CLINICAL LEARNING GUIDE

Semax

Met-Glu-His-Phe-Pro-Gly-Pro | ACTH(4-7)-PGP Analog | Neuroprotective / Nootropic Melanocortin Peptide

Mechanisms, Evidence, and Clinical Applications

Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education

For educational and research purposes only. Not medical advice. Semax is APPROVED in Russia and Ukraine (for stroke, cognitive disorders, and optic-nerve disease, and is on Russia's Vital & Essential Drugs list) but is NOT FDA- or EMA-approved; outside Russia/Ukraine it is research use only. All randomized controlled trials are Russian; there are no Western RCTs, no GLP-compliant toxicology data in the English-language literature, and no established long-term safety data (studies are largely ≤14-day courses). Note that acute-stroke dosing is in MILLIGRAMS while all other indications use MICROGRAMS — do not confuse them. Consult qualified healthcare providers before clinical use.

SECTION 1 · PROFILE OF THE PEPTIDE

Overview

Semax is a synthetic heptapeptide (Met-Glu-His-Phe-Pro-Gly-Pro, MW ~813.4 Da) built from the ACTH(4-7) fragment with a C-terminal Pro-Gly-Pro ("PGP" / glyproline) extension. Developed at the Institute of Molecular Genetics of the Russian Academy of Sciences, it is classified as a melanocortin-derived neuropeptide and nootropic. Its design captures a clever idea: by using only a short ACTH(4-10)-scaffold fragment rather than the whole hormone, Semax retains ACTH's neurotrophic and cognitive effects while shedding ACTH's endocrine actions — there is no HPA-axis (cortisol) stimulation at nootropic doses. The glyproline tail also adds metabolic stability.

Mechanistically it is a multi-target neuroprotectant working through three main routes: it upregulates the BDNF/TrkB neurotrophin system (and related NGF, NT-3, TrkA/TrkC), it engages melanocortin (MC4R) signaling for cognitive/nootropic and attention effects, and it chelates copper — stripping Cu(II) from amyloid-beta to reduce aggregation and oxidative damage. Layered on top is a broad anti-inflammatory, anti-ischemic effect (cytokine suppression, blood-brain-barrier protection).

Semax is approved in Russia and Ukraine for acute ischemic stroke, cognitive disorders, and optic-nerve disease, and sits on Russia's Vital & Essential Drugs list — a genuine clinical pedigree, with its strongest evidence in stroke and cerebrovascular insufficiency. Dr. Seeds regards it as a very good, possibly underutilized, intranasal peptide. The countervailing truth is the familiar one for this class: all of the randomized controlled trials are Russian, there are no Western RCTs, no GLP toxicology data in English, and no long-term safety data, and it is not FDA- or EMA-approved. A real approved indication in one region and a coherent multi-target mechanism are not the same as Western-validated, FDA-grade evidence — and holding both at once is the central thing to convey.

Peptide Profile

Property	Detail
Name / sequence	Semax; Met-Glu-His-Phe-Pro-Gly-Pro (MEHFPGP), a synthetic heptapeptide

Property	Detail
Identity	ACTH(4-7) fragment + C-terminal Pro-Gly-Pro (PGP); melanocortin-derived neuropeptide/nootropic
MW / formula	~813.4 Da; $C_{37}H_{51}N_7O_{10}S$; developed at the Institute of Molecular Genetics, RAS
Primary targets	BDNF/TrkB neurotrophin system; melanocortin MC4R; Cu(II) chelation (anti-amyloid)
Other effects	Anti-inflammatory/anti-ischemic (cytokine suppression, MMP-9/BBB protection); no HPA-axis stimulation at nootropic doses
Approved route	Intranasal (0.1% solution); also intranasal drops and endonasal electrophoresis (optic-nerve protocols)
Approved indications	Stroke, cognitive disorders, optic-nerve disease (Russia/Ukraine); on Russia's Vital & Essential Drugs list
Human PK/ADME	No GLP toxicology in English; rapid CNS penetration via olfactory route; long-term human data lacking
Regulatory	APPROVED in Russia/Ukraine; NOT FDA/EMA approved; research use only in the West; off US 503A category-1 list (possible return discussed)
Evidence	Russian RCTs (stroke n=30, n=187; optic nerve n=74) + animal/in-vitro; no Western RCTs

