EDUCATIONAL CLINICAL OVERVIEW

Semax (MEHFPGP) Nasal Spray

ACTH(4-7)PGP Heptapeptide · Compounded Nasal Spray · Not FDA-Approved — Investigational / Foreign-Registered Use Only

Drug Class	Synthetic ACTH(4-7)PGP heptapeptide (MEHFPGP); studied in the literature as a neuroprotective / nootropic peptide; not an FDA-approved drug
Compounded Form	Intranasal solution (commonly 0.1%–1% concentration); compounded under USP <797>
Regulatory Status	Not FDA-approved for any indication in the United States. Registered in Russia since 2001 for select neurological indications under Russian regulatory standards — a foreign approval, not a U.S. FDA approval
Literature-Discussed Areas	Ischemic stroke rehabilitation (Russian clinical literature) / Cognitive and nootropic support / Neuroprotection (preclinical) — all discussed here for scientific background only, not as promoted indications
Revision Date	July 2026

IMPORTANT — NOT FDA-APPROVED / FOR PROVIDER EDUCATION ONLY

Semax is not an FDA-approved drug and has not been evaluated by the FDA for safety, efficacy, or quality for any indication in the United States. It is not approved by the FDA for the treatment, cure, mitigation, or prevention of any disease, including ischemic stroke, cerebrovascular insufficiency, encephalopathy, or optic nerve atrophy. This document is a literature summary for the education of licensed healthcare providers only. It is not intended for patient distribution and is not promotional or marketing material. Nothing in this document should be construed as a recommendation by ReviveRX that Semax be prescribed, compounded, or administered for any particular patient or condition. All prescribing and compounding decisions rest solely with the treating provider.

1 · Regulatory Status

Status	Detail
FDA Status	Semax is not FDA-approved for any indication. No FDA Investigational New Drug (IND) application or registered Western clinical trial program exists as of 2025–2026.
Compounded Semax	Compounded intranasal solutions are prepared under USP <797> sterile compounding regulations. Quality, sterility, and potency of compounded formulations are not subject to FDA manufacturing standards.
Foreign Registration	Registered in Russia since 2001 for ischemic stroke, cerebrovascular insufficiency, optic nerve atrophy, and encephalopathy under Russian regulatory standards. This foreign registration, and the preclinical animal data supporting it, should not be equated with U.S. FDA-level substantiation of safety or efficacy.
Prescriber Responsibility	All prescribing decisions, patient selection, dosing, monitoring, informed consent, and regulatory compliance are the sole responsibility of the licensed prescriber.

2 · Evidence Limitations

The evidence base for Semax has significant limitations that should inform how this literature is discussed with colleagues and patients. These limitations apply throughout this document and are not offset by the volume of preclinical or foreign clinical literature available.

- All human controlled trials identified originate from Russian institutions; no independent Western randomized, double-blind, placebo-controlled trials have been published.
- The largest available human trial (Gusev et al., 2018) was non-randomized and lacked a placebo control.

- No FDA IND application or registered Western clinical trial program exists as of 2025–2026.
- Long-term human safety data, and human reproductive/developmental safety data, are not available in systematically published form.
- No published randomized, placebo-controlled human pharmacokinetic studies characterize CNS penetration or CSF concentration after intranasal administration; bioavailability is inferred from clinical outcome studies rather than direct PK measurement.
- Registration and clinical use in Russia since 2001, and preclinical animal data, are a supportive but non-definitive body of foreign and preclinical literature — not a substitute for U.S. FDA-level evidence.

3 · Overview

Semax (Met-Glu-His-Phe-Pro-Gly-Pro; MEHFPGP) is a synthetic heptapeptide derived from the N-terminal fragment 4–10 of adrenocorticotropic hormone (ACTH), stabilized at the C-terminus by the tripeptide Pro-Gly-Pro (PGP). It was developed by the Institute of Molecular Genetics of the Russian Academy of Sciences and has been registered in Russia since 2001 for intranasal use in several neurological indications under Russian regulatory standards; this is foreign regulatory registration, not FDA approval, and is discussed here strictly as scientific background.

Semax is described in the literature as a neuroprotective and nootropic peptide studied for effects distinct from the steroidogenic activity of full-length ACTH, as it appears to lack the sequence required for MC2R (adrenal ACTH receptor) activation. Proposed mechanisms discussed below — melanocortin receptor modulation, neurotrophic factor effects, monoaminergic modulation, transcriptomic anti-inflammatory signals, and enkephalinase inhibition — are mechanistic hypotheses drawn largely from preclinical and limited clinical data, not established mechanisms of clinical benefit.

