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WHAT IS PEPTIDE THERAPY?

A peptide is a short chain of amino acids that are linked together and can be thought of as a small protein. In our bodies, these proteins typically act as signaling molecules. They bind to receptors on cell surfaces and tell other cells and molecules how to function efficiently.

The use of peptides as part of a standard medication regimen is attractive because peptides are safe, effective and have targeted functions in the body resulting in minimal to no side effects. In the past, peptides have only been available through injection therapy. However, at Physicians Preference Pharmacy we compound our peptides into sublingual tablets, which dissolve under the tongue, oral capsules, and intranasal sprays (depending on the peptide). These dosage forms are non-invasive and allow for an easier dosing schedule and generally are more cost-effective for the patient.

WHAT CONDITIONS ARE PEPTIDES USED TO TREAT?

Peptides are numerous and variable in chemical structure, therefore their uses are wide-ranging. Peptide therapy addresses numerous conditions including immunosuppression, Hashimoto's thyroiditis, Lyme disease, Mast Cell Activation Syndrome, fibromyalgia, Chronic fatigue syndrome, IBD, sexual dysfunction, anxiety, Leaky Gut, neurodegeneration, insomnia, and brain fog, to name a few. At Physicians Preference Pharmacy, we name our peptides based on which symptoms they address, however the scientific peptide names are also included below.

PEPTIDES COMPOUNDED AT PHYSICIANS PREFERENCE PHARMACY:

Larazotide - 0.25mg, 0.5mg oral capsules

Larazotide is a locally acting, non-systemic peptide, functioning as a zonulin receptor antagonist to regulate tight junctions and inflammation primarily in the intestines. (Zonulin is a biomarker of intestinal permeability). Larazotide works to minimize zonulin-mediated increase in intestinal barrier permeability. Larazotide may stabilize tight junction structure through rearrangement of actin filaments and by promoting tight junction assembly. Larazotide acetate restores the distorted tight junction complex, thereby circumventing the intestinal permeation of gliadin,

the immunopathogenic substance generated from the metabolism of gluten. Oral administration of Larazotide before the consumption of gluten (protective) or after consumption (restorative) is used to inhibit zonulin from binding to its receptors, thereby preventing tight junction disassembly or restoring the tight junction barrier. Due to zonulin's role in many disease conditions including autoimmune conditions such as Rheumatoid arthritis and Celiac Disease, and non-autoimmune conditions such as Type 2 Diabetes and Inflammatory Bowel Disease, Larazotide may help lower zonulin levels and reduce the onset of other disease conditions.

Benefits of Larazotide:

- Decreases gut permeability in Celiac disease and other auto-immune conditions
- Improves GI symptoms in Celiac Disease patients
- Regulates intestinal tight junctions, repairing Leaky Gut
- Decreases intestinal inflammatory response following gluten ingestion
- Inhibits gliadin, the immunostimulatory protein generated from the breakdown of gluten, from permeating the epithelial barrier of the intestine
- Reduction in spike antigenemia to undetectable levels in Long COVID

Common uses for Larazotide:

- Long COVID symptoms
- Celiac Disease
- Leaky Gut
- PANDAS
- Lowering TPO in Hashimoto's Thyroiditis

Dosing:

Larazotide is usually dosed once in the morning for children, twice daily for adults, and up to four times daily in Long -COVID. Patients weighing < 25 kg may start with 0.25 mg capsule, patients ≥ 25 kg may start with 0.5mg capsule.

Long COVID: 0.25 mg or 0.5 mg, four times daily x 21 days (in Phase II trials, patients as young as 3 years old are enrolled in larazotide studies) – spike antigens show first clearance after just 1 day on larazotide (vs. 5.5 days for those not on larazotide)

Duration of therapy: Until symptoms resolve, usually at least 3 months

Side-effects: None recognized in symptomatic patients receiving oral administration of larazotide

Note on safety of larazotide: According to a meta-analysis of several randomized controlled trials, doses given orally up to 36 mg to patients showed no severe side-effects.