Where Semax Sits

Semax is the neuroprotective-nootropic counterpart to Selank within this group — both are small, Russia-approved, intranasal peptides, and Dr. Seeds often discusses them together. The contrast is instructive: Selank (a tuftsin-derived heptapeptide) is primarily anxiolytic and calming, whereas Semax (an ACTH-derived heptapeptide) is neurotrophic, neuroprotective, and mildly stimulating, with its center of gravity in stroke, cognition, and optic-nerve disease. Against the broader field, Semax differs from the porcine-brain hydrolysate Cerebrolysin (which supplies exogenous neurotrophins and has Austrian/Russian RCTs) and from the small-molecule AMPA-modulator piracetam — Semax instead drives the brain's own neurotrophin production while chelating copper and damping inflammation. Dr. Seeds frames it as another tool in the toolbox: a clinically approved (in its home region) neuroprotective adjunct — strongest as post-stroke support and optic-nerve neuroprotection — used intranasally, often intermittently, and frequently in combination with other peptides.

> **⚠ Semax is APPROVED in Russia/Ukraine (stroke, cognitive disorders, optic-nerve disease) but is NOT FDA/EMA approved — research use only in the West. ALL randomized controlled trials are Russian; there are NO Western RCTs, NO GLP toxicology data in English, and NO long-term safety data (studies are largely ≤14-day courses). DOSING ALERT: acute-stroke dosing is in MILLIGRAMS (12–18 mg/day) while cognitive, cerebrovascular, and optic-nerve dosing use MICROGRAMS (200–1200 mcg/day) — a ~1000-fold difference; do not confuse them. Mild anxiogenic potential at higher doses; caution in anxiety disorders, diabetes (glucose fluctuation), pregnancy/lactation, and hepatic/renal impairment. Full informed consent is essential.**

SECTION 2 · MODES OF ACTION AND MECHANISMS

Semax works through three converging molecular targets — the BDNF/TrkB neurotrophin system, melanocortin (MC4R) signaling, and copper chelation — wrapped in a broad anti-inflammatory, anti-ischemic effect. The unifying theme is endogenous neuroprotection: rather than supplying a drug effect, Semax mobilizes the brain's own growth factors and protective responses while removing a source of oxidative and amyloid damage. Most mechanistic data are preclinical (rat ischemia models and in-vitro systems), complementing the Russian clinical work.

BDNF / TrkB Neurotrophin System

The best-characterized mechanism is rapid neurotrophin upregulation. A single dose drives an approximately 3-fold increase in BDNF (exon III) mRNA and a ~1.4-fold rise in BDNF protein, with a ~2-fold increase in TrkB mRNA and ~1.6-fold TrkB tyrosine phosphorylation — peaking around 3 hours — plus specific binding in the basal forebrain (KD = 2.4 nM) and increased hippocampal CA1 calcium-oscillation frequency. After ischemia, Semax also upregulates a wider neurotrophin program: TrkA and TrkC at 3 hours, NT-3 at 24 hours, and NGF at 24 and 72 hours, selectively in the ischemic cortex. This BDNF/TrkB activation underlies its learning, memory, and neuroprotective effects.

Melanocortin (MC4R) Signaling — ACTH Without the Endocrine Cost

Because Semax is built from the ACTH(4-10) scaffold, it engages melanocortin MC4 receptors to mediate cognitive, nootropic, and selective-attention effects (with a proposed augmentation of dopamine release). Critically, using only the short fragment rather than full ACTH means it reproduces the neurotrophic/behavioral effects without ACTH's endocrine actions — there is no HPA-axis or cortisol stimulation at nootropic doses. This decoupling of the central, cognition-enhancing melanocortin effect from the peripheral steroidogenic effect is the core rationale of the molecule (see the note below).