Intranasal administration is the route studied in essentially all available clinical literature, intended to deliver peptide via the olfactory epithelium and trigeminal pathways while avoiding first-pass hepatic metabolism. This is a pharmacokinetic hypothesis consistent with published dosing protocols, not a confirmed human PK finding (see Evidence Limitations above).

4 · Mechanism of Action (Literature-Reported, Largely Preclinical)

The mechanisms below are drawn from preclinical models and a limited number of human studies. They are reported hypotheses in the literature, not confirmed clinical mechanisms of action in humans.

- **Melanocortin Receptor Modulation (MC4R/MC3R) —** Semax contains the ACTH(4-7) core sequence, reported to confer affinity for central melanocortin receptors. Published receptor binding studies describe Semax as a partial agonist or competitive antagonist of alpha-MSH at MC4R and MC5R, distinct from full agonists such as bremelanotide (Vyleesi) — see Drug Interaction Considerations.
- **BDNF and NGF — Preclinical and Limited Human Data —** Animal studies report increased BDNF mRNA expression in hippocampus, frontal cortex, and basal forebrain. A single non-randomized, non-placebo-controlled human study (Gusev et al., 2018) reported an association between intranasal Semax and elevated plasma BDNF in ischemic stroke patients, correlating with Barthel Index scores — an association from an uncontrolled trial, not a confirmed treatment effect. NGF changes have been reported only in animal models.
- **Neurotransmitter Modulation —** Preclinical studies report modulation of dopaminergic and serotonergic pathways and possible support of cholinergic neuron survival. These remain proposed mechanisms rather than established clinical effects.
- **Enkephalin-Degrading Enzyme Inhibition —** An in vitro human serum study (Kost et al., 2001) reported that Semax inhibited enkephalinase activity (IC50 ~10 μM). The authors proposed this may contribute to anxiolytic, anti-ischemic, and nootropic effects described elsewhere in the literature; this is a proposed downstream effect, not a measured clinical outcome in that study.
- **Anti-Inflammatory / Transcriptomic Signals (Animal Model) —** RNA-Seq analysis in a rat MCAO ischemia model reported reduced pro-inflammatory gene expression alongside increased neurotransmission-associated gene expression. This is a preclinical finding not replicated in human tissue.

- **Proliferative Effects (Preclinical) —** Rat ischemia model histology has reported increased markers interpreted by study authors as cell proliferation in periventricular tissue. These are animal findings and should not be presented as evidence of neural repair in human patients.

5 · Route-Specific Considerations: Intranasal Delivery

Rationale Discussed in the Literature

- Intranasal administration (1% nasal drops) is the route registered in Russia since 2001 and used in essentially all published clinical studies of Semax.
- Proposed to reduce first-pass hepatic metabolism and GI degradation, relevant given Semax's reported short plasma half-life (minutes).
- Olfactory/trigeminal pathways are proposed — but not directly confirmed in humans — to provide CNS proximity advantages over systemic routes.
- The PGP C-terminal sequence is reported to confer relative resistance to proteolytic degradation.

Limitations

- No published randomized, placebo-controlled human PK studies characterize CNS penetration or CSF concentration after intranasal administration.
- Bioavailability estimates are extrapolated from clinical outcome studies, not direct PK measurement.
- Nasal mucosal irritation is a possible adverse effect and may be formulation- and preservative-dependent.

6 · Clinical Evidence Summary

Studies below are summarized for literature-review purposes only. Design limitations (Evidence Level column and Section 2 above) should be considered before extrapolating to clinical practice.

Study	Design / Population	Reported Findings	Evidence Level	Key Limitation
Gusev et al. (2018)	Non-randomized controlled trial; 110 ischemic stroke patients	Reported BDNF elevation vs. control; correlation with Barthel Index and motor scores over ~5 months	Level III	No randomization; no placebo control
Gusev et al. (1997)	Comparative clinical-EEG study; 30 treated vs. 80 conventional-therapy controls	Reported faster regression of neurological deficits; supportive EEG/evoked potential findings	Level III–IV	Older study; limited methodological detail available
Kaplan et al. (1996)	Observational study; healthy adult volunteers	Reported subjective improvements in decision-making, attention, short-term memory	Level IV–V	Small, observational; not placebo-controlled
Lebedeva et al. (2018)	fMRI pilot; small healthy cohort	Reported measurable Default Mode Network activity changes	Level IV (pilot)	Very small sample; exploratory only
Kost et al. (2001)	In vitro/ex vivo serum study; pooled human serum	Reported enkephalinase inhibition, IC50 ~10 μM	Mechanistic (in vitro)	Enzymatic assay only; not a clinical outcome study

Broader supporting literature includes preclinical ischemia models (rat carotid occlusion and MCAO) and transcriptomic analyses; these are preclinical findings noted for scientific context, not clinical evidence of efficacy in patients. Decades of use in Russia provide a real-world pharmacovigilance history, but this experience is not systematically published in Western peer-reviewed literature and should not be treated as equivalent to FDA-reviewed safety data.