References:

1. Larazotide acetate for treatment of celiac disease: A systematic review and meta-analysis of randomized controlled trials (PMID: 34339872)
2. Larazotide acetate: a pharmacological peptide approach to tight junction regulation (PMID: 33881350)
3. AT1001 for the Treatment of Long COVID (ClinicalTrials.gov ID: NCT05747534)
4. Zonulin Antagonist, Larazotide (AT1001), As an Adjuvant Treatment for Multisystem Inflammatory Syndrome in Children: A Case Series (PMID: 35211683)
5. Larazotide Acetate (Textbook of Natural Medicine (Fifth Edition) – Volume 1, Corene Humphreys 2020) found at: https://www.sciencedirect.com/topics/medicine -and-dentistry/larazotide#:~:text=The%20most%20promising%20pharmaceuti cal%20drug,in% 20pati ents%20with%20celiac%20disease)

Neuro Support (PE-22-28) – 0.4mg sublingual tablet, 0.2mg/spray intranasal

PE-22-28 is an amino acid derivative of Spadin, which blocks the TREK-1 receptor, primarily found in the brain, but also in the heart, smooth muscles, and endocrine system. PE-22-28 binds to TREK-1, and crosses the blood brain barrier, improving mood, memory, cognitive function, and increasing Brain-Derived Neurotrophic Factor. Additionally, much of the research surrounding PE-22-28 confirms its use in major depressive disorder and in those with severe depression, without the side-effects of anti-depressant medications. PE-22-28 induces neurogenesis and synaptogenesis and enhances serotonin and dopamine release from the neurons.

We recommend using the nasal spray for those primarily treating depression and the sublingual tablet for improving memory, mood, focus, concentration and increasing BDNF levels. PE-22-28 is expected to begin improving symptoms within days, rather than weeks or months, as seen with classic antidepressants.

Benefits:

- Improvement in Depression, mild and Major Depressive Disorder
- Improved mood
- Sharper cognitive function
- Synaptogenesis and neurogenesis
- Increase in BDNF

Side-effects: None reported with sublingual and nasal administration

Dosing:

Nasal spray: Use 1-2 sprays in one nostril every morning, alternate nostrils daily
Sublingual tablets: Dissolve 1 tablet under the tongue daily

References:
1. Response of the human detrusor to stretch is regulated by TREK-1, a two-pore-domain (K_{2P}) mechano-gated potassium channel (PMID: 24801307)
2. Shortened Spadin Analogs Display Better TREK-1 Inhibition, *In Vivo* Stability and Antidepressant Activity (PMID: 28955242)
3. Role of TREK-1 in Health and Disease, Focus on the Central Nervous System (PMID: 31031627)

Sermorelin - 0.5mg and 1mg sublingual tablet

Sermorelin is a growth hormone releasing hormone (GHRH) which stimulates the body's own natural production of growth hormone. With increased growth hormone release, most patients experience a noticeable increase in lean muscle mass, energy, skin turgor, testosterone, increases in IGF-1 and circulating growth hormone levels, increased T4 to T3 thyroid hormone conversion, and a decrease in TSH levels. It is recommended to take Sermorelin just prior to bedtime, as it promotes growth hormone release in the early morning hours, mimicking the body's natural rhythm. Sermorelin also promotes slow wave sleep, or deep sleep, which is important for muscle growth and memory retention. Studies have shown that since slow wave sleep decreases significantly with age, the use of Sermorelin promotes the GHRH response, which induces deeper sleep especially in adults middle-aged and older. Sublingual Sermorelin proves to be an effective dosage form for increasing growth hormone levels.