Copper Chelation & Amyloid Protection

Semax binds Cu(II) with an albumin-like affinity through an N4 coordination geometry anchored by its histidine residue. This lets it extract copper from copper-amyloid-beta species and prevent Aβ:Cu^{2+} complex formation — "stripping" the redox-active metal so it can no longer catalyze reactive-oxygen-species (ROS) production via Fenton-type chemistry. In vitro, this anti-aggregating, copper-silencing action is cytoprotective in SH-SY5Y neuronal cells and reduces amyloid-beta(1-42) toxicity by up to ~90%. Because copper-amyloid dysregulation is a recognized mechanism in Alzheimer's disease, Semax is hypothesized to interrupt the copper-amyloid cascade; an in-vivo APP/PS1 mouse model showed reduced plaque burden. The important caveat: the copper/amyloid data are in vitro (with one animal model), and the Alzheimer's translation is not validated in humans.

Anti-Inflammatory & Anti-Ischemic Signaling

In rat transient-MCAO (ischemia) models, Semax significantly suppresses pro-inflammatory mRNAs — IL-1α, IL-1β, IL-6, and the chemokines Cxcl2 and Ccl3 — and reduces TNF-α pathway activation; genome-wide, the immune response is the single most affected process. At the protein level (24 h post-ischemia) it upregulates CREB in subcortical structures, suppresses active JNK in both cortex and subcortex, downregulates c-Fos in frontoparietal cortex, and downregulates MMP-9 (matrix metalloproteinase-9), which helps preserve blood-brain-barrier integrity. The Pro-Gly-Pro (glyproline) fragment contributes meaningfully to these anti-inflammatory effects. Together these actions — angioprotective, antihypoxic, anti-inflammatory, and neurotrophic — are the basis for its stroke benefit.

Key mechanistic point: Semax is a multi-target neuroprotectant that (1) rapidly upregulates the BDNF/TrkB neurotrophin system (≈3× BDNF mRNA, peaking ~3 h; plus NGF/NT-3/TrkA/TrkC after ischemia), (2) engages melanocortin MC4R signaling for cognitive/attention effects WITHOUT ACTH's HPA/cortisol stimulation, and (3) chelates Cu(II) — stripping copper from amyloid-beta to cut aggregation and ROS (reducing Aβ toxicity up to ~90% in vitro). It also broadly suppresses ischemic neuroinflammation (IL-1/IL-6/chemokines down; CREB up, JNK/c-Fos/MMP-9 down, protecting the BBB). The mechanism is coherent and multi-system, but most data are preclinical, with human evidence confined to Russian clinical trials.

A Note on the ACTH Heritage Without the Endocrine Cost

The defining structural idea of Semax is worth stating plainly. Full ACTH is a 39-amino-acid hormone whose central effects (arousal, attention, neurotrophic support) are inseparable, in the whole molecule, from its peripheral job of driving adrenal cortisol release. Semax keeps only the ACTH(4-7) "message" fragment — the part responsible for the melanocortin/CNS effects — and adds a Pro-Gly-Pro tail for stability. The result is a peptide that behaves as a melanocortin-system nootropic and neurotrophic agent (via MC4R, BDNF, dopamine) while producing no HPA-axis or steroidogenic stimulation at the doses used. This is the same fragment-not-the-whole-hormone logic that makes the molecule attractive: it isolates the desired neuroprotective and cognitive signaling from the endocrine consequences that would otherwise accompany it. It also explains why Semax is classed as a melanocortin peptide and why its mild stimulating/pro-attention character — occasionally tipping into anxiety or restlessness at higher doses — differs from the calming profile of the tuftsin-derived Selank.

SECTION 3 · POINTS OF CLINICAL RELEVANCE

- **The defining tension.** Real Russia/Ukraine approval and stroke RCTs — but Russian-only evidence and no Western validation.

