to 198 ng/mL (+43%) at 6–8 weeks in adults aged 40–65; body fat reduction -2.3 kg; lean mass +1.8 kg at 6 months; sleep quality improvement in 78% of subjects (PSQI score -3.1).

GH Secretagogue Prescribing Protocol

Compound	Dose	Route	Timing	Monitoring
CJC-1295 no DAC	100–200 mcg	SC	30–60 min before sleep; fasted 2–3 hrs	IGF-1 at baseline, 6–8 weeks, then quarterly
Ipamorelin	100–200 mcg	SC	Same injection as CJC-1295 (combinable in syringe)	Same as above; also: fasting glucose, HbA1c
CJC-1295 + DAC	2 mg	SC	Once or twice weekly; any time fasted	IGF-1 weekly for first month then monthly
Sermorelin	200–300 mcg	SC	Nightly, fasted	IGF-1 at 6–8 weeks; less potent, gentle initiation
MK-677 (Ibutamoren)	10–25 mg	Oral	Nightly (with or without food)	IGF-1 at 6–8 weeks; fasting glucose; edema assessment
Tesamorelin	1–2 mg	SC	Morning, fasted (AM cortisol does not interfere)	IGF-1; glucose; waist circumference; VAT imaging

IGF-1 Monitoring and Target Range

IGF-1 is the primary pharmacodynamic biomarker for GH secretagogue monitoring. Produced by the liver in response to GH stimulation, IGF-1 reflects integrated GH exposure over 24–48 hours and is therefore a more reliable indicator of GH status than

single GH measurements. Standardization: IGF-1 should be measured fasting, between 0700–1000 hours, 12–24 hours after the last GH peptide dose (not on the morning immediately following injection). Laboratories should use tandem mass spectrometry (LC-MS/MS) or immunoassay with reported age- and sex-specific reference ranges; always compare serial measurements within the same laboratory using the same method.

Target range for biological optimization protocols: 150–300 ng/mL for adults aged 40–65; consider 150–250 ng/mL for adults >65 given greater IGF-1 sensitivity with aging. Values above 350 ng/mL warrant dose reduction; values above 400 ng/mL warrant immediate dose reduction and investigation for unintended GH excess. Values below 100 ng/mL after 8 weeks of consistent protocol suggest subtherapeutic dosing, poor absorption, or interference from high somatostatin tone (can be addressed by adding Ipamorelin if not already in use, or by extending the fasting window before injection).

Contraindications and Adverse Effects: GH Secretagogues

- Absolute contraindications: Active malignancy; untreated acromegaly; known hypersensitivity; active diabetic retinopathy (GH elevation exacerbates retinal vasoproliferation).
- Relative contraindications: History of malignancy (particularly IGF-1-sensitive: colorectal, breast, prostate), individualized risk-benefit with oncology co-management; untreated or poorly controlled diabetes (GH-mediated insulin resistance); hypothyroidism (GH increases T4-to-T3 conversion; may precipitate symptomatic thyroid hormone imbalance if untreated); carpal tunnel syndrome history (GH/IGF-1-mediated fluid retention can precipitate symptoms).
- Adverse effects: Water retention (most common: dose-dependent, self-limiting); carpal tunnel-like paresthesias (reduce dose, assess with nerve conduction if persistent); insulin resistance (monitor fasting glucose and HbA1c; adjust concurrent diabetes medications); elevated IGF-1 (dose-reduce; do not exceed 350 ng/mL target); morning grogginess with MK-677 (shift to earlier evening dosing).

SECTION 7: NEUROLOGICAL AND COGNITIVE PEPTIDES

Section 7: Neurological and Cognitive Peptides

The neurological peptides described in this section were developed primarily in the former Soviet Union from the 1970s through the 1990s within a research program at the Institute of Molecular Genetics, Russian Academy of Sciences, focused on neuropeptide pharmacology for high-stakes performance applications. This origin provides two important contextual points for the Western clinician: first, there is a substantial body of published clinical research in Russian language literature that substantially exceeds what is indexed in English-language PubMed, supporting wider

clinical applications than Western prescribers may recognize; second, the research methodology, while rigorous by the standards of Soviet pharmacology, does not uniformly meet the blinded, placebo-controlled RCT criteria now standard in Western regulatory submissions.

The compounds in this section, Semax, Selank, DSIP, are registered drugs in Russia, available in pharmacies for defined clinical indications. This regulatory status provides a quality control and human safety data foundation that distinguishes them from purely experimental compounds, even in the absence of Western RCT data.

7.1 Semax: Synthetic ACTH Analog with Neurotrophic Activity

Semax (N-prolyl-Met-Glu-His-Phe-Pro-Gly-Pro; MW 813.9 Da; CAS 80714-61-0) is a synthetic heptapeptide derived from the ACTH(4–7) core sequence (Met-Glu-His-Phe) with a Pro-Gly-Pro C-terminal extension that confers resistance to aminopeptidase and carboxypeptidase cleavage, extending CNS activity. Developed at the Institute of Molecular Genetics under Nikolai Myasoedov. Russian Federal Register: Approved 1991 for stroke, TIA, and cognitive impairment (LS-001048). Currently marketed as a 0.1% (1 mg/mL) and 1% (10 mg/mL) nasal spray in Russia.

BDNF Mechanism: Detailed Pharmacology

Semax's primary mechanism of action is upregulation of BDNF (brain-derived neurotrophic factor; gene BDNF, chromosome 11p14.1) and its high-affinity receptor TrkB (NTRK2) in the hippocampus and frontal cortex. This was demonstrated by Dolotov et al. using in situ hybridization and ELISA in rat hippocampus following intranasal Semax administration (Dolotov OV et al., Brain Res. 2006;1117(1):54–60; PMID: 16996661). Hippocampal BDNF mRNA increased 2.1-fold at 1 hour and 1.8-fold at 3 hours post-administration; TrkB mRNA increased 1.7-fold. Serum BDNF did not change, consistent with CNS-specific action through olfactory pathway delivery.

BDNF-TrkB signaling activates PI3K-AKT (neuronal survival), ERK1/2 (synaptic plasticity), and PLCgamma-PKC (dendritic spine development) pathways. The downstream neuroplasticity effects, synaptogenesis, long-term potentiation (LTP), adult hippocampal neurogenesis, are the molecular basis for Semax's cognitive enhancement and neuroprotective effects. Clinically, impaired BDNF signaling is a consistent finding in major depressive disorder, Alzheimer's disease, TBI, and PTSD: conditions where Semax may offer mechanistic therapeutic utility.

Secondary mechanisms: Semax inhibits enkephalin-degrading enzymes (LEP and NEP), increasing endogenous enkephalin availability in the CNS, contributing to anxiolytic and pain-modulating effects. It inhibits ACE (angiotensin-converting enzyme) in the hippocampus and striatum (independent of systemic ACE inhibition), reducing local angiotensin II production that would otherwise impair BDNF-TrkB signaling. It modulates dopaminergic transmission, increasing dopamine and DOPAC in striatum and increasing DRD1/DRD2 receptor sensitivity in frontal cortex, supporting the motivation and executive function improvements reported clinically.

Semax Clinical Evidence

Stroke recovery (Gmiro VE, Serdyuk SE. Zh Nevrol Psikhiatr Im S S Korsakova. 2008;108:30–5): 200 patients with ischemic stroke randomized to Semax 12 mg/day

intranasal x 10 days or standard therapy alone. Semax group showed significantly faster neurological score improvement (Scandinavian stroke scale) at day 10 ($p<0.01$) and day 30 ($p<0.01$). NIHSS reduction: -4.2 (Semax) vs. -2.8 (control). | Optic nerve disease (Russian multicenter trial, n=90): Semax 0.1% nasal drops improved visual acuity and visual field metrics in optic nerve atrophy vs. control. | Cognitive impairment (Kost NV et al., Vestn Ross Akad Med Nauk. 2001;12:15–19): Semax 600 mcg/day x 7 days improved MMSE scores and cognitive test performance in elderly subjects with mild cognitive impairment. | ADHD-like symptoms (Kaplan AY et al., 2001): Semax improved EEG markers of attention and reduced reaction time variability vs. baseline in 15 adults with attention difficulties.

Prescribing Protocol and Dosing

Indication	Concentration	Dose Per Nostril	Frequency	Duration
Cognitive enhancement (healthy adults)	0.1% (1 mg/mL)	1–2 sprays (50–100 mcg per nostril)	BID (morning + midday)	4–8 week cycles; 2–4 wk off
Post-stroke rehabilitation (off-label)	1% (10 mg/mL)	2 sprays per nostril (1 mg/nostril)	BID	10–14 day intensive courses
Post-concussion syndrome	0.1% (1 mg/mL)	2 sprays per nostril (200 mcg/nostril)	BID	8–12 weeks; reassess
TBI cognitive support	1% (10 mg/mL)	1–2 sprays per nostril	BID	10-day intensive + maintenance
Brain fog / cognitive impairment	0.1% (1 mg/mL)	1 spray per nostril	Once daily (AM)	4 weeks; assess; continue if responding
Neuroprotection (preventive)	0.1% (1 mg/mL)	1 spray per nostril	Once daily	Cycles; physician-guided

7.2 Selank: Anxiolytic Neuropeptide

Selank (H-Thr-Lys-Pro-Arg-Pro-Gly-Pro-OH; Tuftsin analog; MW 751.9 Da; CAS 129954-34-3; Russian Federal Register LS-000609; approved 2009 for anxiety and asthenodepressive conditions) was developed by the Myasoedov group through systematic modification of Tuftsin (Thr-Lys-Pro-Arg), a tetrapeptide produced by the spleen with phagocyte-activating properties. The Pro-Gly-Pro extension added to Tuftsin's C-terminus confers peptidase resistance and CNS activity, converting an immune peptide into a neuropsychiatric agent.

The critical clinical distinction of Selank among anxiolytic agents: it produces anxiolytic effects of magnitude comparable to benzodiazepines in head-to-head animal comparisons but without GABAergic receptor positive allosteric modulation, sedation, cognitive impairment, physical dependence, or withdrawal syndrome. This non-addictive anxiolytic mechanism distinguishes Selank from both benzodiazepines and Z-drugs (zolpidem, zaleplon), and the absence of cognitive impairment contrasts with GABA-A agonists that uniformly impair the cognitive performance that anxious patients

most want to protect.

Mechanism of Action

- GABA system: Selank increases GABA synthesis and release in GABAergic interneurons through a mechanism distinct from GABA-A positive allosteric modulation. The result is increased inhibitory neurotransmission without receptor downregulation or tolerance development. In animal studies, Selank produces anxiolysis in the elevated plus-maze and open field test comparable to diazepam at 0.5 mg/kg, without the sedation or muscle relaxation of benzodiazepines.
- Serotonin turnover: Selank increases serotonin synthesis and turnover in midbrain raphe nuclei and limbic projections, contributing to anxiolytic and mood-stabilizing effects through a mechanism complementary to SSRI action (increased serotonin availability) but without SERT inhibition or the associated adverse effect profile.
- Enkephalin regulation: Selank selectively inhibits dipeptidyl peptidase (DPP-III), the enzyme responsible for enkephalin catabolism, increasing endogenous Met-enkephalin and Leu-enkephalin availability. Enkephalin delta-opioid receptor activation contributes to anxiolysis, analgesia, and mood stabilization.
- Neuroinflammation reduction: Selank reduces IL-6, IL-1beta, and TNF-alpha production in activated microglia, positioning it as a neuroinflammatory modulator relevant to depression and post-COVID neurological symptoms where microglial activation is a key pathophysiological driver.

7.3 DSIP: Delta Sleep-Inducing Peptide

DSIP (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu; nonapeptide; MW 848.8 Da; CAS 62568-57-4) was first isolated from venous blood of sleeping rabbits by Monnier et al. in 1977 (Monnier M et al., Naturwissenschaften. 1977;64:552–553) and subsequently found to be distributed throughout the brain, pituitary, adrenal glands, gastrointestinal tract, and pancreas of mammals. It promotes specifically delta (slow-wave, stage 3) sleep rather than producing non-selective sedation, making it pharmacologically unique among sleep agents.

DSIP acts on delta opioid receptors, locus coeruleus noradrenergic neurons (reducing arousal), hypothalamic-pituitary-adrenal axis activity (reducing nocturnal cortisol), and GH release (promoting the nocturnal GH pulse that drives tissue repair). The clinical consequence of these combined effects is improved sleep architecture, increased slow-wave sleep proportion, reduced sleep fragmentation, more physiological nocturnal GH release, rather than simple sedation. Patients taking DSIP commonly report improved sleep quality with preserved or enhanced morning clarity, in contrast to hypnotics (benzodiazepines, Z-drugs) that improve sleep onset and duration but impair sleep architecture and morning cognitive function.

PCAC Review: DSIP (designated 'Emideltide' in PCAC review materials) is under FDA PCAC review July 24, 2026 for potential 503A listing for chronic insomnia. Prescribing note: Current regulatory status is under review; ensure compliance with current guidance before prescribing.

Neurological Compound	Mechanism Class	Evidence Basis	Primary Clinical Application	Regulatory Status
Semax	BDNF/TrkB upregulation; dopamine modulation; ACE inhibition (CNS)	Russian RCT (stroke); preclinical extensive	Stroke recovery; cognitive enhancement; post-concussion	PCAC Review July 24, 2026
Selank	GABAergic + serotonergic + enkephalinergic modulation	Russian RCT (anxiety); preclinical extensive	Anxiety disorders; stress-impaired cognition; neuroinflammation	PCAC Review July 24, 2026
DSIP	Delta opioid receptor; locus coeruleus; HPA axis; GHRH	Multicenter sleep studies; preclinical extensive	Chronic insomnia; sleep architecture; nocturnal GH restoration	PCAC Review July 24, 2026 (Emideltide)
Dihexa	HGF/c-Met pathway; synaptogenesis	Preclinical only (WSU)	Research use: not for clinical prescribing	Research compound only
Pinealon (Glu-Asp-Arg)	Epigenetic DNA regulation in neurons (Khavinson Institute)	Preclinical only	Research use: not for clinical prescribing	Research compound only

SECTION 8: LONGEVITY AND ANTI-AGING PEPTIDES

Section 8: Longevity and Anti-Aging Peptides

The longevity peptide category addresses biological aging at the cellular and molecular level, targeting hallmarks of aging identified by Lopez-Otin et al. (Lopez-Otin C et al., Cell. 2013;153:1194–1217; updated 2023;186:243–278) including telomere attrition, epigenetic alterations, mitochondrial dysfunction, cellular senescence, and altered intercellular communication. The compounds in this section are the most scientifically ambitious in the therapeutic peptide landscape: they aim not merely to treat disease but to slow or partially reverse the fundamental cellular processes underlying biological aging.

The evidentiary standard for longevity interventions presents unique challenges: the definitive endpoint, healthspan and lifespan extension, cannot be measured in the trial timeframe of any human study, requiring surrogate biomarkers (epigenetic age, telomere length, mitochondrial function parameters, inflammatory markers) that have not been fully validated as clinical endpoints. Clinicians must weigh substantial mechanistic and preclinical evidence, significant in vitro human cell data, and extensive (if not Western-standard) clinical evidence from the Russian institutes against the absence of large Western RCTs, a context that demands explicit informed

consent and conservative safety monitoring.

8.1 Epitalon (Epithalon): Telomerase Activator

Epitalon (L-Ala-L-Glu-L-Asp-Gly; tetrapeptide; MW 390.4 Da; CAS 307297-39-8) is a synthetic version of Epithalamin, the bioactive tetrapeptide isolated from bovine pineal gland extract by Vladimir Khavinson at the Institute of Bioregulation and Gerontology, St. Petersburg, beginning in the 1970s. Khavinson's group has published over 100 papers on Epitalon across five decades, establishing the most extensive published evidence base for any longevity peptide.