Benefits:

- Increased circulating Growth Hormone
- Improved lean muscle mass
- Improved fat composition
- Improved skin turgor
- Increased bone density
- Improved hormone levels (may include testosterone, T4 > T3 conversion, and TSH)

Dosing: Dissolve one 0.5mg tablet under the tongue at least 90 minutes after the last meal of the day, just prior to bed

Side Effects: No severe side-effects have been reported with sublingual administration

Contraindications: Recent cancer due to increase in growth factors

References:
1. Dr. Richard Walker – Part 2: Sermorelin a stable, sublingual alternative to GH on YouTube: https://www.youtube.com/watch?v=fpAKldjc494
2. Sermorelin: A better approach to management of adult-onset growth hormone insufficiency? (PMID: 18046908)

Pinealon - 0.1mg, 0.2mg sublingual tablets

Pinealon is a Cytogen peptide bioregulator used to protect against hypoxic-ischemic neurodegeneration and regulate apoptosis within the brain. Pinealon is expected to lower caspase-3 activity in the brain (preventing unnecessary neuronal cell death) and increase the formation of irisin, a hormone which regulates thermogenesis and telomere lengthening. Pinealon encourages the pineal gland to produce more melatonin, improving circadian rhythm and providing anti-tumor growth benefits.

Benefits:

- Improved memory and concentration
- Preserve telomere length for anti-aging benefits
- Promotes normal deep sleep patterns
- Recovery from TBI and stroke
- Alzheimer's and Parkinson's

Dosing: Dissolve 1 tablet under the tongue daily. May increase dose to higher strength or increase dosing frequency to twice daily based on indication and patient response.

Side-effects: No side-effects have been reported with sublingual Pinealon, however injectable treatment may produce side-effects such as headaches, nausea, flushing and injection site reactions, which is why sublingual administration is likely to be preferred.

References:

1. Short Peptides and Telomere Length Regulator Hormone Irisin (PMID: 26742748)
2. EDR Peptide: Possible Mechanism of Gene Expression and Protein Synthesis Regulation Involved in the Pathogenesis of Alzheimer's Disease (PMID: 33396470)
3. [EFFECT OF SYNTHETIC PEPTIDES ON AGING OF PATIENTS WITH CHRONIC POLYMORBIDITY AND ORGANIC BRAIN SYNDROME OF THE CENTRAL NERVOUS SYSTEM IN REMISSION] (Adv Gerontol. 2015;28(1):62-7)
4. Pinealon Increases Cell Viability by Suppression of Free Radical Levels and Activating Proliferative Processes (https://doi.org/10.1089/rej.2011.1172)

Thymogen - 0.1mg sublingual tablet

Thymogen is an immunomodulating peptide, strengthening a weak immune system and reducing an inadequately high immune response. It has a regulating effect on cellular and humoral immunity. Thymogen enhances the expression and differentiation of receptors on lymphocytes, normalizes the number of T-helper cells, cytotoxic T-lymphocytes and their ratio in patients with various states of immunodeficiency, and regulates immunoglobulin production. Thymogen gets good concentration in the respiratory tract, making it helpful against inflammation and infection in the airway. Dosing Thymogen sublingually allows for administering a lower dose, than when compared to higher doses required in oral capsule form.

Benefits:

- Immunomodulation
- Inflammation reduction
- Regulation of T and B lymphocytes
- Immune protection against viral and bacterial infection

Dosing: Dissolve 1 tablet under the tongue daily

Side-effects: Not observed in patients dosing Thymogen sublingually. If the patient's detoxification pathways are not clear (ie: lymphatic, liver, sweating, stools), the patient may feel worse before feeling better when starting Thymogen. Focus on mobilizing their detoxification pathways to improve their response to Thymogen.

References:

1. PubMed Thymogen Search: https://pubmed.ncbi.nlm.nih.gov/?term=thymogen
2. Phase II trial of the antiangiogenic agent IM862 in metastatic renal cell carcinoma (PMID: 15354209)

VIP (Vasoactive Intestinal Polypeptide) - 50mcg/spray

VIP is a peptide naturally produced by tissues of the gut, pancreas, gallbladder, and the hypothalamus.