Semax is approved in Russia and Ukraine (and on Russia's Vital & Essential Drugs list) with genuine clinical-trial support, especially in stroke. But all the RCTs are Russian, there are no Western RCTs, no GLP toxicology in English, and no long-term safety data, and it is not FDA/EMA-approved. A real regional approval and a coherent mechanism are not the same as Western-validated evidence, and that must be disclosed.

- **Strongest evidence is stroke and cerebrovascular insufficiency.** And it is an adjunct, not a replacement.

The most robust human data are in acute ischemic stroke (motor-deficit regression) and cerebrovascular insufficiency (reduced stroke/TIA risk, disease stabilization). Dr. Seeds is explicit that Semax is an adjunct to standard care — to tPA, mechanical thrombectomy, and rehabilitation — not a substitute for any of them.

- **A three-target neuroprotective mechanism.** BDNF/TrkB, melanocortin MC4R, and copper chelation.

Few peptides combine rapid neurotrophin upregulation, melanocortin-receptor cognitive signaling, and metal (copper) chelation in one molecule, layered over a broad anti-inflammatory, BBB-protective effect. This breadth is its appeal and the reason its benefit can't be pinned to a single pathway.

- **ACTH-derived nootropic without the endocrine cost.** Melanocortin effects, no cortisol/HPA stimulation.

By using only the ACTH(4-7) fragment, Semax delivers melanocortin-mediated cognition and attention effects (and proposed dopamine augmentation) without ACTH's steroidogenic, HPA-axis actions — the structural rationale that makes it usable as a nootropic.

- **Optic-nerve/glaucoma neuroprotection, and an emerging copper-amyloid/AD angle.** Moderate and emerging evidence, respectively.

Clinical optic-nerve work (74 patients/98 eyes; plus glaucoma electrophoresis) showed improved acuity, visual fields, and color vision — moderate-tier evidence. Separately, the in-vitro copper-stripping/anti-amyloid action and an APP/PS1 plaque-reduction model make Alzheimer's an emerging hypothesis — promising but not yet validated in humans.

- **The dosing distinction is a safety issue.** Stroke uses milligrams; everything else uses micrograms.

Acute-stroke protocols use 12–18 mg/day intranasally, whereas cognitive, cerebrovascular, and optic-nerve protocols use 200–1200 mcg/day — a roughly 1000-fold difference. Dr. Seeds stresses not confusing the two; a microgram protocol dosed in milligrams would be a serious error.

- **A nootropic that can over-stimulate.** Anxiety is more likely with Semax than with Selank.

Because Semax is mildly stimulating (its nootropic/dopaminergic character), it can occasionally cause anxiety or restlessness, especially at higher doses — something Dr. Seeds sees more with Semax than with the calming Selank. For anxious or panic-prone patients, Selank is the better fit; the two are sometimes paired (Semax earlier in the day, Selank later).

SECTION 4 · GENERAL DOSING INSTRUCTIONS AND DELIVERY OPTIONS

> **Intranasal is the validated route. DOSING ALERT: acute-stroke dosing is in MILLIGRAMS (12–18 mg/day); cognitive, cerebrovascular, and optic-nerve dosing use MICROGRAMS (200–1200 mcg/day) — a ~1000-fold difference. Do NOT confuse them. All dosing derives from Russian-approved labeling and trials and is NOT FDA-approved guidance; subcutaneous use is preclinical only. Start low, especially in anxiety-prone patients; Dr. Seeds advises against routine daily use for nootropic purposes.**

Dosing by Indication (Russian-Approved / Trial-Derived)

Indication	Route	Dose	Duration	Evidence
Acute ischemic stroke	Intranasal	12–18 mg/day (MG)	5–10 days	Clinical trial
Cerebrovascular insufficiency	Intranasal	200–600 mcg/day	10–14 days	Clinical trial
Optic-nerve disease	IN drops / electrophoresis	600–1200 mcg/day (drops); 400–600 (electro)	8–10 days	Clinical trial
Cognitive / nootropic	Intranasal	200–600 mcg/day	10–14 days	Clinical trial
Preclinical models	Intranasal / SC	50–250 mcg/kg	Single / short course	Animal