7 · Safety Profile

Safety information below is drawn from limited published literature, most involving short courses (5–10 days) in specific populations. It should not be characterized as an established or comprehensive safety profile.

Reported Short-Term Observations

- No serious adverse events attributable to Semax were reported across the human studies identified; this reflects the studies as published, not a guarantee of safety, given small samples and short durations.
- Semax has not been reported to activate MC2R and is therefore not expected to stimulate adrenal cortisol production in the studies reviewed; this has not been systematically confirmed in dedicated endocrine safety studies.
- Sedation, addiction, and withdrawal have not been reported in the available literature; absence of reports in a small evidence base does not establish absence of risk.
- Blood pressure and heart rate changes have not been reported for Semax in the literature reviewed, in contrast to full melanocortin agonists such as bremelanotide — based on limited published literature, not dedicated comparative safety trials.
- Nasal mucosal irritation and, theoretically, increased anxiety in sensitive individuals have been noted as potential adverse effects, particularly at higher doses.
- One published report (Kolomin et al., 2013) noted increased blood glucose in approximately 7.4% of diabetic patients studied; glucose monitoring is advisable if use is considered in patients with diabetes.

Long-Term Safety — Not Established

- Long-term human safety data are not available in systematically published form; statements about long-term tolerability should not be made.
- Given the ACTH-derived structure, melanocortin receptor modulation in patients with active or suspected neuroendocrine malignancy warrants caution; no such events have been reported, but this reflects a limited evidence base, not confirmed safety.
- No human reproductive or developmental safety data exist.

8 · Adverse Reactions Reported in the Literature

Adverse Effect	Reported Frequency	Severity	Notes
Nasal mucosal irritation	Uncommon; formulation-dependent	Mild	May relate to preservatives; not systematically quantified across studies
Increased anxiety / CNS activation	Rare; dose-related in reports	Mild–Moderate	Reported anecdotally; not systematically quantified in the trials reviewed
Blood glucose elevation	~7.4% in one study of diabetic patients	Mild	Kolomin et al., 2013; single report; monitor in diabetic patients
Headache	Not systematically reported	Mild (theoretical)	Not characterized in published trials
Nausea / GI effects	Not reported with intranasal route in studies reviewed	N/A	Contrast with bremelanotide's reported ~40% rate noted for mechanistic context only
Cardiovascular effects (BP/HR)	Not reported in studies reviewed	N/A	Based on limited published literature, not dedicated cardiovascular safety trials

9 · Contraindications & Precautions

Relative Contraindications (Literature-Based, Not FDA Labeling)

- Active or suspected neuroendocrine malignancy (theoretical concern given ACTH-fragment origin; no confirmed cases reported)
- Known hypersensitivity to Semax or any formulation component
- Pregnancy and breastfeeding (no human reproductive or developmental safety data exist)
- Active seizure disorder (theoretical concern given proposed CNS-excitatory activity; insufficient data)

Use With Caution

- Patients with diabetes mellitus — consider blood glucose monitoring
- Patients on other CNS-active medications (see Drug Interactions)
- Patients with severe hepatic or renal impairment — no dedicated pharmacokinetic data exist in these populations

10 · Drug Interaction Considerations: Semax and Bremelanotide (Vyleesi)

The following discussion is theoretical and mechanism-based. No dedicated co-administration or drug interaction studies of Semax and bremelanotide have been published. This is not a definitive clinical directive; providers should apply independent judgment and consider a conservative separation of dosing given the absence of direct data.

Reported Pharmacodynamic Distinctions

Parameter	Semax (MEHFPGP)	Bremelanotide (Vyleesi)
Receptor activity (reported)	Described as a partial agonist / competitive antagonist at MC4R and MC5R; does not appear to activate MC2R	Full non-selective agonist across MC1R>MC4R>MC3R>MC5R>>MC2R per FDA labeling
Regulatory status	Not FDA-approved; registered in Russia for neurological indications	FDA-approved for premenopausal HSDD
Route	Intranasal	Subcutaneous injection
Cardiovascular signal	No BP/HR effects reported in literature reviewed	Transient BP/HR change reported per FDA labeling; contraindicated in uncontrolled hypertension/CVD
Plasma half-life	Reported as minutes	~2.7 hours (range 1.9–4.0) per FDA labeling