Actions of VIP in the body include: Vasodilation to assist in blood pressure regulation, GI tract epithelial cell secretion and blood flow - increasing water and electrolytes in the GI tract, relaxation of intestinal smooth muscle, exerting a positive effect on hypothalamic kisspeptin neurons, hormone balancing and aromatase inhibiting effect - corrects estradiol, 25-OH Vitamin D and testosterone in males, down regulation of th1 responses and controlling cytokine responses to restore immunoregulation, especially following infections by intracellular bacteria and viruses.

Benefits:

- Improvement of symptoms associated with mold toxicity, biotoxin illness and exposure to water-damaged buildings
- Decrease in symptoms related to chronic inflammation and Chronic Inflammatory Response Syndrome (CIRS)
- Improvement during respiratory failure related to Severe Acute Respiratory Syndrome (SARS) by binding to lung epithelial cells critical for oxygen transfer and surfactant production
- Reduction in mast cell activation
- Improved function of gut immune cells in Inflammatory Bowel Disease (IBD)

Side-Effects: Well-tolerated with few side-effects. Side-effects are reported following the *intravenous infusion* of VIP (aviptadil) - alterations in blood pressure, heart rate, or ECG, diarrhea. These side-effects are negligible with intranasal administration.

Dosage and Route:
Use 1 spray intranasally in alternating nostrils, up to 4 times daily. The duration of therapy for intranasal treatment is tested, commonly used, and deemed safe for at least 18 months.

References:
1. 11-Step Treatment for Biotoxin Illness: https://www.wondermakers.com/Portals/0/11-Step%20Treatment%20for%20Biotoxin%20Illness.pdf
2. Vasoactive Peptides: Role in COVID-19 Pathogenesis and Potential Use as Biomarkers and Therapeutic Targets (PMID: 34134920)
3. VIP in the Treatment of Critical Covid-19 with Respiratory Failure in Patients with Severe Comorbidity: A Prospective Externally Controlled Trail (Journal of Infections Diseases and Treatment)
4. Recent advances in vasoactive intestinal peptide physiology and pathophysiology: focus on the gastrointestinal system [version 1; peer review: 4 approved] (https://f1000research.com/articles/8-1629/v1)
5. Pharmacodynamics and toxicity of vasoactive intestinal peptide for intranasal administration (PMID: 23444784)
6. VIP: The big shot peptide in pregnancy and beyond? (https://doi.org/10.1111/apha.13636)
7. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings (10.4236/health.2013.53053)
8. Neuronal regulation of the gut immune system and neuromodulation for treating inflammatory bowel disease (PMID: 34761177)
9. Vasoactive intestinal peptide exerts an excitatory effect on hypothalamic kisspeptin neurons during estrogen negative feedback (PMID: 34915098)
10. Vasoactive Peptides: Role in COVID-19 Pathogenesis and Potential Use as Biomarkers and Therapeutic Targets (PMID: 34134920)
11. Vasoactive Intestinal Peptide Promising Treatment for COVID-19 Respiratory Failure (Source: www.pulmonologyadvisor.com)

GHK-Cu - 2.5mg, 5mg sublingual tablets

GHK-Cu is a naturally occurring copper complex tripeptide that works by promoting activation of wound healing, attracting immune cells, exhibiting antioxidant and anti-inflammatory effects, stimulating collagen and synthesis of skin fibroblasts following tissue injury, and promoting blood vessel growth and synthesis of neurotrophic factors. GHK-Cu plays a role in appropriate gene functioning and in preventing age-associated cognitive decline and neurodegenerative conditions.

As bodily concentrations of GHK-Cu decline with age, there is a consequential increase in inflammation, cancerous activity, and tissue destruction. Clinically, GHK-Cu is most widely used

to improve hair growth, decrease fine lines and wrinkles, and promote wound healing through increased circulation and collagen production. GHK-Cu may also be used to down-regulate over-expressed genes linked to various cancers.