Administration & Formulation

- Intranasal spray (0.1% solution) is the most-studied route and is preferred for nootropic and chronic use — rapid CNS penetration via the olfactory epithelium.
- Intranasal drops (0.1%, 600–1200 mcg/day) and endonasal electrophoresis (400–600 mcg/day) are the optic-nerve/glaucoma protocols.
- Subcutaneous dosing (50–250 mcg/kg) appears only in animal models and is not routinely used in human protocols.
- Western compounding reality: nasal sprays are typically formulated so that one spray delivers roughly 500–750 mcg (e.g., ~5,000 mcg/mL → ~500 mcg/spray, or ~7,500 mcg/mL → ~750 mcg/spray, in ~6 mL vials).

Dr. Seeds's Practice Approach (Intranasal, Intermittent)

- Use intranasally — the validated route; in Western practice roughly one spray (~500–750 mcg) per dose, e.g., one nostril in the morning and the other midday.
- For cognitive/nootropic use, prefer intermittent dosing (e.g., 2–3× per week) rather than daily, in short courses (up to ~2 weeks, mirroring the trials), with rotation/cycling.
- Dosing is highly patient-specific — Dr. Seeds calls it "the art of using Semax," titrating to the individual, since responses vary widely; start conservatively, particularly where anxiety is a concern.
- For stroke/cerebrovascular indications, the milligram-range, daily, short-course protocols from the trials apply — as an adjunct to standard care.

Combinations & the Semax–Selank Pairing

Dr. Seeds highlights a complementary pairing with Selank that exploits their opposite characters: Semax (stimulating, BDNF/nootropic) earlier in the day and Selank (calming, anxiolytic) later in the day or afternoon, used same-day or on alternating days. This lets one peptide drive cognition/neurotrophic support while the other manages anxiety — useful given Semax's mild anxiogenic potential. For post-stroke and cerebrovascular cases, Semax can be combined with other modalities and standard rehabilitation. All combinations are practice-derived and lack human combination-trial data, so they should be approached as individualized, documented, investigational use.

SECTION 5 · EVIDENCE PROFILE

Clinical & Preclinical Evidence by Domain

Domain / Study	Type	Key Finding
Acute stroke (Gusev 1997)	Clinical (Russia)	30 patients, intranasal 12–18 mg/day, 5–10 d: increased regression of motor deficits
Cerebrovascular insufficiency (Gusev 2005)	Clinical (Russia)	187 patients: disease stabilization; reduced stroke/TIA risk; neurotrophic, angioprotective
Stroke mechanism (Miasoedov 1999)	Clinical (Russia)	Anti-inflammatory neuroprotection confirmed in acute period
Optic-nerve disease (Polunin 2000)	Clinical (Russia)	74 patients / 98 eyes: improved acuity, visual fields, color vision, electrosensitivity

Domain / Study	Type	Key Finding
Glaucoma (Kurysheva 2001)	Clinical (Russia)	Electrophoresis: neuroprotection advantage vs standard treatment
BDNF/TrkB (Dolotov 2006)	Animal	~3× BDNF mRNA, ~1.6× TrkB phosphorylation; basal-forebrain binding (KD 2.4 nM)
Neurotrophins post-ischemia (Dergunova 2010)	Animal	BDNF/TrkA/TrkC at 3 h; NT-3 at 24 h; NGF at 24/72 h in ischemic cortex
Anti-inflammatory (Dergunova 2021; Sudarkina 2021)	Animal	IL-1/IL-6/chemokines down; CREB up; JNK/c-Fos/MMP-9 down (BBB protection)
Copper/amyloid (Sciacca 2022; Tomasello 2025)	In vitro	Cu(II) stripping from Aβ; reduced Aβ(1-42) toxicity up to ~90%; lower ROS
Alzheimer model (Radchenko 2025)	Animal	Improved cognition (open field, novel object, Barnes maze); reduced plaque

Mechanistic Checklist (Evidence-Tiered)