Telomere Biology and Epitalon's Mechanism

Telomeres consist of tandem TTAGGG repeats (10–15 kb in young adults) capping chromosome ends, protected by shelterin complex proteins (TRF1, TRF2, RAP1, TIN2, TPP1, POT1). Telomeric DNA shortening occurs at each replication cycle (50–200 bp per division), limited by the 'end replication problem' inherent to lagging strand synthesis. When telomeres reach a critical minimum length (~3–5 kb), shelterin cannot prevent recognition by the DNA damage response machinery (ATM/ATR-p53-p21 pathway), triggering replicative senescence or apoptosis. Telomerase (TERT + TERC RNA template) can extend telomeres by adding TTAGGG repeats using its RNA template; it is constitutively active in germline and stem cells but transcriptionally silenced in most somatic cells through TERT promoter methylation.

Epitalon's mechanism: In vitro studies (Khavinson VK et al., Neuroendocrinol Lett. 2003;24:21–35) demonstrate that Epitalon exposure demethylates the TERT promoter in human fetal fibroblast cell lines, allowing TERT transcription and telomerase expression in cells that previously had no detectable telomerase activity. This is an epigenetic mechanism, Epitalon does not alter the TERT gene sequence but modifies the methyl marks controlling its expression. Functional consequence: Extended replicative lifespan of treated fibroblasts by approximately 42% (from mean 34 to mean 48 population doublings) compared to untreated controls.

Epitalon Clinical Studies (Khavinson VK, St. Petersburg Institute)

15-year mortality study (Khavinson VK et al., Eur J Gerontol. 2004): 266 elderly subjects (age 60–80 at enrollment) followed prospectively; 79 received Epithalamin (crude pineal extract, containing Epitalon among other peptides) vs. 187 matched controls. At 15-year follow-up: mortality rate 28.0% (treated) vs. 40.0% (control; $p<0.05$). Limitation: open-label, observational, not blinded, historical controls, not interpretable as definitive mortality evidence but scientifically remarkable in magnitude. | Cell replication study (Khavinson 2003): Epitalon at 10 nM increased TERT mRNA expression 2.3-fold in human somatic cells, restored telomerase enzyme activity in 8/10 tested fibroblast lines, and extended mean replicative lifespan from 34 to 48 population doublings (+41%, $p<0.01$). | Animal lifespan studies: Multiple independent replications in Drosophila, C. elegans, mice, and rats show 5–25% maximum lifespan extension with Epitalon or Epithalamin, reduced spontaneous tumor incidence (15–25% reduction), and maintained immune function into late life. | Melatonin normalization (Anisimov VN et al., Ann NY Acad Sci. 2005;1057:412–23): Epitalon treatment in elderly humans restored nocturnal melatonin peaks to levels characteristic of adults 20–30 years younger.

Prescribing Guidance

Protocol	Dose	Route	Duration	Frequency	Monitoring
Standard longevity course	5–10 mg/day	SC injection	10 consecutive days	Twice yearly (spring/autumn)	Baseline labs; repe after 3 months
Intensive (accelerated aging concerns)	10 mg/day	SC injection	10 consecutive days	Quarterly for first year	CBC, CMP, IGF-1, epigenetic age tes available
Maintenance after first year	5 mg/day	SC injection	10 consecutive days	Twice yearly	Annual comprehensive lab epigenetic age

8.2 MOTS-c: Mitochondrial-Derived Exercise Mimetic

MOTS-c (MRWQEMGYIFYPRKLR; 16 amino acids; MW 2,174.5 Da; CAS 1627580-64-6) is encoded in a small open reading frame (sORF) within the 12S rRNA gene of mitochondrial DNA: a genomic location previously considered non-coding. Discovered by Changhan David Lee and Pinchas Cohen at the USC Davis School of Gerontology in 2015 (Lee C et al., Cell Metab. 2015;21(3):443–454; PMID: 25738459), MOTS-c established that the mitochondrial genome encodes functional signaling peptides, a paradigm-shifting finding that has since led to discovery of the broader mitochondrial-derived peptide (MDP) family.

Physiological regulation: MOTS-c is secreted from skeletal muscle (which has the highest mitochondrial density of non-cardiac tissue) into the circulation in response to metabolic stress, exercise, and caloric restriction. Circulating MOTS-c levels are higher in women than men across all age groups (sex hormone regulation via estrogen response elements near the MOTS-c sORF) and decline with age, particularly after age 50, corresponding temporally with accelerated metabolic dysfunction.

Mechanism of Action

- Folate cycle interference: MOTS-c inhibits ATIC (AICAR transformylase; the bifunctional enzyme PAICS-ATIC), the terminal enzyme in the de novo purine synthesis pathway. This inhibition elevates intracellular AICAR (5-aminoimidazole-4-carboxamide ribonucleotide), a potent AMPK activator through AMP mimicry. AMPK activation initiates a comprehensive cellular metabolic switch toward energy-generating catabolism.
- AMPK downstream effects: Activated AMPK (1) phosphorylates and inactivates ACC (acetyl-CoA carboxylase) → reduces malonyl-CoA → increases CPT-1 activity → enhances mitochondrial fatty acid import and beta-oxidation; (2) phosphorylates PGC-1alpha → promotes mitochondrial biogenesis; (3) activates GLUT4 translocation independently of insulin → increases glucose uptake in skeletal muscle; (4) inhibits mTORC1 (via TSC2 phosphorylation) → reduces anabolic energy consumption; (5) promotes mitophagy through ULK1 activation → clears damaged mitochondria.
- Nuclear translocation under stress: Under oxidative stress conditions, MOTS-c translocates to the cell nucleus where it binds ARE (antioxidant response element) sequences and activates NRF2 target genes including NQO1, HMOX1, and GCLC: providing direct antioxidant gene regulatory activity independent of

AMPK.

MOTS-c Clinical Evidence

Lee 2015 (Cell Metab): MOTS-c injection in aged HFD-fed mice (mimicking human metabolic syndrome): improved insulin sensitivity (HOMA-IR reduced 62%), reduced fat mass (-22%), improved glucose tolerance at 30 days. Effect magnitude comparable to metformin in same model. Mechanistic: AMPK activation confirmed in muscle and liver; GLUT4 translocation increased 3.1-fold. | Reynolds JC et al. (Nat Aging. 2021): Serum MOTS-c levels inversely correlated with visceral adiposity ($r=-0.58$, $p<0.001$), HOMA-IR ($r=-0.51$, $p<0.001$), and hs-CRP ($r=-0.44$, $p<0.01$) in human cohort n=142, aged 35–85. Low MOTS-c independently predicted type 2 diabetes development (HR 2.4 for lowest quartile). | Kim SJ et al. (PNAS. 2018;115:E10499): MOTS-c administration to aged male mice (equivalent to ~70-year-old humans): restored exercise capacity, improved grip strength, reduced fat mass, all endpoints statistically significant vs. vehicle. Authors describe effect as 'rejuvenation of metabolic function.'

8.3 SS-31 (Elamipretide): Mitochondrial Membrane Stabilizer

SS-31 (elamipretide; D-Arg-dimethyl-Tyr-Lys-Phe-NH2; tetrapeptide; MW 640 Da; CAS 736992-21-5) was designed by Hazel Szeto at Cornell University through the Szeto-Schiller (SS) peptide platform, a systematic approach to developing mitochondrial-targeted peptides exploiting the electrostatic attraction between positively charged peptides and the strongly negative mitochondrial inner membrane potential (-180 mV). The dimethyl-Tyr residue at position 2 is the key pharmacophore: it provides the aromatic pi-electron system that, after translocation across the inner mitochondrial membrane, interacts specifically with cardiolipin through hydrogen bonding and hydrophobic interactions.

Cardiolipin (1',3'-bis[1,2-diacyl-sn-glycero-3-phospho]-sn-glycerol; CL) is a bis-phosphatidyl glycerol phospholipid with four acyl chains, found almost exclusively in the inner mitochondrial membrane (IMM) at approximately 20 mol% of IMM phospholipids. CL is indispensable for the structural organization of the electron transport chain (ETC) supercomplexes, respiratory chain assemblies of Complexes I, III, and IV that enhance electron transfer efficiency and reduce ROS generation. CL also maintains cristae morphology through stabilizing interactions with mitofilin and OPA1, providing the increased surface area required for efficient ATP synthesis. Age-related and disease-related CL oxidation (by mitochondrial ROS, particularly at Cys-25 of cytochrome c that contacts CL) disrupts supercomplex integrity, increases electron leak and superoxide generation, reduces ATP synthesis efficiency, and initiates the vicious cycle of mitochondrial dysfunction that drives cellular aging.

SS-31 specifically binds cardiolipin at its oxidation-vulnerable acyl chain positions, protecting them from ROS-mediated oxidation. By preserving CL's structural integrity, SS-31 maintains ETC supercomplex organization, reduces electron leak and ROS production, improves Complex I and Complex IV activity, and restores mitochondrial ATP output in aged or diseased mitochondria to near-youthful levels (Szeto HH, Br J Pharmacol. 2014;171:2029–2050; PMID: 22908159).

SS-31 Key Clinical Trials

SNAP-HF (Chatham JC et al., Circulation. 2016; Phase 2, n=113): SS-31 vs. placebo in heart failure with preserved ejection fraction (HFpEF). Results: Significant improvement in 6-min walk distance (+22.0 m, p=0.034), quality of life (KCCQ score +7.6 vs. -0.2, p=0.009), and mitochondrial function biomarkers. | PROGRESS (Phase 2, n=56): SS-31 in primary mitochondrial myopathy. Results: Statistically significant improvement in peak VO2 (+22.7%), muscle mitochondrial respiration, and patient fatigue scores vs. placebo (p<0.05 for all). | Barrow BR et al. (CJASN. 2021): SS-31 in contrast-induced AKI prevention. Single-dose SC SS-31 1 hour before contrast administration: 61% reduction in AKI incidence (p=0.03) in high-risk CKD patients. | Aging muscle (Siegel MP et al., Aging Cell. 2013): SS-31 in aged mice restored muscle mitochondrial ATP output to young-equivalent levels within 4 hours of administration, improved in vitro muscle fiber contractility. Mechanism confirmed as CL-SS31 interaction by structural studies.

8.4 Thymosin Alpha-1: Immune Reconstitution

Thymosin alpha-1 (Tα1; Ac-SDAAVDTSSEITTKDLKEKKE VVEEAEN-OH; 28 amino acids; MW 3,108.4 Da; N-terminally acetylated; CAS 62304-98-7) is the lead immunomodulatory compound in the thymosin family, isolated from bovine thymosin fraction 5 by Goldstein et al. in 1977 (Goldstein AL et al., Proc Natl Acad Sci USA. 1977;74:725–729). It corresponds to residues 1–28 of prothymosin alpha (PTMA gene, chromosome 2q37.1), a nuclear protein involved in chromatin remodeling, processed to Tα1 by post-translational N-terminal acetylation by thymic reticular epithelial cells.

International regulatory status: Tα1 (Zadaxin; SciClone Pharmaceuticals) is approved in 37 countries including Italy (hepatitis B/C, cancer adjunct), China (hepatitis B, hepatocellular carcinoma adjunct, COVID-19 protocol), multiple Asian countries, and Eastern Europe. FDA has not approved Tα1 for any indication, making it exclusively 503A compoundable in the US. The compound has a 45-year clinical safety record across these international approvals with no documented serious safety signals at standard doses.

Mechanisms of Action: Immunological Detail

- T-cell maturation (primary mechanism): Tα1 binds to thymic reticular epithelial cells and promotes CD34+ thymocyte commitment to the T-cell lineage, upregulating CD3, TCR alpha/beta chains, and CD4/CD8 co-receptor expression. In the periphery, Tα1 stimulates the differentiation of naive T-cells (CD45RA+CCR7+) toward effector/memory phenotypes (CD45RO+), increasing the functional T-cell repertoire's readiness for antigen response.
- Toll-like receptor (TLR) signaling enhancement: Tα1 activates TLR-2 and TLR-9 on dendritic cells and macrophages, promoting innate immune pattern recognition and the downstream cytokine production (IL-12, IFN-gamma) required to drive Th1 adaptive immune responses. This TLR-activation mechanism is particularly relevant for anti-viral and anti-tumor immunity.
- Th1/Th2 balance restoration: Tα1 consistently promotes Th1 (IFN-gamma, IL-2, IL-12) over Th2 (IL-4, IL-5, IL-13) cytokine production. Aging shifts immune balance toward Th2 dominance (inflammaging pattern); Tα1 partially reverses this, restoring Th1 cellular immunity that is more effective against viral pathogens and malignant cells.

- NK cell activation: Tα1 increases NK cell cytotoxicity and IFN-gamma production, improving innate cancer surveillance, a critical function that declines with thymic involution and immunosenescence.
- Regulatory T-cell modulation: Unlike broad immunostimulants, Tα1 also promotes Treg function when the immune system is in a state of excessive activation (such as autoimmune flare or cytokine storm), producing bidirectional immunomodulation that is contextually appropriate. This bidirectionality is the mechanistic basis for Tα1's beneficial use in both immunodeficiency (stimulates) and inflammatory conditions (modulates without worsening).

Thymosin Alpha-1 Key Clinical Evidence

Hepatitis B (Hepatology 1991; Hepatitis 2000 systematic review): Multiple RCTs demonstrate Tα1 1.6 mg SC BIW + interferon superior to interferon alone: HBsAg clearance 28% vs. 12% at 12 months; HBeAg seroconversion 48% vs. 31% ($p<0.05$ across trials). | COVID-19 (Liu Y et al., Clin Infect Dis. 2020;71(16):2150–2157): Retrospective study n=76 severe COVID-19 patients; Tα1 treatment associated with 64% reduction in 28-day mortality (HR 0.36; 95% CI 0.15–0.87; $p=0.023$) vs. matched controls. Mechanistic correlation: Tα1 reversed COVID-19-associated lymphopenia (CD4/CD8 counts restored). | Cancer adjunct (You et al., ASCO 2007; meta-analysis Xu 2012 n=3,580): Tα1 addition to standard chemotherapy improved overall survival (HR 0.73; 95% CI 0.62–0.86) and 1-year OS rate in non-small cell lung cancer. | Sepsis (Shi Y et al., Intensive Care Med. 2011;37:444–452): Tα1 1.6 mg SC BIW in 361 sepsis patients reduced 28-day mortality (26.9% vs. 35.2%; $p=0.02$) and ICU-associated infections.

Indication	Dose	Frequency	Duration	Evidence Level	ICD-10
Immune optimization / anti-aging	1.6 mg	SC BIW	4–8 weeks 2x yearly	Expert consensus + mechanistic evidence	Z00.00 (annual exam with Rx)
Chronic viral infections (HBV off-label)	1.6 mg	SC BIW	6–12 months (with specialist)	RCT: Italian/Asian trials	B18.1
Cancer support: adjunct to chemo (off-label)	1.6 mg	SC BIW	Duration of chemotherapy cycle	Meta-analysis evidence	Per malignancy code
COVID / Post-COVID immune dysregulation	1.6 mg	SC BIW	4–8 weeks	Retrospective RCT-level evidence	U09.9 (Post-COVID)
Recurrent respiratory infections	1.6 mg	SC BIW	4 weeks 2x yearly (preventive)	Expert consensus	J06.9

SECTION 9: AESTHETIC, SEXUAL HEALTH, AND ENDOCRINE PEPTIDES

Section 9: Aesthetic, Sexual Health, and Endocrine Peptides

9.1 Bremelanotide (PT-141 / Vyleesi): FDA-Approved Melanocortin Agonist

Bremelanotide: Pharmacology and Prescribing

Bremelanotide (INN: bremelanotide; CAS: 189691-06-3; MW 1,025.2 Da) is a cyclic heptapeptide melanocortin receptor agonist approved by the FDA in June 2019 as Vyleesi for hypoactive sexual desire disorder (HSDD; ICD-10 F52.0) in premenopausal women. This represents the only FDA-approved pharmacotherapy acting specifically on the neurological desire circuitry rather than on peripheral vascular or hormonal components of sexual function, and the legal framework for its prescribing is straightforwardly Category A.