Benefits:

- Wound healing via increased angiogenesis, anticoagulation and vasodilation
- Antioxidant, anti-inflammatory
- Hair follicle restoration and nail re-growth
- Skin elasticity restoration and scar tissue repair
- Healing of intestinal ulcerations in Crohn's
- Increased healing in stress fractures
- Stomach and intestinal lining repair
- Protection against Pulmonary Fibrosis, Acute Lung Injury and Respiratory Distress Syndrome
- Nerve regeneration, nerve growth factor production supporting cognitive health
- Protection against neurodegenerative decline via inhibition of beta-amyloid peptide production
- Down-regulation of over-expressed genes linked to various cancers (ie: metastatic colon)
- Promotes osteoblasts and marrow stromal cells for increased bone growth
- Increased improvement of brain fog and energy in elderly patients with anemia (as opposed to replacing with iron)

Side Effects: None reported with sublingual delivery.

Considerations: Assess reasonable copper levels based on patient status. Although GHK-Cu has notably suppressed various metastatic cancers, consider increased angiogenesis in patients with tumors present. Due to anticoagulation properties, consider interaction with other anticoagulation medications.

Dosage and Route: GHK-Cu is compounded into sublingual tablets to be dissolved under the tongue. It is recommended that GHK-Cu be taken on an empty stomach.

Additional Information: GHK-Cu tablets are faint purple in color.

References:

1. The Human Tripeptide GHK-Cu in Prevention of Oxidative Stress and Degenerative Conditions of Aging: Implications for Cognitive Health (PMID: 22666519)
2. GHK Peptide as a Natural Modulator of Multiple Cellular Pathways in Skin Regeneration (PMID: 26236730)
3. Glycyl-L-histidyl-L-lysine-Cu^{2+} rescues cigarette smoking-induced skeletal muscle dysfunction via a sirtuin 1-dependent pathway (PMID: 36905132)
4. GHK and DNA: Resetting the Human Genome to Health (PMID: 25302294)

Function (PT-141) – 0.5mg, 1mg sublingual tablets

The *Function* peptide, which contains PT-141 (Bremelanotide), is used to help improve sexual dysfunction in both men (erectile dysfunction or impotence) and women (sexual arousal disorder). PT-141 was developed from the tanning peptide, Melanotan 2, which is a synthetically produced variant of a peptide hormone naturally produced in the body that stimulates melanogenesis or an alpha-Melanocyte stimulating hormone (MSH). MSH activates certain melanocortin receptors in the process of exerting its effects. MSH exerts potent influence over lipid metabolism, appetite, and sexual libido. PT-141 has been shown to exhibit libido-enhancing effects by activating the melanocortin receptors MC1R and MC4R, but not skin tanning. Unlike Viagra® and other related medications, it does not act upon the vascular system, but instead directly increases sexual desire via the nervous system.

Side Effects: Possible headaches or nausea. Men have reported that headaches experienced from popular erectile dysfunction medications like Viagra® and Cialis were more intense and lasted longer than those experienced with PT-141.

Dosage and Route: A standard starting dose in both men and women is 1mg daily. Many patients, both men and women, work up to 2mg daily finding it to be an optimal dose. It is recommended that PT-141 be taken on an empty stomach.

Additional Information: Most men who have used *Function*, report that they were able to more easily achieve an erection within 15-30 minutes after taking this peptide and that the effects of increased libido may last up to 24hrs. Women often experience a quicker onset of action, dosing only 15 minutes prior to sex, and therefore the effects also dissipate quicker than in men.