Axis	Status	Evidence Tier
BDNF / TrkB neurotrophin upregulation	Confirmed	Animal
Melanocortin MC4R / nootropic signaling	Confirmed	Animal + clinical (cognition)
Copper chelation / anti-amyloid	Confirmed	In vitro (+ one animal model)
Anti-inflammatory / anti-ischemic (BBB)	Confirmed	Animal
Stroke / cerebrovascular benefit	Supported	Russian RCTs (n=30, n=187)
Optic-nerve neuroprotection	Supported	Russian clinical (n=74; glaucoma)
Alzheimer's disease benefit	Emerging	In vitro + animal only
ADHD / Rett syndrome	Hypothesis	Mechanistic rationale only
Human PK / GLP toxicology	No data	None in English literature

What Can and Cannot Be Confirmed

Can confirm	Cannot confirm
A well-characterized ACTH(4-7)-PGP heptapeptide	Western-validated efficacy (no non-Russian RCTs)
Multi-target mechanism (BDNF/TrkB, MC4R, Cu chelation)	Human pharmacokinetics or GLP toxicology (none in English)
Clinical benefit in stroke and optic-nerve disease (Russian data)	Efficacy vs Western standard of care (no head-to-head trials)
Favorable short-term safety, even at high (stroke) doses	Long-term safety beyond ~14-day courses

Can confirm	Cannot confirm
In-vitro anti-amyloid/copper effect; animal plaque reduction	That the Alzheimer's/ADHD translation holds in humans

Critical Evidence Gaps

- No Western RCTs and no head-to-head trials against standard neuroprotective or nootropic care; all RCTs are Russian.
- No GLP-compliant toxicology data in the English-language literature and no formal human pharmacokinetic/ADME studies.
- No long-term safety data — most studies are ≤14-day courses; repeated/chronic use is uncharacterized.
- Copper/amyloid and Alzheimer's data are in vitro plus one animal model; the human translation is unproven.
- ADHD/Rett applications are mechanistic hypothesis only; no FDA/EMA-accepted data exist for any indication.

SECTION 6 · CLINICAL CONSIDERATIONS

Regulatory & Legal Status

Semax is approved in Russia and Ukraine for stroke, cognitive disorders, and optic-nerve disease, and is included on Russia's Vital & Essential Drugs list. It is not approved by the FDA or EMA, or in any other country, and is research use only in the West — there is no GLP-compliant toxicology in the English-language literature. Dr. Seeds notes Semax is currently off the US 503A compounding category-1 list but that a return has been discussed (a status to verify before any compounding). Regional approval is not global validation.

Safety Profile

Within its evidence base, Semax's safety is favorable: it was well tolerated across published trials with no serious adverse events even at the high (12–18 mg/day) stroke doses, no organ toxicity (liver, kidney, cardiac), and no tolerance or dependence. The minor effects are transient nasal irritation (common, mild), occasional mild headache (rare, at higher doses), mild anxiety/restlessness (rare, at higher doses), and rare glucose fluctuation. Two practical cautions stand out from Dr. Seeds's experience: anxiety/restlessness is more likely with Semax than with Selank (a function of its mild stimulating, nootropic character, and often of too-high dosing), and glucose can move in either direction, so diabetics warrant monitoring. The hard limits remain: limited long-term safety data (repeated use beyond ~14 days is unknown) and no GLP toxicology in English.

Contraindications & Precautions

- Pregnancy/lactation: insufficient safety data — avoid unless clearly necessary (animal data are inadequate).
- Anxiety/panic disorders: mild anxiogenic potential at higher doses — use with caution, start at the lowest effective dose, and consider Selank instead where anxiety is the dominant concern.
- Diabetes: glucose fluctuation has been reported (in either direction) — monitor blood glucose and adjust antidiabetic therapy as needed.

- Hepatic/renal impairment: peptide metabolism may be altered — use with caution, monitor LFTs/renal function; no specific dose-adjustment data exist.