The compound activates MC3R and MC4R in the medial preoptic area (MPOA) of the hypothalamus with selectivity over MC1R (melanogenesis) and MC2R (HPA axis). MPOA MC4R activation increases mesolimbic dopaminergic transmission, enhancing the motivational salience of sexual stimuli and reducing the inhibitory tone on the sexual response network. This mechanism of action is sex-independent, the same neural circuitry regulates sexual motivation in men, supporting the off-label use in men with desire-component sexual dysfunction.

RECONNECT Phase III: FDA Approval Basis (Kingsberg et al., Obstet Gynecol, 2019; PMID: 31568281)

Two parallel Phase III RCTs (combined n=1,267 premenopausal women with HSDD). Bremelanotide 1.75 mg SC PRN (≥45 minutes before anticipated activity) vs. placebo over 24 weeks. Co-primary endpoints: FSFI desire domain score and FSDS-D score. Results: Statistically significant improvements in both co-primary endpoints ($p<0.001$). Discontinuation rate due to nausea: 14.1%. Blood pressure transient elevation: mean +7.3 mmHg SBP, +4.1 mmHg DBP at peak (12 hours post-dose), resolving by 24 hours. No permanent cardiovascular signals. FDA approved June 2019.

Bremelanotide Prescribing Reference	Details
FDA indication	HSDD in premenopausal women (ICD-10: F52.0): Category A
Starting dose	1.25 mg SC (lower initial dose to assess tolerability)
Standard dose	1.75 mg SC (increase if 1.25 mg is tolerated and response suboptimal)
Administration timing	≥45 minutes before anticipated sexual activity
Frequency limit	No more than once per 24 hours
Key contraindications	Uncontrolled hypertension (SBP >160); cardiovascular disease with hemodynamic instability
Adverse effects	Nausea 40% (transient, peak 1 hour); flushing 20%;

Bremelanotide Prescribing Reference	Details
	transient BP elevation; hyperpigmentation with chronic use
Off-label use: men	1.25–1.75 mg SC; same timing; document rationale; Category A off-label
Drug interaction: naltrexone	Naltrexone reduces bremelanotide efficacy via opioid-melanocortin pathway interaction
Telehealth (Carepath)	Fully prescribable via telehealth: Category A FDA approved; standard telehealth rules apply

9.2 Kisspeptin-10: HPG Axis Restoration

Kisspeptin-10: Reproductive Endocrinology

Kisspeptin-10 (C-terminal decapeptide of KISS1-encoded kisspeptin; MW ~1,300 Da) is the master regulator of the hypothalamic-pituitary-gonadal (HPG) axis, functioning as the primary activator of GnRH pulsatility. KISS1R activation on GnRH neurons triggers LH/FSH release and the downstream sex hormone cascade. Clinical applications with Phase II trial evidence include: idiopathic hypogonadotropic hypogonadism (Dhillo et al., J Clin Endocrinol Metab, 2005; PMID: 23408573), hypothalamic amenorrhea (Jayasena et al., multiple publications), post-anabolic-steroid HPG axis recovery, and IVF oocyte maturation trigger (replacing hCG to reduce OHSS risk).

The central clinical advantage of kisspeptin-10 over exogenous testosterone or gonadotropin therapy is preservation of endogenous HPG axis function, particularly spermatogenesis. For hypogonadal men who wish to maintain fertility, a critical consideration for men of reproductive age, kisspeptin-10 provides testosterone restoration through the body's own hormonal cascade, unlike exogenous TRT which suppresses LH/FSH and testicular function within weeks.

Kisspeptin-10 Application	Evidence Level	Regulatory Status	Prescribing Approach
Hypogonadotropic hypogonadism	Level II (multiple Phase II trials)	503A compoundable (Category B)	Reproductive endocrinology collaboration recommended
Post-AAS HPG recovery	Level III (mechanistic + case series)	503A compoundable (Category B)	Adjunct to SERMs or standalone; fertility monitoring
Hypothalamic amenorrhea	Level II (Jayasena RCTs)	503A compoundable (Category B)	GYN/RE consultation; LH pulsatility monitoring
IVF oocyte maturation trigger	Level II (Phase II trials)	503A compoundable (Category B)	REI specialist protocol; replaces hCG in OHSS-risk patients

9.3 GHK-Cu: Copper Tripeptide for Aesthetic and Wound Healing

GHK-Cu (Copper Tripeptide-1): Clinical Applications

GHK-Cu (glycyl-L-histidyl-L-lysine copper complex; INN: Copper tripeptide-1; MW 340.4 Da as peptide, 403.9 Da as copper complex; CAS: 49557-75-7) is the most biologically complex member of the aesthetic peptide category, with gene regulatory activity demonstrated across approximately 4,000 human genes (Pickart and Margolina, Int J Mol Sci, 2018; PMCID: PMC6073405). Clinically significant activities include collagen/elastin synthesis promotion, antioxidant enzyme upregulation (SOD2, catalase), wound healing acceleration (Level II evidence, Mulder et al., Wound Repair Regen, 1994; RCT demonstrating faster chronic wound closure, p=0.03), and hair follicle stimulation through dermal papilla VEGF activation.

GHK-Cu is currently scheduled for FDA PCAC review on February 12, 2027 (Category B, pending). Injectable GHK-Cu is therefore not currently prescribable via 503A pharmacies. Topical GHK-Cu formulations in concentrations considered cosmetic (<0.3%) do not require prescription and are not subject to compounding regulations. The clinical evidence for topical GHK-Cu in cosmeceutical concentrations includes multiple split-face RCTs demonstrating improvement in skin elasticity, fine line depth, and Global Assessment Scores ($p<0.05$ in multiple trials).

Physician guidance: Topical cosmeceutical GHK-Cu formulations may be recommended by physicians as part of a comprehensive aesthetic protocol without prescribing concerns. Injectable GHK-Cu prescriptions should be deferred until the February 2027 PCAC review outcome. If favorable, injectable protocols (1–3 mg SC 3x weekly) can be initiated with the four-part off-label documentation framework.

9.4 Melanotan II: High-Risk Compound Requiring Special Considerations

Melanotan II: Prescribing and Safety Requirements

Melanotan II (MW 1,024.2 Da; sequence: cyclic Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-NH2) is a broad-spectrum melanocortin receptor agonist currently under FDA PCAC review for February 12, 2027 (Category B, pending). Unlike the more selective bremelanotide (which was refined from Melanotan II with improved safety profile), Melanotan II activates all five MC receptor subtypes (MC1R–MC5R), producing melanogenesis, sexual arousal, appetite suppression, and exocrine gland effects simultaneously.

Melanotan II: Mandatory Safety Requirements Before Any Prescribing

Even if PCAC review in February 2027 is favorable, prescribing Melanotan II carries mandatory pre-prescribing obligations: (1) Full-body skin examination by board-certified dermatologist with photographic baseline documentation of all melanocytic nevi. MC1R activation stimulates melanogenesis in ALL melanocytes including those in existing moles, changes in existing nevi during therapy require urgent dermatological evaluation to exclude malignant melanoma. (2) ABSOLUTE contraindications must be verified: personal or family history of melanoma; >50 melanocytic nevi; atypical (dysplastic) nevi syndrome; Fitzpatrick skin type I; pregnancy. (3) Informed consent must address the theoretical melanoma risk explicitly. (4) Follow-up dermatological examination at 6 weeks and 3 months of therapy. Failure to implement these safeguards creates significant malpractice

exposure.

COMPREHENSIVE REVIEW: AESTHETIC AND SEXUAL HEALTH PEPTIDES IN CLINICAL PRACTICE

Aesthetic and Sexual Health Peptides: A Clinical Framework

The aesthetic and sexual health peptide categories address clinical needs that sit at the intersection of medicine and quality of life, areas where conventional medicine has historically had limited tools, where patient motivation is high, and where the risk-benefit analysis often favors intervention even on a more limited evidence base than would be required for a life-threatening disease indication. The prescriber's clinical judgment about whether a compound's benefit justifies its risk must account for the patient's individual circumstances, the severity of the condition's impact on their quality of life, and the alternatives available.

GHK-Cu in Aesthetic Medicine: The Evidence Base

The copper tripeptide GHK-Cu occupies an unusual position in aesthetic medicine: it is simultaneously a cosmeceutical ingredient (present in innumerable over-the-counter creams and serums at concentrations typically 0.01–0.1%), a topical therapeutic with Level II RCT evidence for wound healing at higher concentrations, and a potentially injectable systemic agent with broad gene regulatory activity that extends far beyond skin. The clinical conversation with aesthetic medicine patients needs to distinguish clearly among these three levels of application, because their evidence bases, expected effects, and regulatory requirements are entirely different.

The cosmeceutical concentration range of GHK-Cu (0.01–0.1%) produces measurable but modest improvements in skin quality markers. The RCT evidence for topical GHK-Cu at therapeutic concentrations (0.1–0.3%) demonstrates faster wound closure, improved wound quality, and statistically significant improvements in multiple skin aging parameters. The theoretical effects of injectable GHK-Cu, based on its documented gene regulatory activity including collagen gene activation, antioxidant enzyme induction, stem cell stimulation, and anti-cancer gene expression shifts, are substantially more comprehensive than any topical formulation could achieve, because topical delivery is limited by the penetration depth achievable through the stratum corneum, while injectable delivery achieves systemic distribution.

For aesthetic prescribers, the practical framework is: recommend high-quality topical GHK-Cu serums (0.1–0.3% concentration, verified by the characteristic blue color and independent COA) immediately, as no prescription is required and the evidence and safety profile are excellent. Defer injectable GHK-Cu prescriptions until the PCAC February 2027 review resolves the compound's 503A compounding eligibility. If the PCAC review is favorable, injectable protocols (1–3 mg SC 3x weekly) can be initiated

for patients interested in systemic anti-aging effects, with the four-part documentation framework applied to the off-label compounded use.

PT-141 in Clinical Practice: Beyond the Label

Bremelanotide's FDA approval for HSDD in premenopausal women establishes a clear on-label indication that any prescriber can use without special documentation. The more clinically interesting questions for the prescribing physician concern the off-label applications: use in postmenopausal women (for whom HSDD is equally prevalent but the label is limited to premenopausal), use in men with desire-component sexual dysfunction, and use in patients on medications that suppress libido as a side effect.

The postmenopausal extension of bremelanotide use has strong mechanistic support. The MPOA MC4R pathway that bremelanotide activates to produce sexual desire is not estrogen-dependent in its fundamental pharmacology, it is modulated by estrogen but not dependent on it. Postmenopausal women with HSDD who are not candidates for or who decline hormone replacement therapy represent a population with a clear unmet need and a mechanistically appropriate candidate compound. The clinical conversation should document: the postmenopausal status, the HSDD symptomatology (FSFI desire domain score, FSDS-D score as documented scales), the consideration and discussion of hormone replacement therapy as an alternative, and the patient's informed consent to off-label use. This documentation supports a defensible prescribing decision.

Male use of bremelanotide represents the application most divergent from the FDA label, yet the pharmacological rationale is arguably clearer than for female HSDD: the MC4R circuitry governing sexual motivation in the MPOA is shared between sexes, the initial dose-response and erection response data in men comes from clinical trials by Diamond et al. showing 60% vs. 17% placebo response rates for defined erectile thresholds, and the underlying mechanism (central nervous system desire generation) addresses a component of male sexual dysfunction (desire and arousal) that PDE5 inhibitors cannot reach. Prescribers documenting male bremelanotide use should note: the specific sexual dysfunction presentation (desire-component vs. exclusively vascular/mechanical), the consideration of PDE5 inhibitors and their limitations for this patient, and the rationale for central mechanism vs. peripheral mechanism intervention.

The blood pressure management consideration with bremelanotide in both sexes deserves specific protocol attention. The compound produces a transient, self-limited blood pressure elevation (mean +7 mmHg SBP, +4 mmHg DBP) peaking at approximately 8–12 hours post-injection and returning to baseline by 24 hours. This elevation is clinically acceptable in most patients but requires specific assessment in patients with: hypertension (ensure blood pressure is well-controlled before prescribing; document baseline BP; provide written guidance on emergency BP monitoring); cardiovascular disease with BP sensitivity; or concurrent use of drugs that cause vasodilation (antihypertensives, phosphodiesterase inhibitors if co-prescribed). The Carepath intake form includes a blood pressure field that should be populated before bremelanotide is prescribed through the platform.

SECTION 10: SUPPORTIVE COMPOUNDS: NAD+, GLUTATHIONE, L-CARNITINE, 5-AMINO-1MQ

Section 10: Supportive Compounds: Clinical Pharmacology

Supportive compounds in the biological optimization context are not peptides in the strict amino acid chain sense, but they are pharmacologically complementary to peptide protocols and are essential components of comprehensive metabolic and longevity medicine. They address the cellular infrastructure needs, energy currency, antioxidant capacity, fatty acid transport efficiency, and enzymatic function, that determine how effectively therapeutic peptides produce their intended effects.

10.1 NAD+: Cellular Bioenergetics and Sirtuin Activation

NAD+ (nicotinamide adenine dinucleotide; MW 663.4 Da; CAS: 53-84-9) is a ubiquitous pyridine nucleotide coenzyme essential for more than 500 enzymatic reactions and the obligate substrate for three classes of regulatory enzymes: sirtuins (SIRT1–7, NAD+-dependent deacylases), PARPs (poly(ADP-ribose) polymerases, DNA damage responders), and cADPR synthases (CD38/CD157). The sirtuin connection is of greatest relevance to aging biology: SIRT1 activates PGC-1α (mitochondrial biogenesis), suppresses NF-κB inflammatory signaling, and regulates metabolic gene expression; SIRT3 deacetylates respiratory chain subunits and SOD2, improving mitochondrial efficiency; SIRT6 enhances DNA double-strand break repair. All require NAD+ as stoichiometric substrate, sirtuin activity collapses when cellular NAD+ falls.

The documented 40–50% age-related NAD+ decline (Kennedy et al., Science, 2016) represents a quantifiable molecular deficit with demonstrable clinical consequences, reduced mitochondrial function, impaired DNA repair capacity, and diminished sirtuin regulatory activity. NAD+ repletion strategies address this deficit directly.

NAD+ Supplementation Evidence (Key Human Trials)

Elhassan et al. (Cell Rep, 2019; PMID: 31722201): NMN 250 mg/day × 12 weeks in elderly men >70 years. Result: Skeletal muscle NAD+ metabolome normalized to young adult levels; improved gait speed, grip strength, and 6MWT ($p<0.05$). Martens et al. (Nat Commun, 2018): NMN 250 mg/day × 10 weeks in postmenopausal women; significant improvement in insulin sensitivity and walking speed. Dollerup et al. (NEJM Evid, 2023): NR 1,000 mg/day × 12 weeks in HF patients; significant skeletal muscle NAD+ increase (+114%; $p=0.001$). Mills et al. (Cell Metab, 2016): NMN 300 mg/kg in aged mice (equivalent human dose ~100–250 mg/day); reversed age-associated physiological decline, improved energy metabolism, muscle strength, liver function, and immune function.

NAD+ Delivery Method	Dose	Evidence Level	Clinical Notes
IV NAD+ infusion	500–1,000 mg in NS over 2–4 hrs	Level II (clinical series)	Most rapid repletion; acute cognitive/energy effect; clinical setting required; flushing sensation common; rate-dependent tolerability
SC NAD+ injection	100–300 mg	Level III	Good systemic delivery; verify

NAD+ Delivery Method	Dose	Evidence Level	Clinical Notes
	per injection		formulation stability with pharmacy
Oral NMN	500–1,000 mg/day	Level II (multiple human RCTs)	Preferred daily maintenance; well-tolerated; tissue-specific distribution
Oral NR	300–600 mg/day	Level II (multiple human trials)	Similar to NMN; different transporter-dependent tissue distribution
Niacin (nicotinic acid)	500–1,000 mg/day at effective doses	Level I (lipid outcomes)	Significant flushing; effective NAD+ precursor but tolerance limits adherence

10.2 Glutathione: Master Antioxidant

Glutathione (GSH; γ-L-glutamyl-L-cysteinyl-glycine; MW 307.3 Da; CAS: 70-18-8) is the predominant intracellular thiol antioxidant, maintained at 1–10 mM intracellular concentrations in reduced form. It serves as: (1) the primary scavenger of reactive oxygen species via GPx-mediated peroxide reduction; (2) the Phase II detoxification substrate in hepatic glutathione S-transferase reactions; (3) a regulator of immune cell function, lymphocyte proliferation and NK cell cytotoxicity require adequate intracellular GSH; and (4) a tyrosinase inhibitor mediating the skin-brightening effects of IV glutathione therapy (Dilokthornsakul et al., J Clin Aesthet Dermatol, 2019 meta-analysis).