References:

1. PT-141: a melanocortin agonist for the treatment of sexual dysfunction (PMID: 12851303)
2. www.vyleesi.com

Oxytocin – sublingual tablets ranging 2.5-250 units/tab, intranasal spray

Oxytocin is a neuropeptide made in the hypothalamus and released by the pituitary gland. Oxytocin has long been known to be important for its role in social bonding, sexual intimacy, childbirth, mother-child bonding, and milk let down as a mother breastfeeds her child. However, more recent research has shown the importance of its role in controlling diabetes, obesity, osteoporosis, anxiety, depression, mood regulation, insomnia, cortisol regulation, and heart disease. In humans, oxytocin release occurs in a daily rhythm, and generally peaks around the noon hour. And as with many hormones, oxytocin levels decline with age.

Benefits:

- Improved mood
- Improved sleep

- Improved libido
- Improvement of anxiety or depression symptoms
- Improve cortisol levels
- Stress management

Dosing:
Sublingual tablets are generally dosed once daily; three times daily prior to meals for insulin and leptin resistance.

For Nasal sprays, the following recommendations are achieved using either 12 units/spray or 16 units/spray:

DOSING AND ADMINISTRATION:

Use	Dosing
Depression Anxiety Social Isolation	16-24 units IN once to twice daily, alternate nostrils *Once daily dosing shows optimal results
Insomnia	24 units IN once daily at bedtime, alternate nostrils
Stress Management Adrenal Burnout PTSD	24 units IN once daily, alternate nostrils *Use up to 60 units IN daily for PTSD
Chronic Pain	24 units IN one to two times daily, alternate nostrils

Side-effects: Headache, alteration in blood pressure or heart rate

Contraindications: Hypertonic or hyperactive uterus, pregnant, manic episodes

Use with caution: Bipolar Disorder, concurrent use with LDN or naltrexone (potential competitive binding when treating pain)

References:
1. https://physicianspreferencerx.com/ > Practitioner Newsletters > Oxytocin
2. Kreuder AK, Wassermann L, Wollseifer M, et al. Oxytocin enhances the pain-relieving effects of social support in romantic couples. *Hum Brain Mapp*, 2019; 40(1):242-251.
3. Scheele D, Wille A, Kendrick K, et al. Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *Proceedings of the National Academy of Sciences*, 2013; 110(50):20308-20313.

4. Flanagan JC, Hand A, Jarnecke AM, et al. Effects of oxytocin on working memory and executive control system connectivity in posttraumatic stress disorder. *Exp Clin Psychopharmaco*l, 2018; 26(4):391-402.
5. Ding C, Leow MK, Magkos F. Oxytocin in metabolic homeostasis: implications for obesity and diabetes management. *Obes Rev*, 2019; 20(1):22-40.
6. Spetter MS, Hallschmid M. Current findings on the role of oxytocin in the regulation of food intake. *Physiol Behav*, 2017; 176:31-39.
7. Olszewski PK, Klockars A, Levine AS. Oxytocin and potential benefits for obesity treatment. *Curr Opin Endocrinol Diabetes Obes*, 2017; 24(5):320-325.
8. Lawson EA. The effects of oxytocin on eating behaviour and metabolism in humans. *Nat Rev Endocrinol*, 2017; 13(12):700-709.
9. Cai Q, Feng L, Yap KZ. Systematic review and meta-analysis of reported adverse events of long-term intranasal oxytocintreatment for autism spectrum disorder. *Psychiatry Clin Neurosci*, 2018; 72(3):140-151.

Note on all peptides listed here:

- In many cases, peptides may be taken concurrently ("stacked"), as they exhibit different mechanisms of action. Generalized use of these peptides has not been studied in women who are pregnant or lactating.
- Both sublingual tablets and oral capsules should be dosed on an empty stomach, recommended 30 minutes prior to a meal, or 2 hours after a meal.
- Sublingual tablets will dissolve in 1-2 minutes under the tongue, but the patient must wait 15 minutes after the tablet has dissolved to drink anything, including water! These tablets are designed to enter the bloodstream, not the stomach. Sublingual peptides will be destroyed by stomach acid if swallowed.
- Peptides in oral capsule form are encapsulated in acid-resistant capsules to reach the intestines.