Theoretical Interaction Considerations

- Possible MC4R competition: some literature describes Semax's ACTH(4-7) core as competitively antagonizing alpha-MSH at MC4R/MC5R in preclinical models. Because bremelanotide's labeled mechanism for HSDD involves MC4R agonism, there is a theoretical possibility that concurrent Semax exposure could reduce bremelanotide's effect. This has not been studied directly and should be treated as a hypothesis.
- No additive cardiovascular effect is confirmed or excluded; standard bremelanotide cardiovascular precautions per FDA labeling should still apply, with BP monitoring considered if co-used.
- No pharmacokinetic interaction is anticipated based on the absence of shared metabolic pathways, but this is inferred from general peptide pharmacology, not a dedicated PK interaction study.
- Semax's reported enkephalinase-inhibiting activity raises a theoretical, indirect consideration for patients also taking naltrexone or other opioid-modulating medications, given bremelanotide's separate labeled naltrexone interaction; this warrants a general medication review, not a specific clinical claim.

11 · Dosing and Formulation Information (Literature Reference Only)

DOSING DISCLAIMER

No FDA-approved dosing exists for Semax. The information below is a summary of literature-reported regimens provided strictly as reference material. It is not a ReviveRX-recommended dosing protocol and does not substitute for the treating provider's independent clinical judgment for an individual patient.

Context in Literature	Concentration Reported	Dose Reported	Duration Reported
Ischemic stroke study (moderate severity)	1% solution	6,000–12,000 mcg/day intranasal	5–10 days per course
Ischemic stroke study (severe)	1% solution	12,000–20,000 mcg/day intranasal	5–10 days per course
Gusev 2018 rehabilitation study	Standard preparation	6,000 mcg/day intranasal	2 × 10-day courses, 20-day interval
Nootropic-context literature	0.1% solution	600–1,200 mcg/day (1–2 drops/nostril BID)	Variable; cyclic courses described
Kaplan 1996 (healthy volunteers)	Not specified	~16 mg/kg intranasal	Single dose / short course

12 · Discussion (Literature Context, Not a Treatment Claim)

The available literature on Semax — preclinical mechanistic studies, a limited number of Russian human trials, and over two decades of registered use in Russia — provides scientific background that may be useful for providers evaluating compounded peptide options. This literature does not constitute FDA-level evidence of safety or efficacy for any indication, and this document should not be used to suggest that ReviveRX is promoting Semax for the treatment of ischemic stroke, cerebrovascular insufficiency, encephalopathy, optic nerve atrophy, anxiety, or any other disease or condition.

Distinguishing features noted in the literature — such as the absence of reported hemodynamic effects, addictive potential, or adrenal activation relative to full melanocortin agonists — are based on a limited evidence set and should be described as observations from the available literature rather than established safety advantages. The proposed pharmacodynamic overlap with bremelanotide at MC4R is a theoretical consideration warranting caution and further review, not a confirmed clinical interaction.

13 · Summary

Semax (MEHFPGP) is a heptapeptide with a substantial preclinical literature base and a smaller body of Russian human clinical studies, none of which meet U.S. FDA standards for randomized, placebo-controlled evidence. It is not FDA-approved, has not been evaluated by the FDA, and long-term safety, reproductive/developmental safety, and drug interaction profiles remain insufficiently studied. Any discussion of ischemic stroke, cerebrovascular, cognitive, or other clinical outcomes in this document reflects literature review only and is not a representation that Semax is safe or effective for those purposes, nor a recommendation for its use.

Providers evaluating Semax, including in combination with other melanocortin-pathway agents such as bremelanotide, should rely on independent clinical judgment, review the primary literature cited below, and apply appropriate caution given the theoretical and largely preclinical nature of much of the supporting data.

14 · References & Disclaimer

Key References

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Novosadova EV, Manuilova ES, et al. Investigation of the effect of alpha-MSH on proliferation and early stages of differentiation of human induced pluripotent stem cells. Dokl Biochem Biophys. 2016;467:141-144.

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Kaplan AYa, Kochetova AG, Nezavibathko VN, et al. Synthetic ACTH analogue Semax displays nootropic-like activity in humans. Neurosci Res Commun. 1996;19(2):115-123.

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PMID 9213373: Selectivity of ACTH(4-10) analogues for melanocortin receptors.

DISCLAIMER

This Educational Clinical Overview is intended exclusively for licensed healthcare professionals and is not intended as patient-directed information. The information contained herein is for educational purposes only and does not constitute medical advice or a prescribing protocol.

Semax is not FDA-approved for any indication in the United States. All use of Semax is off-label and investigational in the U.S. and is not supported by Phase 3 randomized controlled trial evidence. Prescribers are solely responsible for all clinical decisions, patient selection, dosing, monitoring, informed consent, and compliance with applicable federal and state compounding regulations. This document is subject to revision.

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