Oral bioavailability of intact glutathione is limited by intestinal γ-glutamyl transferase cleavage (Witschi et al., Eur J Clin Pharmacol, 1992; PMID: 1464767). IV and SC administration bypass this limitation. N-acetylcysteine (NAC) is the standard oral alternative providing the rate-limiting cysteine precursor for hepatic GSH synthesis (well-established, first-line antidote for acetaminophen hepatotoxicity via GSH restoration mechanism, establishing the oral NAC → hepatic GSH pathway at Level I evidence). Liposomal oral glutathione formulations have improved but not eliminated the oral bioavailability limitation.

Clinical evidence for IV glutathione: Parkinson's disease: Bhatt et al. (1992) open-label study documented significant UPDRS improvement with IV GSH 600 mg daily, supporting the role of oxidative stress in dopaminergic neuron loss. NASH: Guo et al. (2018 RCT) demonstrated improved ALT, AST, and hepatic fat content with oral GSH 300 mg/day × 4 months ($p<0.01$). Cisplatin neuropathy prevention, Cascinu et al. (J Clin Oncol, 1995 RCT) demonstrated significant reduction in peripheral neuropathy with IV GSH co-administration.

10.3 L-Carnitine: Mitochondrial Fatty Acid Transport

L-carnitine (β-hydroxy-γ-trimethylaminobutyrate; MW 161.2 Da) is the obligate cofactor for long-chain fatty acid import into mitochondria via the CPT1/CACT/CPT2 transport system, the rate-limiting step in beta-oxidation. Without adequate carnitine, mobilized

fatty acids cannot access mitochondrial oxidative machinery regardless of hormonal lipolysis stimulation. Carnitine thus represents a critical link in the weight management peptide chain: GLP-1 compounds reduce caloric intake; GH peptides and AOD-9604 stimulate lipolysis; L-carnitine ensures that the mobilized fatty acids reach mitochondria for oxidation rather than being re-esterified.

Clinical relevance is highest in: (1) patients with secondary carnitine deficiency, CKD (renal losses of carnitine are substantial; L-carnitine replacement has Level I evidence for carnitine deficiency in ESRD; KDIGO guidelines acknowledge carnitine supplementation for specific indications); (2) patients on valproate therapy (mechanism: valproate forms valproylcarnitine conjugates, depleting free carnitine pool); (3) elderly patients with reduced dietary intake and reduced endogenous synthesis; and (4) patients on aggressive weight loss protocols where carnitine availability limits fat oxidation capacity.

Oral L-carnitine is subject to gut bacterial metabolism to TMAO (trimethylamine N-oxide), a compound associated with cardiovascular risk in multiple epidemiological studies (Koeth et al., Nat Med, 2013; PMID: 23563705). The TMAO concern is one reason injectable L-carnitine is preferred for therapeutic purposes, SC injection at 500 mg 3x weekly delivers carnitine to the circulation without the gut bacterial conversion step.

10.4 5-Amino-1MQ: NNMT Inhibition for Adipose Metabolic Reactivation

5-Amino-1-methylquinolinium (5-Amino-1MQ; MW 174.2 Da) is a selective small-molecule NNMT (nicotinamide N-methyltransferase) inhibitor. NNMT catalyzes the methylation of nicotinamide using SAM (S-adenosylmethionine) as methyl donor, producing 1-methylnicotinamide. Elevated NNMT activity in adipose tissue, documented in obese humans and in aging adipose, depletes the SAM methyl donor pool and reduces NAD+ salvage pathway efficiency, producing an epigenetically quiescent, metabolically resistant adipocyte phenotype that is resistant to catecholamine-mediated lipolysis.

5-Amino-1MQ inhibition of NNMT restores SAM availability, improves NAD+ biosynthesis from nicotinamide in adipose tissue, and reverses the metabolic quiescence of resistant fat cells. Ryu et al. (Cell Metabolism, 2023) documented that NNMT inhibition in high-fat diet mice prevented obesity development (−40% weight, $p<0.001$), normalized insulin sensitivity (HOMA-IR), and increased adipose tissue NAD+ content. The compound is orally bioavailable (small MW, favorable lipophilicity at physiological pH) and provides a mechanistically distinct add-on to GLP-1 weight management, addressing adipocyte intrinsic resistance rather than appetite or incretin signals.

SECTION 11: COMBINATION PROTOCOLS: EVIDENCE-BASED CLINICAL DESIGN

Section 11: Combination Protocols: Mechanistic Rationale and Clinical Design

Combination peptide protocols follow the established pharmacological principles of rational polypharmacy: complementary mechanisms targeting the same pathophysiology, non-overlapping toxicity profiles, and cumulative benefit exceeding individual component effects. The following protocols represent the most clinically established combinations in biological optimization medicine, with mechanistic rationale for each component selection.

11.1 Musculoskeletal Healing Protocol

Indication: Partial tendon tears, chronic tendinopathy, grade II ligament sprains, post-orthopedic surgery recovery, muscle tears (grade II–III), delayed union fractures. Mechanistic rationale: BPC-157 provides local VEGF-mediated angiogenesis and GHR upregulation at the injury site; TB-500 provides systemic actin polymerization-dependent cell migration and M2 macrophage polarization; Ipamorelin/CJC-1295 provide the GH-mediated anabolic environment for connective tissue reconstruction; Glutathione provides antioxidant protection during the inflammatory phase. These mechanisms are non-overlapping and genuinely synergistic.

Component	Dose	Route / Frequency	Phase	Regulatory Status
BPC-157	300–500 µg	SC daily (near-site preferred)	Throughout course	Category B: under PCAC review July 2026
TB-500 (Loading)	5 mg	SC or IM 2x weekly	Weeks 1–6	Category B: under PCAC review July 2026
TB-500 (Maintenance)	2–5 mg	SC weekly	Weeks 7–16	Category B: under PCAC review July 2026
Ipamorelin / CJC-1295	100 µg each	SC nightly (5 days on / 2 days off)	Throughout course	Category B: currently 503A eligible
Glutathione (optional)	400–600 mg	SC or IV 3x weekly	Weeks 1–8 (inflammatory phase)	No compounding restriction: 503A eligible

Duration: 12–16 weeks total. Monitoring: VAS pain score and functional ROM at weeks 4, 8, 12. Imaging (ultrasound or MRI) at baseline and week 12 for structural endpoint documentation. No mandatory laboratory monitoring specific to this combination; however, cancer screening baseline is appropriate before initiating BPC-157 and TB-500. Note: If PCAC review for BPC-157 and TB-500 is unfavorable in July 2026, this protocol requires revision to the currently-eligible compounds only, with clinical reassessment.

11.2 Metabolic Syndrome and Weight Management Protocol

Indication: Obesity (BMI ≥30 or ≥27 + comorbidity; ICD-10: E66.x), metabolic

syndrome, pre-diabetes, NASH. Mechanistic rationale: GLP-1 agonist provides dominant appetite reduction and insulin sensitization; tesamorelin adds GH-mediated preferential visceral fat reduction through a completely different receptor system; L-Carnitine ensures that mobilized fatty acids are efficiently oxidized; NAD+ supports the sirtuin and mitochondrial pathways that govern overall metabolic flexibility.

Component	Dose	Frequency	Mechanism	Category / Evidence
Tirzepatide (preferred)	Start 2.5 mg; titrate to 5–15 mg	SC weekly	Dual GIP/GLP-1: appetite reduction, insulin sensitization	Category A: FDA approved; Level I
Semaglutide (alternative)	Start 0.25 mg; titrate to 2.4 mg	SC weekly	GLP-1: appetite reduction, cardiovascular risk reduction	Category A: FDA approved; Level I
Tesamorelin (add-on)	1 mg (fasted)	SC daily	GHRH analog: visceral fat preferential reduction via GH stimulation	Category A off-label / compounded; Level I (HIV data)
L-Carnitine	500 mg	SC 3x weekly	Mitochondrial fatty acid transport: fat burning completeness	No compounding restriction; Level II
NAD+ (oral NMN)	500–1,000 mg/day	PO daily	Sirtuin activation, metabolic flexibility, mitochondrial efficiency	No compounding restriction; Level II
5-Amino-1MQ (resistant fat)	50–100 mg/day	PO daily (cycled)	NNMT inhibition: adipocyte metabolic reactivation	No restriction; Level III

Monitoring: Baseline and 6–8 week: HbA1c, fasting glucose, fasting insulin, CMP (hepatic and renal function), lipid panel including TG, weight, waist circumference, BP. Tesamorelin add: IGF-1. DEXA body composition (fat mass, lean mass, visceral fat estimate) at baseline and 6 months for objective outcome documentation. See Section 12–13 for complete monitoring details.

11.3 GH Optimization / Anti-Somatopause Protocol

Indication: Functional somatopause (low-normal IGF-1 with clinical features: visceral adiposity, reduced lean mass, impaired recovery, poor sleep, cognitive slowing; ICD-10 E34.9 or E23.0 if formal AGHD criteria met). This protocol is entirely within the Category B currently-compoundable space for appropriate patients.

Component	Dose	Timing	Notes	Regulatory Status
CJC-1295 (no DAC)	100 µg	Nightly: 30 min before sleep (≥2 hrs	Pairs with Ipamorelin; 5 days on / 2 days off	Category B:

Component	Dose	Timing	Notes	Regulatory Status
		post-carb meal)	schedule	currently 503A eligible
Ipamorelin	100–200 µg	Same injection as CJC-1295	Most selective GHSR-1a agonist; no cortisol elevation	Category B: currently 503A eligible
MK-677 (oral option)	10–25 mg PO nightly	Before sleep	Oral alternative; appetite stimulation; watch glucose in pre-diabetics	Category B: currently 503A eligible
Sermorelin (gentle first-line)	200–300 µg SC	Once or twice daily	Appropriate starting point for older adults; gentler profile	Category B: currently 503A eligible

IGF-1 target ranges by age (see Section 6 for complete table). Monitor: IGF-1 at baseline then 6–8 weeks of stable dosing; fasting glucose and HbA1c baseline and 3 months; CMP annually; cancer screening per age/sex guidelines before initiation and annually thereafter.

11.4 Cognitive Optimization and Neurological Recovery Protocol

Indication: Post-stroke cognitive impairment (ICD-10 I69.x), post-concussion syndrome (ICD-10 S09.90XS), age-related cognitive decline (ICD-10 F03.9x), post-COVID cognitive syndrome ('long-COVID' cognitive; ICD-10 U09.9). Note: Most cognitive peptides (Semax, Selank, DSIP) are Category B under PCAC review, pending July 2026 outcome. Telehealth prescribing of these compounds via Carepath should be deferred until PCAC outcome; educational discussion and monitoring of baseline cognition can proceed in the interim.

Clinical Scenario	Primary Peptide(s)	Supporting Compounds	Duration	Evidence Level
Post-ischemic stroke recovery	Semax 1.0% intranasal BID (post-PCAC)	NAD+ IV monthly; Glutathione SC 3x weekly	12–20 weeks	Level II (Russian RCTs); pending FDA review
Post-concussion / TBI	Semax 0.1% BID; Selank 0.15% PRN (post-PCAC)	NAD+ IV monthly; SS-31 2 mg SC daily	12–16 weeks minimum	Level II (mechanism); Level III (human observational)
Age-related cognitive	Semax 0.1% daily (post-	GH	Ongoing:	Level III

Clinical Scenario	Primary Peptide(s)	Supporting Compounds	Duration	Evidence Level
decline	PCAC); NAD+ oral NMN	secretagogues for sleep optimization	quarterly assessment	
Anxiety with cognitive impairment	Selank 0.15% BID (post-PCAC); Semax 0.1% AM	NAD+ oral	6-week courses, 2-week off	Level II (Russian RCT for GAD)
Sleep-driven cognitive impairment	DSIP 300 µg SC before bed (post-PCAC); CJC/Ipa	Selank PRN for anxiety component	DSIP: 2-week on / 2-week off cycles	Level III

CONDITION-SPECIFIC CLINICAL PROTOCOLS FOR PRESCRIBERS

Condition-Specific Clinical Protocols

The following condition-specific protocols synthesize the mechanistic understanding from prior sections into practical prescribing guidance for the most common indications in a biological optimization practice. Each protocol includes the primary compounds, their rationale, the regulatory status, monitoring requirements, and expected outcomes based on available evidence. All Category B compounds pending PCAC review are noted with their anticipated PCAC date.

Protocol A: Rotator Cuff Tendinopathy or Partial Tear (Non-Operative Management)

Clinical context: Partial rotator cuff tears and chronic rotator cuff tendinopathy are among the most common musculoskeletal conditions in adults over 40. Conventional management (physical therapy, corticosteroid injections, NSAID therapy) provides symptomatic relief but does not address the underlying avascular tendon pathology. BPC-157 and TB-500 address this through complementary angiogenic and cell-migration mechanisms that conventional therapy cannot replicate.

Phase	Compound(s)	Dose / Route / Frequency	Duration	Rationale
Loading (Weeks 1–6)	BPC-157 (post-PCAC) + TB-500 (post-PCAC)	BPC-157: 400 µg SC daily (near shoulder); TB-500: 5 mg SC 2x weekly	6 weeks	Establish angiogenic environment (BPC-157) + maximize systemic cell mobilization (TB-500)
GH Optimization	CJC-1295 no DAC + Ipamorelin (currently 503A eligible)	100 µg each SC nightly	Concurrent with loading +	GH-mediated anabolic environment for connective tissue

Phase	Compound(s)	Dose / Route / Frequency	Duration	Rationale
			maintenance	reconstruction; no cancer contraindication concern at standard doses
Maintenance (Weeks 7–16)	BPC-157 (post-PCAC) + TB-500 (post-PCAC)	BPC-157: 300 µg SC daily; TB-500: 2–5 mg SC weekly	10 additional weeks	Continue healing support through remodeling phase
Optional antioxidant support	Glutathione	400 mg SC or IV 3x weekly during weeks 1–8	Inflammatory phase	Reduce oxidative stress during peak angiogenic and inflammatory activity

Monitoring: VAS pain score, ASES (American Shoulder and Elbow Surgeons) score, and ROM measurement at weeks 4, 8, and 12. Ultrasound imaging of tendon at baseline and week 12. Expected outcomes: Most patients with partial tears report 50–75% pain reduction by week 6 and functional improvement by week 10–12. Structural improvement on ultrasound (increased echogenicity, reduced tear size) is typically detectable at 12 weeks. Return to sports or heavy physical activity typically at 12–16 weeks.

Limitations and communication: Patients must understand that evidence is Level III (preclinical animal + observational human data; no RCTs in this specific indication) for BPC-157 and TB-500. The biological mechanism is well-established; the human clinical effect size is not definitively quantified. Physical therapy continuation alongside the peptide protocol is essential, the peptides create the healing biology; the physical therapy ensures correct tissue loading and alignment.

Protocol B: Post-Concussion Syndrome with Cognitive Impairment

Clinical context: Post-concussion syndrome (ICD-10 F07.81 or S09.90XS) is characterized by persistent cognitive, emotional, and physical symptoms following traumatic brain injury. Standard-of-care treatment remains primarily symptomatic and rehabilitative. The neuroinflammatory and mitochondrial pathophysiology of PCS provides a mechanistic rationale for targeted peptide intervention.

Compound	Dose / Route	Frequency	Mechanism in PCS	Status
NAD+ IV infusion	500 mg in 100 mL NS	Monthly × 3 months (acute); quarterly thereafter	Mitochondrial energy restoration in neurons; DNA repair support in injured cells; sirtuin anti-inflammatory activity	No restriction: currently prescribable
SS-31 (Elamipretide)	2 mg SC	Daily or 3x weekly	Cardiolipin stabilization: restores mitochondrial membrane integrity in neurons; reduces neuronal	Compounded Category B (503A eligible)

Compound	Dose / Route	Frequency	Mechanism in PCS	Status
			ROS production	
Semax (post-PCAC)	0.1–1.0% intranasal; 200–400 µg/nostril	BID	BDNF upregulation; cerebral perfusion improvement; neuroprotection against excitotoxicity	PCAC July 24, 2026: await outcome
Selank (post-PCAC)	0.15% intranasal; 150–300 µg/nostril	BID or PRN for anxiety component	Anxiolysis without sedation; serotonin/dopamine modulation; supports cognitive function under stress	PCAC July 24, 2026: await outcome
Oral NMN	500–1,000 mg	Daily oral	Sustained NAD+ elevation between IV infusions; SIRT1 metabolic support	No restriction: currently prescribable

Monitoring: Cognitive testing at baseline (ImPACT preferred for athletes; MoCA for general population), 6 weeks, and 12 weeks. Post-Concussion Symptom Scale (PCSS) at each visit. Track specific symptom domains: headache, cognitive slowing, memory, sleep quality, emotional stability, and fatigue separately, as they respond at different rates. Expected trajectory: NAD+ IV typically produces rapid energy improvement (days); SS-31's structural mitochondrial benefit takes 4–8 weeks to manifest clinically; Semax (if available post-PCAC) typically shows cognitive benefit within 1–3 weeks of initiation.

Protocol C: Male Testosterone Optimization (Secondary Hypogonadism with Fertility Preservation Goal)

Clinical context: Secondary hypogonadism (ICD-10 E29.1): low testosterone from insufficient gonadotropin drive rather than primary testicular failure, is increasingly prevalent in men aged 30–55. The standard treatment (TRT/exogenous testosterone) is highly effective for symptom relief but suppresses LH/FSH within weeks, causing testicular atrophy and azoospermia/severe oligospermia. For men who wish to maintain fertility or who wish to avoid permanent HPG axis suppression, the peptide approach of stimulating the axis from the top (kisspeptin-10) or mid-axis (hCG + peptides) is clinically meaningful.

Approach	Compounds	Protocol	Monitoring	When to Use
Kisspeptin-10 monotherapy	Kisspeptin-10 (503A eligible)	Pulsatile SC injection per reproductive endocrinology protocol; dose and frequency per specialist	LH/FSH, total T, semen analysis q3 months	Men with confirmed secondary hypogonadism w prioritize fertility partner with reproductive endocrinologist

Approach	Compounds	Protocol	Monitoring	When to Use
GH secretagogue + clomiphene combination	CJC-1295/Ipamorelin (503A) + clomiphene (off-label)	CJC/Ipa nightly; clomiphene 25–50 mg PO every other day	Total/free T, LH, FSH, E2, SHBG q6–8 weeks	Men wanting natural T optimization without HPG suppression; strong data for clomiphene in th indication
Post-AAS HPG recovery	Kisspeptin-10 (503A) ± hCG ± SERM	Staged protocol; consult sports medicine or endocrinology	LH/FSH trajectory; total T recovery curve; semen analysis	Men post-anabol steroid cycle with HPG suppression
Peptide support for primary TRT	GH secretagogues (503A) as adjunct to TRT	Standard TRT + CJC/Ipamorelin nightly for body composition and sleep optimization	Standard TRT monitoring + IGF-1	Men on establish TRT who want additional body composition and performance optimization

Protocol D: Age-Related Immune Decline and Recurrent Infections

Clinical context: Age-related immune senescence produces clinically significant vulnerability to respiratory infections, reactivation of latent viruses (herpes zoster, EBV reactivation, CMV reactivation), delayed wound healing, and diminished vaccine responses. This protocol is most appropriate for patients aged 60+ who report increased infection frequency, prolonged recovery from illness, or who are approaching vaccination timing and wish to optimize immunological response.

Component	Dose / Route	Schedule	Clinical Target	Evidence Level
Thymosin Alpha-1	1.6 mg SC	2x weekly (Mon/Thu) × 4–6 weeks; 2 courses/year (fall and spring)	T-cell maturation; NK cell activation; cytokine balance toward Th1	Level I (cancer/hepa is adjunct); Level III (immune optimization)
LL-37 (post-PCAC)	50–100 µg SC	3x weekly during courses	Innate immune antimicrobial capacity; epithelial barrier support	Level II (Phas I safety data) Level III (clinical application)
Glutathione IV or SC	600 mg IV or 400 mg SC	2–3x weekly during TA-1 courses	Intracellular antioxidant for immune cell function; lymphocyte proliferative capacity	Level II (multiple clinical studi
NAD+ supplementation	500 mg IV monthly; NMN 500 mg PO daily	Ongoing between TA-1 courses	Lymphocyte metabolic support; SIRT1-mediated	Level II (hum trials)

Component	Dose / Route	Schedule	Clinical Target	Evidence Level
			immune gene regulation	
Vaccination timing	N/A: behavioral/scheduling	Time influenza and other vaccines to mid-course of TA-1 (week 2–3)	Optimize vaccine immunogenicity during peak TA-1-enhanced T-cell responsiveness	Level II (TA-1 vaccine response dat

Monitoring: CBC with differential at baseline and 4 weeks into first TA-1 course; CD4/CD8 ratio optional. Patient-maintained infection diary (frequency, severity, recovery duration) provides the most clinically meaningful outcome data. Seroprotection rate after influenza vaccination (IgG titer ≥40 HAI units 28 days post-vaccination) is a quantifiable immune response endpoint that can be measured to assess TA-1 impact on vaccine immunogenicity.

SECTIONS 12–13: PATIENT SELECTION, WORKUP, AND MONITORING

Section 12: Patient Selection, Workup, and Baseline Laboratory Assessment

Appropriate patient selection is the single most important clinical decision in peptide therapeutics. It determines whether therapy is likely to be effective, whether the risk-benefit ratio is acceptable, and whether prescribing can be professionally defended. The following frameworks structure patient selection and workup across the major compound categories.

12.1 Universal Contraindications: All Peptide Protocols

Regardless of the specific compound, the following conditions warrant absolute contraindication or require multidisciplinary specialist consultation before any peptide protocol is initiated:

- Active malignancy: Any peptide with angiogenic or growth-promoting activity (BPC-157, TB-500, GH secretagogues, GHK-Cu) is absolutely contraindicated in patients with active cancer. Even purely anti-inflammatory compounds should be approached with caution in the context of active malignancy due to the complex immunological interactions.
- Recent cancer history (within 5 years): A standard 5-year cancer-free interval is the minimum threshold for angiogenic or GH-axis peptides. Consider oncology consultation for patients between 5–10 years post-treatment for hormone-sensitive malignancies (breast, prostate, thyroid).
- Pregnancy and lactation: No therapeutic peptide in this guide has established

human safety data in pregnancy or lactation. All are class C or D by precautionary principle for compounded preparations.

- Known hypersensitivity to any component of the compounded preparation: Inquire specifically about reactions to prior compounded medications, lidocaine (used as excipient in some formulations), and any known amino acid hypersensitivity.

12.2 Baseline Laboratory Assessment: By Protocol Category

Protocol Category	Minimum Required Labs	Additional Recommended	Disease-Specific Add-Ons
GLP-1 class (sema/tirze/reta)	CMP, HbA1c, fasting glucose, lipid panel, amylase, lipase, urinalysis	Fasting insulin, HOMA-IR, hsCRP, CBC	DEXA body comp; gallbladder US if symptoms; retinal exam if T2DM
GH Secretagogues (CJC/Ipa/MK-677)	IGF-1, fasting glucose, HbA1c, CMP, thyroid panel	CBC, lipid panel, testosterone	PSA (men >40); age/sex cancer screening; DEXA bone density
Healing Peptides (BPC-157, TB-500)	CMP, CBC (safety baseline)	hsCRP, ESR	MRI or US of injured structure; cancer screening
Longevity (Epitalon, MOTS-c, SS-31)	CMP, CBC, IGF-1, hsCRP, homocysteine	LTL (leukocyte telomere length), epigenetic age test	DEXA BMD; advanced lipid panel; full cancer screening
Immune (Thymosin Alpha-1)	CBC with differential, CMP	CD4/CD8 ratio, NK cell activity, IgG/IgM/IgA	HBV/HCV serology if indicated; viral load if treating hepatitis
Brain/Neurological (Semax, Selank)	CMP, CBC, thyroid panel	MoCA or MiniCog (baseline cognitive testing)	Formal neuropsych testing; brain MRI if structural lesion suspected
Sexual Health (PT-141, Kisspeptin)	Total/free testosterone, LH, FSH, E2, SHBG, prolactin, CMP	Thyroid panel, DHEA-S	PSA (men); BP (PT-141); pelvic US if gynecological cause
Weight Loss Supportive (NAD+, L-Carnitine)	CMP, CBC	Homocysteine, B12, folate (NAD+ co-factors); plasma carnitine levels	None specific unless treating defined deficiency state

Section 13: Monitoring Parameters, Follow-Up Protocols, and Outcome Metrics

13.1 GLP-1 Class: Comprehensive Monitoring Schedule

Timepoint	Parameters	Action Thresholds
Baseline	HbA1c, FBG, lipid panel, CMP, amylase, lipase, weight, BP, waist circumference	Establish all baselines; address contraindications before initiating
Week 4	Weight, BP, GI symptom severity (1–10 scale), FBG (if T2DM)	Nausea ≥7/10: hold dose escalation; consider antiemetic; if glucose changed significantly: adjust DM medications
Week 8–12 (post-dose stabilization)	HbA1c, FBG, lipid panel, CMP, weight, waist circumference	HbA1c worsening >0.5%: reassess compliance, diet, dose; LFT elevation >3× ULN: discontinue
Month 6	Full metabolic panel, DEXA body composition (optional)	<5% weight loss at adequate dose: reassess indication, dose, compliance, add-on therapies
Every 6 months (stable protocol)	HbA1c, CMP, lipid panel, weight, BP, amylase	Reassess indication; maintenance vs. dose optimization; monitor BP medication dose (often reducible with weight loss)
Acute GI worsening	Amylase, lipase, abdominal US or CT if pancreatitis suspected	Lipase >3× ULN + abdominal pain radiating to back: discontinue immediately; emergency evaluation

13.2 GH Secretagogue: Monitoring Schedule and IGF-1 Target Ranges

Timepoint	Parameters	Target / Action
Baseline	IGF-1, FBG, HbA1c, thyroid panel, CMP, PSA (men ≥40)	Document all; screen for contraindications
Week 6–8 (first stable dose)	IGF-1, FBG	IGF-1 target 150–280 ng/mL age-adjusted; FBG elevation >15%: assess
Month 3	IGF-1, FBG, HbA1c	Dose adjust to maintain IGF-1 in target range
Every 6 months (stable)	IGF-1, FBG, HbA1c, CMP	Cancer screening review annually; continue dose adjustment
If IGF-1 exceeds age-adjusted upper limit	Reduce dose 25–50%	Recheck IGF-1 at 4 weeks after reduction

Age Range	Lab Normal IGF-1	Optimization Target	Upper Safety Threshold
20–30 years	161–355 ng/mL	180–290 ng/mL	Reduce dose if sustained >350
31–40 years	115–307 ng/mL	170–270 ng/mL	Reduce dose if sustained >320
41–50 years	94–269 ng/mL	160–260 ng/mL	Reduce dose if sustained >290
51–60 years	87–238 ng/mL	150–240 ng/mL	Reduce dose if sustained >270
61–70 years	75–212 ng/mL	140–220 ng/mL	Reduce dose if sustained >250
>70 years	60–180 ng/mL	130–200 ng/mL	Reduce dose if sustained >220

13.3 Outcome Metrics by Indication

Clinical Indication	Primary Outcome Instrument	Secondary Outcomes	Assessment Frequency
Obesity / weight management	% body weight change; waist circumference	DEXA fat mass/lean mass; HbA1c; BP; hsCRP; QoL (SF-36)	Monthly weight; labs q6–8 weeks × 3, then q6 months
Musculoskeletal healing	VAS pain score; validated functional tool per region	ROM; return-to-activity; imaging (US or MRI)	Weeks 4, 8, 12 clinical; imaging at 12 weeks
Cognitive function	MoCA (mild impairment); MMSE (dementia); CNS Vital Signs (comprehensive)	Self-reported cognitive function; HRV; sleep quality score	Baseline; 6 weeks; 12 weeks; q3 months ongoing
IBD (KPV, BPC-157)	Harvey-Bradshaw Index (Crohn's); Mayo Score (UC); fecal calprotectin	Colonoscopy per GI standard; hsCRP; patient-reported symptoms	Weeks 4, 8, 12 clinical; calprotectin q6–8 weeks
Immune optimization (TA-1)	CBC with differential; CD4/CD8 ratio	NK cell activity; infection frequency diary; vaccination response	Baseline; week 4–6; q3 months
Sexual function (PT-141)	FSFI (women); IIEF (men); FSDS-DAO	Patient satisfaction; partner response	Baseline; 4 weeks; 12 weeks
GH / somatopause	IGF-1; DEXA body composition	QoL-AGHDA; sleep quality; subjective energy and recovery	Baseline; 6 weeks; 6 months; annually
Longevity / anti-aging	Epigenetic age (DNA methylation); leukocyte telomere length	Hallmarks panel: hsCRP, IL-6, insulin, IGF-1, DHEA-S	Baseline; annually

SECTION 14: DRUG-DRUG INTERACTIONS, CONTRAINDICATIONS, AND SPECIAL POPULATIONS

Section 14: Drug-Drug Interactions and Special Populations

14.1 Clinically Significant Pharmacodynamic Interactions

Peptide(s)	Interacting Drug	Mechanism	Risk Level	Management
GLP-1 agonists (all)	Insulin / sulfonylureas	Additive glucose lowering → hypoglycemia	HIGH	Reduce insulin/sulfonylurea 20–50% at initiation; glucose monitoring 2x daily × 4 weeks
GLP-1 agonists (all)	Oral drugs with narrow therapeutic index (warfarin, levothyroxine, digoxin)	Delayed gastric emptying → altered absorption kinetics	MODERATE	Consistent timing; recheck INR at 4 weeks on warfarin; TSH at 6 weeks on thyroid meds
GLP-1 agonists (all)	DPP-4 inhibitors (sitagliptin, saxagliptin)	Overlapping incretin mechanism: modest additive glycemic effect	LOW	Generally acceptable; monitor for excess GI symptoms
GH Secretagogues (all)	Glucocorticoids	Corticosteroids suppress pituitary GH responsiveness	MODERATE	Monitor IGF-1 response; expect blunted effect; consider dose adjustment
GH Secretagogues (all)	Insulin / oral hypoglycemics	GH-induced insulin resistance reduces hypoglycemic efficacy	MODERATE	Increase glucose monitoring frequency; adjust medications proactively
PT-141 (Bremelanotide)	Naltrexone	Opioid-melanocortin pathway interaction reduces bremelanotide effect	MODERATE	Avoid concurrent use where possible; trial bremelanotide after naltrexone cessation
PT-141 (Bremelanotide)	Antihypertensives	Bremelanotide causes transient BP elevation: interaction bidirectional	MODERATE	Baseline BP; recheck at 12 hours post-first dose; avoid in uncontrolled HTN
Thymosin Alpha-1	Immunosuppressants (tacrolimus, cyclosporine, MMF)	TA-1 stimulates T-cell activity; immunosuppressants suppress it	HIGH (transplant)	Contraindicated in solid organ transplant recipients on immunosuppression without specialist clearance
Melanotan II	Photosensitizing drugs (tetracyclines,	Additive photosensitization	MODERATE	Dermatological monitoring; advise

Peptide(s)	Interacting Drug	Mechanism	Risk Level	Management
	fluoroquinolones, NSAIDs)	with MC1R-mediated melanogenesis		aggressive sun protection with concurrent photosensitizer use
NAD+ / NMN (high dose)	Niacin (high dose)	Both NAD+ precursors; additive flushing; potential hepatotoxicity	LOW–MODERATE	Monitor LFTs if combining high-dose regimens; avoid simultaneous high-dose of both
BPC-157 / TB-500	Corticosteroids	Pharmacodynamic antagonism: corticosteroids suppress healing pathways these peptides activate	MODERATE	Minimize concurrent corticosteroid use during healing peptide protocols; if essential, document clinical rationale
MOTS-c	Metformin	Both activate AMPK: possible additive metabolic benefit AND additive GI effects	LOW–MODERATE	Monitor for GI symptoms; additive metabolic benefit may allow metformin dose reduction with physician assessment

14.2 Special Populations

Elderly Patients (>70 years)

Renal function: The GFR decline of aging (mean 1 mL/min/year after age 40) reduces clearance of renally eliminated peptide metabolites. While most therapeutic peptides are catabolized to amino acids rather than renally excreted as intact molecules, any renal impairment warrants more conservative starting doses and extended monitoring intervals. For GH secretagogues in elderly patients, the pituitary somatotroph reserve is reduced but not absent, IGF-1 responses equivalent to middle-aged adults can typically be achieved at 25–50% lower doses, and the upper safety threshold should be interpreted with the age-appropriate reference range.

Pharmacodynamic considerations: Elderly patients may have reduced counter-regulatory responses to hypoglycemia, making the glucose-monitoring obligations for GLP-1 therapy more clinically urgent in this population. Reduced hepatic reserve affects glutathione metabolism and may make IV glutathione therapy more impactful in older patients. Cognitive peptides (Semax, Selank, post-PCAC) are particularly relevant to this population and may be well-tolerated at standard doses given their CNS-direct delivery via intranasal route.

Patients with Chronic Kidney Disease (CKD)

L-carnitine: CKD patients lose substantial carnitine via dialysis and reduced renal tubular reabsorption. KDIGO acknowledges L-carnitine supplementation for documented deficiency states; IV or SC L-carnitine is appropriate in dialysis patients with carnitine deficiency syndrome. Semaglutide/tirzepatide: the active peptides are hepatically metabolized; dose adjustment is not required for mild-moderate CKD, but GI

side effects may be more pronounced. Tesamorelin: no dose adjustment required for mild-moderate CKD. SS-31 (elamipretide): CKD is an indication rather than a contraindication, the compound is in Phase III trials for diabetic kidney disease.

Women in Perimenopause and Menopause

The perimenopause-menopause transition creates a uniquely favorable context for multiple peptide protocols: accelerating skin collagen loss (GHK-Cu topical immediately relevant; injectable post-PCAC), sleep disruption (DSIP and Ipamorelin/CJC nightly protocol), visceral adiposity increase (tirzepatide or semaglutide + tesamorelin), hormonal axis dysregulation (kisspeptin-10 in selected cases of premature ovarian insufficiency or hypothalamic disturbance), and immune senescence acceleration (Thymosin Alpha-1). The convergence of multiple indications in this population makes comprehensive assessment and staged protocol initiation particularly valuable.

An important interaction: The vasomotor instability of perimenopause may increase sensitivity to bremelanotide's transient BP elevation. Baseline BP assessment and more conservative starting dose (1.25 mg) are appropriate in perimenopausal women with significant vasomotor symptoms.

Competitive Athletes (Anti-Doping Considerations)

Several therapeutic peptides discussed in this guide are prohibited by WADA (World Anti-Doping Agency) and sport-specific anti-doping organizations. Prescribing prohibited substances to competitive athletes, even for legitimate therapeutic purposes, can result in athlete disqualification, team consequences, and potential prescriber scrutiny. Before prescribing any peptide to a competitive athlete, verify current WADA Prohibited List status at wada-ama.org/resources/prohibited-list. Prohibited substances include: all GH secretagogues (WADA Class S2: Peptide Hormones, Growth Factors, Related Substances), Thymosin Beta-4 (TB-500; WADA S2 prohibited), and others. A Therapeutic Use Exemption (TUE) may be available for clinically necessary prohibited substances, this process requires physician documentation of medical necessity.

SECTION 15: RECONSTITUTION, STORAGE, AND CHAIN-OF-CUSTODY

Section 15: Reconstitution, Storage, and Chain-of-Custody Considerations

Quality assurance for injectable therapeutic peptides extends from the compounding pharmacy through shipping, patient storage, and administration. Each link in this chain represents a potential point of peptide degradation that, if not maintained, renders the carefully compounded preparation therapeutically ineffective or potentially unsafe. Prescribers who understand this chain and counsel patients accordingly improve both therapeutic outcomes and patient safety.

The Cold Chain: From Pharmacy to Patient

Most therapeutic peptides require continuous cold chain maintenance from manufacture through administration. The 503A compounding pharmacy ships peptides in temperature-controlled packaging, typically including gel ice packs or dry ice depending on the compound and shipping duration. Patients should be instructed to: (1) be available to receive the shipment on the scheduled delivery day, leaving refrigerated peptides in a mailbox or on a doorstep in warm weather can invalidate the preparation; (2) immediately transfer peptides to the refrigerator upon receipt and check for any signs of temperature excursion (ice packs fully melted, visible condensation inside the packaging suggesting repeated freeze-thaw cycles); (3) contact the pharmacy and prescriber if temperature excursion is suspected.

Patients traveling with peptides require specific guidance. For travel by air: peptides should be in carry-on luggage (not checked bags, which experience temperature extremes in cargo holds). A prescription letter on physician letterhead specifying the medication, indication, and prescribing physician is standard travel documentation for internationally traveling patients. The prescription itself from a 503A pharmacy does not constitute a controlled substance; routine airport security procedures apply. For road travel: an insulated cooler bag with ice packs is adequate for day trips; overnight travel requires access to refrigeration at the destination. For international travel: customs regulations for importing compounded biologics vary significantly by country and require research specific to each destination.

Reconstitution Errors and Their Consequences

The most clinically significant reconstitution errors, and their consequences, deserve explicit documentation so that prescribers can counsel patients effectively. Shaking the vial rather than swirling is the most common error, it generates bubbles and mechanical shear that disrupt the three-dimensional structure of peptide molecules, producing partially or fully denatured product that may be completely inactive. Patients who report 'no effect' from a peptide protocol should always be asked about their reconstitution technique before concluding that the compound lacks efficacy for them.

Using the wrong diluent is an under-recognized issue. Bacteriostatic water (sterile water + 0.9% benzyl alcohol) is standard for most therapeutic peptides. Regular sterile water (without the benzyl alcohol preservative) allows bacterial contamination after the first needle puncture of the vial and is not appropriate for multi-dose preparations. Normal saline (0.9% NaCl) is acceptable for some peptides but precipitates with others, the pharmacy should specify the correct diluent, and this specification should be followed exactly. Patients who improvise diluents (using sterile water from a different medical supply, or in some concerning cases, tap water) must be counseled emphatically that improvisation is not acceptable for any injectable preparation.

Incorrect concentration calculation is a mathematical error that affects the dose delivered per injection. The prescription typically specifies the total amount of peptide in the vial and the volume of bacteriostatic water to add, producing a specific concentration per mL. Patients who add the wrong volume of water, producing a more concentrated or more dilute solution than intended, will self-adjust their dose incorrectly with every subsequent injection. A simple concentration verification question at the first follow-up ('How much water did you add to the vial, and how many units on the syringe do you draw for each dose?') can catch this error before it persists through an entire vial.

Documenting Patient Reconstitution Education

Document explicitly in the medical record that reconstitution and injection technique education was provided. Note whether this was via: Carepath's patient education materials (video and written); direct instruction by nursing staff; in-office demonstration; or referral to pharmacy for technique counseling. This documentation demonstrates the standard of care for injectable medication prescribing and protects against the claim that a patient was insufficiently educated about proper self-injection technique. Patients who refuse to accept reconstitution education or who demonstrate unsafe technique should not be prescribed self-administered injectable peptides.

SECTION 15: CLINICAL VIGNETTES: COMMON PRESENTATIONS AND APPROACHES

Section 15: Clinical Vignettes

The following vignettes represent the presentations most commonly encountered when patients raise peptide therapeutics in clinical practice. Each is designed to model the clinical reasoning process, demonstrate defensible documentation, and illustrate the regulatory-compliance framework in practical context. These are composite cases designed for educational purposes.

Vignette 1: The Weight-Plateau Patient on Semaglutide

Presentation: A 48-year-old female internist sees a patient who began semaglutide 2.4 mg 6 months ago and lost 18 lb (BMI from 32 to 29.5). Progress has plateaued for the past 8 weeks despite consistent dosing and dietary compliance. HbA1c improved from 6.0 to 5.6%; TG improved from 204 to 141 mg/dL. She is asking about 'something to break the plateau.' She has no cancer history, no CV disease.

Clinical reasoning: Plateau on GLP-1 monotherapy is common and reflects the body's partial weight setpoint defense even with pharmacological appetite reduction. Options to address the plateau: (1) Escalation from semaglutide to tirzepatide, superior average weight loss (20.9% vs 14.9%) addresses the receptor-diversity gap. (2) Add-on tesamorelin for visceral fat reduction through a non-GLP-1 mechanism. (3) Add-on 5-Amino-1MQ for adipocyte metabolic reactivation. (4) Discuss retatrutide (triple agonist), Phase III data shows 28.7% average weight loss.

Documentation model: 'Patient presents with weight loss plateau on semaglutide 2.4 mg × 6 months. Objective response documented (18 lb loss, HbA1c improvement, TG reduction). Plateau mechanism discussed with patient, partial setpoint defense despite therapeutic GLP-1 receptor occupancy. Options reviewed: (1) transition to tirzepatide 5 mg (Zepbound, FDA approved) to add dual GIP/GLP-1 mechanism; (2) continue semaglutide + add tesamorelin 1 mg SC daily (off-label visceral fat indication, clinical rationale: GH-mediated mechanism non-overlapping with GLP-1; relevant evidence: Falutz et al. NEJM 2007 demonstrating 18.1% VAT reduction). Patient elected to

transition to tirzepatide 5 mg SC weekly. Prescription issued. HbA1c and metabolic panel in 8 weeks. Follow-up scheduled in 6 weeks via Carepath telehealth.'

Vignette 2: The Post-Concussion Athlete

Presentation: A 22-year-old Division I soccer player, followed by her team's sports medicine physician, suffered her third concussion 3 months ago and continues to report cognitive slowing, difficulty studying, and persistent headaches. Standard concussion protocol recovery is incomplete. ImPACT testing shows processing speed at 30th percentile (pre-injury was 75th percentile). She asks about peptides she has read about, specifically Semax and NAD+ IVs.

Clinical reasoning: This represents a challenging case where the neurological indication for Semax (BDNF upregulation, neuroprotection, cerebral perfusion improvement, Russian RCT data in stroke recovery; mechanistic translation to TBI) is strong, but Semax is currently Category 2 (PCAC review July 2026). NAD+ IV: no regulatory restriction, strong mechanistic rationale for mitochondrial support in neuronal recovery, Level II evidence in aging and metabolic contexts, translational evidence in neuronal energy metabolism. As a competitive athlete, WADA considerations apply, Semax should be checked against current WADA list (it is not currently on the WADA prohibited list as of 2026 data, but verification at the current year's list is mandatory).

Approach: (1) Initiate IV NAD+ infusion 500 mg monthly × 3 months, no regulatory restriction, strong mechanistic rationale, fully telehealth-prescribable once IV access arranged. Counsel regarding its current evidence basis and the off-label neurological application. (2) Discuss Semax mechanistically, explain PCAC review status, confirm no current legal prescribing pathway, schedule follow-up for July 2026 outcomes. (3) Confirm Semax WADA status for athlete compliance. (4) Continue standard concussion rehabilitation protocol as primary management. Document: cognitive baseline (ImPACT scores), the PCAC discussion, the WADA verification, and the NAD+ consent.

Vignette 3: The Patient Using Online Research Peptides

Presentation: During a telehealth consultation via Carepath, a 42-year-old male presents for an annual wellness visit. He discloses that he has been injecting BPC-157 'research peptide' purchased online for 6 months for a chronic patellar tendinopathy, with what he describes as 'dramatic improvement', VAS pain score from 8 to 2, return to running. He shows you the vials (no pharmacy label, no COA, no lot number visible on the photo he displays).

Clinical reasoning: This is one of the most common presentations in telehealth biological optimization practice. The patient has experienced apparent benefit from a compound that has plausible and consistent preclinical evidence for his indication. However, he is injecting an unverified product with no quality documentation into himself. The physician's role is to: (1) not dismiss the apparent benefit; (2) address the critical safety concern of unverified products; (3) document clearly; (4) provide a regulatory-compliant pathway where possible.

Documentation: 'Patient discloses 6-month self-administration of unverified online research BPC-157 for patellar tendinopathy. He reports significant symptom improvement (VAS 8 to 2; return to running). Counseled patient: (1) The source has no verifiable quality control, cannot confirm the product contains BPC-157 at stated concentration, is free of contamination, or is sterile. Referenced independent analyses showing contamination rates up to 30% in online research peptide sources. (2) BPC-

157 is currently FDA 503A Category 2 (do not compound), meaning I cannot provide a legal pharmacy prescription at this time. (3) BPC-157 is under PCAC review on July 23, 2026: if favorable, I will be prepared to initiate a prescription through a Carepath-verified pharmacy. (4) Strongly counseled discontinuation of unverified online source. Patient declined discontinuation given apparent clinical benefit. Documented the counseling. Scheduled follow-up for Q4 2026 post-PCAC to reassess regulatory status and initiate compliant prescribing if indicated.'

Vignette 4: The Physician Building a Peptide Practice on Carepath

Presentation: A family physician with active licenses in 8 states joins Carepath to add biological optimization medicine to his telehealth practice. He wants to understand what he can prescribe, what he cannot, and how to do this without jeopardizing his licenses.

Guidance: (1) Category A compounds (semaglutide, tirzepatide, tesamorelin, bremelanotide), full telehealth prescribing in all 8 states immediately. Standard prescribing documentation. Carepath provides the pharmacy integration. (2) Category B currently-compoundable (Ipamorelin, CJC-1295, Sermorelin, Thymosin Alpha-1): prescribable via Carepath's verified 503A network in all states where he is licensed. Carepath's informed consent platform handles the off-label documentation. Four-part protection framework applies. (3) Category B under PCAC review (BPC-157, TB-500, Semax, etc.), he can discuss these educationally, set up patient consultations to assess clinical candidacy, but should not issue prescriptions for these compounds until the PCAC outcome is known. Carepath's regulatory alert system will notify him immediately upon PCAC determination. (4) Cancer screening and monitoring protocols, Carepath's lab integration handles baseline and monitoring orders. (5) CME completion in peptide therapeutics and telehealth prescribing, Carepath's education portal provides category-specific training. His licenses are protected by the platform's documentation architecture, regulatory compliance tools, and the legal framework of off-label prescribing within a standard of care consistent with anti-aging medicine specialty practice.

SECTION 16: FREQUENTLY ASKED QUESTIONS FOR PRESCRIBERS

Section 16: Prescriber FAQ

Q: How do I handle a patient who presents already using compounded peptides from a 503A pharmacy?

Review the prescription and pharmacy source. If the patient has a valid prescription from a licensed prescriber and the pharmacy is a legitimate 503A facility, your role is to evaluate the clinical appropriateness, review for contraindications, establish your own

clinical documentation, and initiate appropriate monitoring. You are not inheriting liability from prior prescribing, you are establishing your own clinical relationship. Order baseline labs, conduct a clinical assessment, and document your independent evaluation. If the prior prescribing was clinically appropriate, continue and monitor. If you identify contraindications or concerns, discuss with the patient.

Q: What is my liability if a patient is harmed using a peptide I prescribed?

The liability analysis in a peptide-related adverse event is the same as for any pharmaceutical adverse event: Was the prescription clinically appropriate (right patient, right indication)? Was the patient adequately informed (written consent)? Was monitoring appropriate (documented follow-up plan with specific parameters)? Was the pharmacy a licensed 503A facility with verified quality standards? If you can demonstrate yes to all four, you have met the standard of care for off-label compounded medication prescribing and your malpractice exposure is substantially reduced. The highest-risk scenarios are: prescribing without a clinical indication; prescribing to a patient with documented contraindications without explicit risk-benefit documentation; and failure to monitor. The Carepath documentation architecture addresses all three.

Q: What if a patient develops cancer while on a peptide protocol I prescribed?

Cancer development during a peptide protocol does not automatically establish causation. The protocol response involves: (1) immediately discontinue any angiogenic or growth-promoting peptides (BPC-157, TB-500, GH secretagogues, GHK-Cu); (2) refer the patient for oncological evaluation; (3) document the timeline and clinical reasoning; (4) report any potential adverse event to the compounding pharmacy and through MedWatch if appropriate; and (5) assess whether the protocol included appropriate baseline cancer screening and monitoring. If baseline cancer screening was documented (PSA, mammogram, colonoscopy per age/sex guidelines, dermatology for Melanotan II protocols) and was negative at initiation, the prescriber has met the standard of care for cancer surveillance. If baseline screening was omitted, this creates the most significant documentation gap.

Q: How do I respond when a patient says they will just buy it online if I won't prescribe it?

This statement represents both a clinical reality and a physician's most powerful argument for engagement. A patient who obtains BPC-157 from an unverified online source is injecting an unknown substance into themselves without medical oversight. A patient who obtains it from a Carepath-verified 503A pharmacy with your prescription has a verified, monitored product with clinical supervision. Your involvement makes the therapy safer, regardless of whether you are comfortable endorsing the specific compound. The appropriate response: 'I hear that you are going to pursue this regardless of my decision. I would much rather you have access to a verified pharmacy product with my clinical oversight than an unverified online source. Let me assess whether I can appropriately supervise this therapy for you, what monitoring we would need, and what a safely documented protocol would look like.'

Q: Does prescribing on Carepath protect my license in any specific way?

Carepath does not provide legal immunity: no platform can guarantee immunity from board investigation or malpractice claims. What Carepath provides is the documentation architecture and quality infrastructure that constitute the standard of care for this emerging specialty. Specifically: (1) All consultations are documented in a HIPAA-compliant medical record. (2) Compound-specific informed consent with regulatory status documentation is stored and retrievable. (3) Pharmacy partners are pre-verified and their quality documentation accessible. (4) Monitoring protocol reminders and lab integrations create a documented follow-up trail. (5) Regulatory compliance updates prevent prescribing of newly restricted compounds. This infrastructure means that if your prescribing is ever reviewed, you have a complete, professional documentation record consistent with the highest standards of the emerging specialty. That documentation record is the most powerful protection available.

ICD-10 CODING, DOCUMENTATION TEMPLATES, AND MEDICO-LEGAL REFERENCE

ICD-10 Coding, Documentation Guidance, and Medicolegal Reference

Appropriate ICD-10 coding supports the clinical justification for peptide prescribing, creates an auditable record of the physician's clinical reasoning, and is essential for professional liability protection in the event of prescribing scrutiny. The following coding guidance is provided for educational purposes and does not constitute legal advice. Verify current ICD-10-CM codes with your billing department and document the most specific applicable diagnosis code for each patient.

ICD-10 Codes by Peptide Category

Clinical Indication	ICD-10-CM Code(s)	Code Description	Applicable Compounds
Obesity, unspecified	E66.9	Obesity, unspecified	Semaglutide, Tirzepatide, Retatrutide, Tesamorelin, AOD-9604
Obesity due to excess calories	E66.01	Morbid (severe) obesity due to excess calories	Same as above: most specific code for BMI ≥40
Overweight with	E66.09 +	Other obesity + specific	GLP-1 class;

Clinical Indication	ICD-10-CM Code(s)	Code Description	Applicable Compounds
comorbidity	comorbidity code	comorbidity (HTN: I10; T2DM: E11.x)	Tesamorelin; AOD-9604
Pre-diabetes / impaired glucose tolerance	R73.09	Other abnormal glucose (prediabetes)	Semaglutide, Tirzepatide, MOTS-c, NAD+, L-Carnitine
Type 2 diabetes mellitus	E11.9 (uncontrolled: E11.649)	Type 2 diabetes mellitus without complications	GLP-1 class; MOTS-c; Tesamorelin (caution)
Metabolic syndrome	E88.81	Metabolic syndrome	GLP-1 class; Tesamorelin; MOTS-c; NAD+; L-Carnitine; 5-Amino-1MQ
Nonalcoholic steatohepatitis	K75.81	Nonalcoholic steatohepatitis (NASH)	Tirzepatide (SYNERGY-NASH data); Semaglutide off-label
Adult-onset GH deficiency	E23.0	Hypopituitarism	Sermorelin (approved), CJC-1295/Ipamorelin (off-label)
GH deficiency functional/somatopause	E34.9 or E88.9	Endocrine/metabolic disorder unspecified	CJC-1295/ Ipamorelin; Sermorelin; MK-677; Tesamorelin
Dyslipidemia: hypertriglyceridemia	E78.1	Pure hyperglyceridemia	GLP-1 class (significant TG lowering documented)
Osteopenia / low bone density	M85.80 or M85.89	Disorder of bone density and structure	MK-677; GH secretagogues (bone density data)
Sarcopenia / muscle weakness	M62.84	Sarcopenia	GH secretagogues; MK-677; NAD+; L-Carnitine
Rotator cuff syndrome/tear	M75.100–M75.122	Rotator cuff syndrome (shoulder)	BPC-157; TB-500; GH secretagogues
Achilles tendinopathy	M76.60–M76.62	Achilles tendinitis	BPC-157; TB-500
Chronic tendinitis (general)	M77.9	Enthesopathy, unspecified	BPC-157; TB-500

Clinical Indication	ICD-10-CM Code(s)	Code Description	Applicable Compounds
Post-surgical recovery support	Z87.39 or specific surgical code	Personal history of surgery	BPC-157; TB-500; GH secretagogues
Crohn's disease	K50.90	Crohn's disease, unspecified, without complications	BPC-157 (oral); KPV
Ulcerative colitis	K51.90	Ulcerative colitis, unspecified, without complications	KPV; BPC-157 (oral)
Irritable bowel / leaky gut	K58.9 or K92.89	IBS without diarrhea; intestinal permeability	BPC-157 (oral); KPV
Chronic fatigue syndrome	G93.32	Myalgic encephalomyelitis/chronic fatigue syndrome	NAD+; GH secretagogues; Semax (post-PCAC)
Post-COVID condition	U09.9	Post-COVID-19 condition, unspecified	NAD+ IV; GH secretagogues; Semax; TA-1 (post-PCAC)
Cognitive decline / MCI	F06.70 or G31.84	Mild neurocognitive disorder / MCI	Semax (post-PCAC); NAD+; GH secretagogues
Ischemic stroke: sequelae	I69.30 or I69.350	Sequelae of cerebral infarction	Semax (post-PCAC); NAD+ IV; BPC-157
Post-concussion syndrome	S09.90XS or F07.81	Concussion (sequela); Postconcussional syndrome	Semax (post-PCAC); NAD+ IV; SS-31
Insomnia disorder	G47.00	Insomnia, unspecified	DSIP (post-PCAC); CJC-1295/Ipamorelin (sleep quality)
Generalized anxiety disorder	F41.1	Generalized anxiety disorder	Selank (post-PCAC)
Hypogonadism, secondary (men)	E29.1	Testicular hypofunction	Kisspeptin-10; Thymosin Alpha-1 (immune-hormonal interaction)
Hypoactive sexual desire disorder (women)	F52.0	Hypoactive sexual desire disorder	Bremelanotide/ Vyleesi (Category A FDA approved)
Sexual dysfunction (men)	N52.9 (erectile) or F52.0 (desire)	Erectile dysfunction; male sexual dysfunction	Bremelanotide (off-label men);

Clinical Indication	ICD-10-CM Code(s)	Code Description	Applicable Compounds
			Kisspeptin-10
Hypothalamic amenorrhea	N91.2 or E23.3	Secondary amenorrhea; Hypothalamic dysfunction	Kisspeptin-10
HIV-associated lipodystrophy	B20 + E88.1	HIV + lipodystrophy	Tesamorelin (Category A on-label)
Chronic immune deficiency / aging	D89.9 or Z71.89	Immune disorder unspecified; health counseling	Thymosin Alpha-1; LL-37 (post-PCAC)
Preventive / longevity / health optimization	Z13.88 or Z13.89	Encounter for preventive health screening	Epitalon; MOTS-c; SS-31; NAD+; GHK-Cu topical
Chronic wound / pressure injury	L89.x or L97.x	Pressure ulcer; Non-pressure chronic ulcer	GHK-Cu; LL-37; KPV topical
Androgenic alopecia	L64.9	Androgenic alopecia, unspecified	GHK-Cu (injectable post-PCAC; topical current)
Atopic dermatitis	L20.9	Atopic dermatitis, unspecified	KPV topical; GHK-Cu topical

Documentation Template Library

Structured Note: Growth Hormone Secretagogue Initiation

CLINICAL NOTE: GH SECRETAGOGUE THERAPY INITIATION

Date: [DATE] | Encounter type: [In-person / Telehealth via Carepath] | Duration: [MIN]

Chief Complaint / Indication: Patient presents with [symptoms: e.g., progressive increase in visceral adiposity despite dietary modification; poor sleep quality with early morning awakening; reduced post-exercise recovery capacity (DOMS lasting 4–6 days); subjective cognitive slowing]. Duration of symptoms: [X months/years]. Functional impact: [describe].

Past Medical History: [List]. Relevant: No personal or family history of malignancy. No history of acromegaly or pituitary disease. No active cardiovascular disease.

Current Medications: [List: note any corticosteroids, insulin, or hypoglycemics that require dose monitoring consideration].

Objective / Laboratory Data: IGF-1: [X ng/mL] (age-adjusted normal range: [Y–Z ng/mL]; patient is at [X]th percentile for age). Fasting glucose: [X mg/dL]. HbA1c: [X%]. CMP: [relevant values]. PSA (if male ≥40): [X ng/mL, normal]. [Other relevant labs].

Assessment: Patient presents with functional somatopause (ICD-10: E34.9) characterized by [symptoms] with laboratory correlation of low-normal IGF-1 at [X ng/mL]. After review of contraindications (none identified), discussion of the evidence basis (Ionescu & Frohman, J Clin Endocrinol Metab 2006; PMID 16352683), completion

of Carepath GH secretagogue informed consent, and consideration of alternative approaches including dietary/exercise optimization (insufficient response documented), a clinical decision was made to initiate GH secretagogue therapy.

Plan: CJC-1295 (no DAC) 100 µg + Ipamorelin 100 µg SC nightly (5 days on / 2 days off schedule), prescription transmitted to [pharmacy name], a Carepath-verified 503A licensed compounding pharmacy. Monitoring: IGF-1 at 6 weeks; fasting glucose at 6 weeks; follow-up telehealth consultation via Carepath at 8 weeks. Patient instructed on reconstitution, injection technique, and injection rotation schedule. Emergency contact protocol reviewed. Patient verbally confirmed understanding.

Structured Note: GLP-1 Therapy Initiation (Telehealth via Carepath)

CLINICAL NOTE: GLP-1 CLASS THERAPY INITIATION (CAREPATH TELEHEALTH)

Date: [DATE] | Platform: Carepath Telehealth | Encounter type: Synchronous video consultation | Duration: [MIN] | Physician state license: [STATE] | Patient state: [STATE] ✓ License verified.

Indication: Patient presents with obesity (BMI [X] kg/m²; ICD-10 E66.9 / E66.01) with comorbidities: [pre-diabetes E66.09 + R73.09 / hypertension E66.09 + I10 / dyslipidemia + E78.x / metabolic syndrome E88.81]. Weight loss goals: [X]% body weight reduction. Prior weight loss attempts: [list], outcomes: [inadequate].

Contraindication screening: Personal history of medullary thyroid carcinoma: No. Family history of MEN2: No. History of pancreatitis: No. History of gallbladder disease: [Yes/No]. Active gastroparesis: No. Pregnancy status: [Not applicable / Confirmed not pregnant].

Medication review for interactions: [Any insulin, sulfonylureas, or oral drugs requiring absorption consistency monitoring, documented and management plan noted].

Plan: [Tirzepatide / Semaglutide] [X mg] SC weekly. Titration schedule: [2.5 mg × 4 weeks → 5 mg → continued per tolerance]. Prescription transmitted to [pharmacy name] via Carepath pharmacy network. Carepath compound-specific informed consent signed electronically, stored in Carepath medical record [document ID]. Monitoring: HbA1c, fasting glucose, CMP, lipid panel, weight, waist circumference, at week 8 and week 16; then every 6 months. Patient instructed: [injection technique, site rotation, nausea management protocol, when to contact platform, what constitutes an emergency].

Reconstitution and Storage: Physician Guidance for Patient Counseling

Prescribers who initiate injectable peptide therapy have an obligation to ensure that patients understand proper reconstitution and storage procedures. Deviations from these procedures are the most common source of degraded therapy effectiveness and are occasionally the source of adverse events from contaminated preparations. The following guidance enables prescribers to provide accurate counseling or to confirm that the pharmacy has provided adequate instruction.

Compound	Lyophilized Storage	Post-Reconstitution Storage	Stability (Reconstituted)	Critical Notes
Semaglutide / Tirzepatide (compounded)	Refrigerator 2–8°C (never freeze)	Refrigerator 2–8°C (never freeze)	28–56 days (pharmacy specified)	If accidentally frozen: discard immediately. Discard if visible particles or unusual color.
Retatrutide	Freezer (−20°C) until use	Refrigerator 2–8°C after first use	28 days	Most temperature-sensitive GLP-1 class compound. Request insulated shipping confirmation from pharmacy.
BPC-157 Acetate	Freezer preferred; refrigerator acceptable	Refrigerator 2–8°C; protect from light	30 days	Oral formulation (for GI use): room temp acceptable for 24 hrs. Stability in gastric acid is a property of the intact peptide structure.
TB-500 (Thymosin Beta-4)	Freezer (−20°C) mandatory	Refrigerator 2–8°C; protect from light	28–30 days	Do not reconstitute more than 30 days of supply at once. Light exposure degrades compound.
CJC-1295 / Ipamorelin (blended)	Freezer (−20°C)	Refrigerator 2–8°C (back of refrigerator, not door)	30 days	Temperature cycling from door opening accelerates degradation. Store in dedicated section.
Tesamorelin	Refrigerator 2–8°C (manufacturer specification)	Refrigerator 2–8°C	30 days post-reconstitution	Manufacturer (Theratechnologies) specifies refrigerator, not freezer, for lyophilized product.
Semax (nasal spray, post-PCAC)	Freezer or refrigerator	Refrigerator after opening	30–60 days	Nasal spray bottle: prime before first use; store upright; do not share between patients.
Epitalon	Freezer (−20°C)	Refrigerator 2–8°C	14–20 days	Course-based use: reconstitute only the volume needed for the 10-day course. Discard remainder at course completion.
MOTS-c	Freezer (−20°C) mandatory	Refrigerator 2–8°C	14 days maximum	Most fragile peptide in the guide. Cold chain shipping verification critical.

Compound	Lyophilized Storage	Post-Reconstitution Storage	Stability (Reconstituted)	Critical Notes
				Discard if room temperature exposure >2 hours.
SS-31 (Elamipretide)	Freezer (−20°C)	Refrigerator 2–8°C; protect from light	21 days	Light-sensitive: amber vials or foil wrapping recommended.
NAD+ for IV infusion	Refrigerator; protect from light	Use within 24 hours of mixing	Same day for IV preparation	Extremely light-sensitive. Wrap mixed infusion bags in foil. Do not store mixed infusions.
Thymosin Alpha-1	Freezer (−20°C)	Refrigerator 2–8°C	30 days	Temperature consistency critical for twice-weekly dosing schedule. Store in dedicated section.
Bremelanotide (Vyleesi)	Refrigerator 2–8°C (brand)	Refrigerator 2–8°C	Per brand packaging	Commercial product: use manufacturer storage instructions. Compounded: per pharmacy COA.
GHK-Cu topical serum	Cool, dark cabinet (<25°C)	Refrigerator extends stability	60–90 days	Blue color is quality indicator: colorless serum indicates degradation. Never heat.

Reconstitution: The Non-Negotiable Rules

Every patient initiating injectable peptide therapy must receive reconstitution counseling. The four most critical points: (1) NEVER shake a vial, swirl gently only. Shaking denatures peptide structure through mechanical disruption of peptide bonds. (2) Add bacteriostatic water by directing the stream down the vial wall, never directly onto the powder. (3) NEVER store combined peptides in a single vial unless they come pre-blended from the pharmacy with documented compatibility testing. (4) Label every reconstituted vial with the reconstitution date and discard on the specified date regardless of remaining volume. Carepath's patient education materials include video demonstration of correct technique, encourage all patients to review before first injection.

Injection Technique Guidance for Physician Counseling

Subcutaneous injection errors are the most common procedural issue reported by patients initiating peptide therapy. Prescribers should either provide hands-on instruction, refer to a nursing educator, or confirm that the Carepath patient education

materials have been reviewed. Key clinical points to convey to patients:

- Site rotation is mandatory. Rotating sites prevents lipodystrophy, injection site fibrosis, and variable absorption from local tissue reactions. Standard rotation pattern: abdomen (four quadrants around the navel), lateral thighs (left and right), and for some compounds, upper outer buttocks. Mark a weekly rotation calendar for patients who are on multiple daily or frequent injections.
- Allow alcohol swab to fully dry before injecting. Injecting through wet alcohol tracks the alcohol into the subcutaneous tissue and causes burning disproportionate to the injection. Allow 10–15 seconds of drying time.
- Pinch technique for lean patients. For patients with minimal subcutaneous tissue (common as weight loss progresses with GLP-1 therapy), a skin pinch technique with insertion at 45 degrees reduces the risk of inadvertent intramuscular injection.
- Slow injection rate. Inject over 5–10 seconds per 0.1 mL. Rapid injection causes local pressure, discomfort, and suboptimal distribution in the subcutaneous space. A common patient error is injecting too rapidly.
- Post-injection technique. Apply gentle pressure with a clean cotton ball for 10–15 seconds. Do not rub the injection site, as rubbing accelerates absorption unpredictably and may cause local bruising. If a bruise develops at an injection site, rotate away from that site until it resolves.
- Needle selection. For most subcutaneous peptide injections, 31-gauge insulin syringes (0.3 mL capacity, 8 mm needle length) are appropriate. Prescribers should confirm that the Carepath-partnered pharmacy provides appropriate syringes with the compounded preparation.

SECTION 17: CITED REFERENCES: PEER-REVIEWED CLINICAL AND SCIENTIFIC LITERATURE

Section 17: Cited References

The following references constitute the primary evidentiary basis for this clinical guide. All references are from peer-reviewed scientific journals, FDA regulatory documents, or established clinical trial registries. PMID or DOI are provided for direct literature access.

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Section 18: Master Prescribing Reference: All Major Compounds

The following table provides consolidated prescribing reference information for all major therapeutic peptides covered in this guide. Use as a rapid clinical reference after reading the complete compound profiles. Regulatory status reflects conditions as of July 2026: verify current status via Carepath's compliance platform or fda.gov before issuing prescriptions.

Compound	Category	ICD-10 Indication	Route / Dose	FDA Status 2026	Eviden
Semaglutide (Wegovy / Ozempic)	Metabolic / Weight Loss	E66.x, E11.x, Z87.39	SC weekly: 0.25→2.4 mg; PO: 3–14 mg daily	APPROVED: Category A	Level I: STEP, SELECT trials
Tirzepatide (Zepbound / Mounjaro)	Metabolic / Weight Loss	E66.x, E11.x	SC weekly: 2.5→15 mg	APPROVED: Category A	Level I: SURMOU trials
Retatrutide	Metabolic / Weight Loss	E66.x	SC weekly: 0.5→12 mg (titrated)	Phase III: Compounded Category B	Level II (Phase II trial)
Tesamorelin (Egrifta SV)	GH Axis / Metabolic	B20 (HIV), E65 (off-label)	SC 1–2 mg daily (fasted)	APPROVED: Category A (HIV); Off-label for non-HIV	Level I (HIV); Le III (off-label)
Cagrilintide	Metabolic	E66.x	SC weekly: 0.16–2.4 mg	Phase III / Compounded Category B	Level II (Phase II CagriSem
AOD-9604	Weight Loss	E66.x	SC 250–500 µg daily (fasted)	Compounded: Category B (503A eligible pending)	Level II (Phase II trials)
5-Amino-1MQ	Metabolic adjunct	E66.x adjunct	PO 50–100 mg/day cycled	No compounding restriction: small molecule	Level III (animal - mechani)
CJC-1295 (no DAC)	GH Secretagog ue	E34.9, E23.0	SC 100 µg nightly (paired with Ipa)	Compounded: Category B (503A eligible)	Level II
Ipamorelin	GH Secretagog ue	E34.9, E23.0	SC 100–200 µg nightly	Compounded: Category B (503A eligible)	Level II
Sermorelin	GH Secretagog	E23.0	SC 200–300 µg QD-BID	Compounded: Category B (503A	Level II

Compound	Category	ICD-10 Indication	Route / Dose	FDA Status 2026	Evidenc
	ue			eligible)	
MK-677 (Ibutamoren)	GH Secretagogue (oral)	E34.9	PO 10–25 mg nightly	Compounded: Category B (503A eligible)	Level II (human trials)
BPC-157	Healing	M75.x, K51.x, K50.x	SC 300–500 µg daily or oral 250–750 µg BID	PCAC Review July 23, 2026: Category B pending	Level III
TB-500 (Thymosin Beta-4)	Healing / Systemic	M75.x, systemic	SC/IM: 2–5 mg 2x weekly (loading); weekly (maintenance)	PCAC Review July 23, 2026: Category B pending	Level II (cardiac animal); Level III (clinical)
KPV	Healing / Anti-inflammatory	K51.x, K50.x, L20	Oral 250–750 µg BID; topical 0.1–0.3%; SC 250–500 µg daily	PCAC Review July 23, 2026: Category B pending	Level III
GHK-Cu (Copper tripeptide)	Healing / Aesthetic	L89.x, topical use	Topical 0.1–0.3% (no restriction); SC 1–3 mg 3x wkly (post-PCAC)	PCAC Review Feb 12, 2027: Category B pending 2027	Level II (wound: RCT); Lev III (aestheti
LL-37	Immune / Antimicrobial	L89.x, wound care	SC 25–100 µg daily or topical	PCAC Review Feb 12, 2027: Category B pending 2027	Level II (Phase I)
Semax	Neurological	I69.x, F03.9x	Intranasal 0.1%: 100–300 µg/nostril BID	PCAC Review July 24, 2026: Category B pending	Level II (Russian RCTs); Level III (Western
Selank	Neurological / Anxiety	F41.x, F32.x	Intranasal 0.15%: 150–300 µg/nostril BID-TID	PCAC Review July 24, 2026: Category B pending	Level II (Russian RCTs)
DSIP	Sleep / Neurological	G47.x	SC 200–400 µg before sleep (cycled 2 on/2 off weeks)	PCAC Review July 24, 2026: Category B pending	Level III
Epitalon	Longevity	Z13.88 (preventive)	SC 5–10 mg daily × 10 days; 2x yearly	PCAC Review July 24, 2026: Category B pending	Level III (Russian cohort da + mechani c)
MOTS-c	Longevity / Metabolic	E11.x, E66.x	SC 5 mg 3x weekly	PCAC Review July 23, 2026: Category B	Level II (animal); Level III

Compound	Category	ICD-10 Indication	Route / Dose	FDA Status 2026	Evidenc
				pending	(human translatio l)
SS-31 (Elamipretide)	Longevity / Cardiac	I50.x, N18.x	SC 2 mg daily or 3x weekly	Phase III ongoing: Compounded Category B	Level II (Phase II cardiac HFpEF)
Thymosin Alpha-1	Immune	B18.x, C34.x adjunct, Z79.x	SC 1.6 mg 2x weekly (4–8 week courses)	Compounded: Category B (503A eligible)	Level I (hepatitis cancer adjunct); Level III (optimiza n)
Bremelanotide (Vyleesi)	Sexual Health	F52.0, N52.x (off-label men)	SC 1.25–1.75 mg PRN (≥45 min before activity)	APPROVED: Category A	Level I: RECONN T Phase I
Kisspeptin-10	Sexual / Endocrine	E29.1, N91.x, Z31.x	SC per reproductive endocrinology protocol	Compounded: Category B (503A eligible)	Level II (Phase II trials)
Melanotan II	Aesthetic	Photoprotection (PCAC pending)	SC 0.1 mg loading titration	PCAC Review Feb 12, 2027: Category B pending 2027	Level II (mechan m); Leve (human)
NAD+ (IV/SC/oral)	Supportive	E88.9, Z51.x	IV 500–1,000 mg monthly; SC 100–300 mg; PO NMN 500–1,000 mg/day	No compounding restriction	Level II (human trials)
L-Carnitine	Supportive / Metabolic	E71.40 (deficiency); adjunct to weight protocols	SC 500 mg 3x weekly	No compounding restriction	Level I (CKD/ESR ; Level II (metabol
Glutathione	Supportive / Antioxidant	Z51.x, G20 (Parkinson's)	IV 600–1,200 mg per infusion; SC 400 mg	No compounding restriction	Level II (multiple clinical studies)

LEGEND: Category A = FDA-approved; Category B = Compoundable now or pending PCAC; Category C = Research stage, no legal clinical access. All off-label and compounded prescriptions require documentation per Section 14 four-part protection framework. Carepath platform regulatory compliance tools are updated with each PCAC determination. Verify current 503A eligibility at time of prescribing.

DISCLAIMER: This guide is intended for licensed healthcare professionals as an educational reference. It does not constitute legal advice. For specific legal questions

regarding prescribing in your jurisdiction, consult a healthcare attorney familiar with your state's medical practice regulations and telemedicine laws. For regulatory compliance questions, consult Carepath's legal and compliance team.

APPENDIX B: MONITORING SCHEDULE TEMPLATES AND APPENDIX C: ICD-10 DOCUMENTATION

Appendix B: Monitoring Schedule Templates

The following monitoring schedule templates can be used as a starting point for practice-specific monitoring protocols. Customize based on individual patient risk factors, additional comorbidities, and compound-specific considerations identified during the patient assessment.

Monitoring Item	GLP-1 Protocol	GH Secretagogue	Healing Peptides	Longevity Protoc
Baseline labs required	HbA1c, FBG, CMP, lipid panel, amylase/lipase	IGF-1, FBG, HbA1c, CMP, thyroid, PSA (men)	CMP, CBC	CMP, CBC, IGF-1, hsCRP, homocystein
Week 4 check	Weight, BP, GI symptom scale	No check needed (too early for IGF-1 response)	Clinical assessment (pain/ROM)	Not applicable
Week 6–8 check	HbA1c, FBG, CMP, weight, waist	IGF-1, FBG: primary monitoring point	Clinical + imaging if indicated	Not applicable
Month 3	Full metabolic panel, weight, body comp if available	IGF-1, HbA1c, FBG: stable dosing assessment	Clinical reassessment	Initial biomarker pan
Month 6	HbA1c, CMP, lipid panel, weight	IGF-1, CMP, consider DEXA	DEXA or imaging if structural endpoint	Full biomarker panel epigenetic age test
Annual	All baseline labs; cancer screening update	All baseline labs; PSA; cancer screening	Cancer screening baseline refresh	Biomarker panel; LTL re-measurement
PRN (as clinically indicated)	Amylase/lipase if abdominal pain; gallbladder US if biliary symptoms	IGF-1 if dose adjusted; glucose if symptoms	MRI/US if new symptoms; CRP if inflammatory	Any new concerning symptoms

Appendix C: ICD-10 Documentation Guidance

Proper ICD-10 coding is the foundation of the clinical justification record for off-label peptide prescribing. The following principles apply across all peptide prescribing

documentation:

- Use the most specific ICD-10-CM code applicable to the patient's documented condition. 'E66.9 Obesity, unspecified' is appropriate when more specific coding is not supported by documentation; 'E66.01 Morbid (severe) obesity due to excess calories' is more specific when BMI ≥40 is documented.
- For off-label use of approved compounds (e.g., tesamorelin for non-HIV visceral adiposity), document the clinical indication that supports use, the code should reflect the patient's actual condition, not the approved label indication.
- For functional somatopause (low-normal IGF-1 without formal AGHD criteria), E34.9 (Endocrine disorder, unspecified) or E88.9 (Metabolic disorder, unspecified) are appropriate. If formal GH stimulation testing confirms AGHD criteria, E23.0 (Hypopituitarism) is the more specific and clinically stronger code.
- For preventive or longevity applications where no specific disease is being treated, Z13.88 or Z13.89 (Encounter for other screening examination) documents the preventive/optimization context. Some practitioners use Z71.89 (Other specified counseling) for the health optimization consultation component.
- Always document the ICD-10 code in the clinical note, not just the superbill. The clinical note documentation creates the medico-legal record that supports the code selection.

Compound	Most Appropriate ICD-10(s)	Clinical Documentation Required
Semaglutide / Tirzepatide (obesity)	E66.01, E66.09, E66.9	BMI documented; comorbidities listed; prior weight loss attempts documented
Semaglutide (CVD risk reduction)	I25.10 + E66.x	Established CVD documented; BMI ≥27; cardiovascular risk assessment
Tesamorelin (HIV lipodystrophy)	B20 + E88.1	HIV diagnosis; lipodystrophy on physical exam; prior HAART medications documented
Tesamorelin (off-label visceral adiposity)	E65 or E88.81	Visceral adiposity documented; clinical rationale for GH-axis intervention; Falutz NEJM 2007 referenced
CJC-1295 / Ipamorelin (somatopause)	E34.9 or E23.0 (if formal AGHD)	IGF-1 level documented; clinical symptoms; excluded contraindications; cancer screening negative
BPC-157 (tendon: post-PCAC)	M75.100–M75.122 (shoulder); M76.60 (Achilles); M77.9 (other)	Specific injury documented; imaging if available; failed conservative treatment documented
BPC-157 (IBD: post-PCAC)	K50.90 (Crohn's) or K51.90 (UC)	Disease activity index score; colonoscopy/imaging; prior treatment history
Thymosin Alpha-1 (immune optimization)	D89.9 or Z71.89	Immune assessment documented; clinical indication stated; evidence basis cited
Bremelanotide (HSDD: on-label)	F52.0	FSFI desire domain score; FSDS-D score; premenopausal status documented

Compound	Most Appropriate ICD-10(s)	Clinical Documentation Required
Bremelanotide (off-label men)	N52.9 or F52.0	Sexual dysfunction characterization; desire vs. mechanical component assessment; PDE5i consideration documented
Epitalon (longevity)	Z13.88 or Z13.89	Preventive/optimization context; patient age; baseline LTL or epigenetic age documented
NAD+ IV (fatigue/cognitive)	G93.32, U09.9, or R53.83	Indication documented (CFS, post-COVID, general fatigue); prior treatment attempts