Monitoring

Reasonable monitoring (extrapolated from the trials and the peptide's pharmacology): a baseline cognitive assessment (MoCA/MMSE) and neurological exam (especially in stroke patients), blood pressure and cardiovascular baseline, fasting glucose in diabetics/pre-diabetics, anxiety screening (e.g., GAD-7) where there is an anxiety history, and LFTs/renal panel at baseline (and end-of-course if prolonged use is planned), plus inspection of the nasal mucosa. Frequency: daily clinical assessment in acute stroke; every 2–4 weeks during chronic courses; and a follow-up about 4 weeks after course completion. No Semax-specific lab markers are validated.

Patient Selection & Practitioner Posture

Semax fits adults with a documented neurological indication, used under supervision: post-stroke neuroprotection (its strongest evidence) and cerebrovascular insufficiency, optic-nerve neuroprotection including glaucoma, and cognitive support in neurological conditions — always as an adjunct to standard care, never a replacement for tPA, thrombectomy, intraocular-pressure control, or rehabilitation. It is not appropriate in pregnancy/lactation, should be used cautiously (or deferred to Selank) in anxiety/panic disorders, and warrants monitoring in diabetes and hepatic/renal impairment. The responsible posture mirrors the evidence: present the genuine Russian/Ukrainian approval and clinical data honestly alongside the absence of Western RCTs, GLP toxicology, and long-term safety data; use the validated intranasal route with correct (microgram vs milligram) dosing; favor intermittent rather than daily nootropic use; obtain full informed consent that names the research-use status and Russian-only evidence base; and document indication, dose, response, and adverse events — weighting the evidence tier (strong for stroke, moderate for optic nerve, emerging for Alzheimer's, hypothesis for ADHD) when counseling patients.

SECTION 7 · A FINAL NOTE

Semax is, alongside Selank, one of the more clinically grounded peptides in this group — and its natural complement. It is an ACTH(4-7)-PGP heptapeptide engineered to keep ACTH's central, neurotrophic, melanocortin effects while shedding the hormone's endocrine actions, and it works through three converging routes: rapid BDNF/TrkB neurotrophin upregulation, melanocortin MC4R cognitive signaling, and copper chelation that strips redox-active Cu(II) from amyloid-beta — all layered over a broad anti-inflammatory, blood-brain-barrier-protective, anti-ischemic effect. It is approved in Russia and Ukraine and sits on Russia's essential-medicines list, with its strongest evidence in acute ischemic stroke and cerebrovascular insufficiency, moderate evidence in optic-nerve and glaucoma neuroprotection, and an emerging (in-vitro and animal) copper-amyloid rationale in Alzheimer's disease. Dr. Seeds regards it as a very good, possibly underutilized, intranasal neuroprotective adjunct.

And yet the honest accounting holds. All of the randomized controlled trials are Russian; there are no Western RCTs, no head-to-head comparisons with standard care, no GLP toxicology in the English literature, and no long-term safety data beyond short courses. The copper-amyloid and Alzheimer's findings are preclinical, and the ADHD/Rett applications are hypothesis only. By formal standards, Semax remains research-use and investigational in the West, an adjunct rather than a primary therapy, and not a substitute for established stroke, glaucoma, or cognitive care.

For the practitioner, the posture is measured optimism with a few specific disciplines. Semax's mechanism is coherent and multi-system, its regional approval and stroke data are real, and its short-course safety — even at high doses — is reassuring. Used thoughtfully — intranasally, with scrupulous attention to the milligram-versus-microgram distinction, intermittently for cognitive purposes, as an adjunct in stroke and optic-nerve disease, with caution in anxiety-prone and diabetic patients, and often paired with the calming Selank — it can be a useful tool, provided every use carries full informed consent about its Russian-only evidence base and is carefully documented to help build the Western evidence it still lacks.

> **Bottom line: Semax is an ACTH(4-7)-PGP melanocortin heptapeptide (MEHFPGP) that delivers ACTH-derived neurotrophic/nootropic effects WITHOUT HPA/cortisol stimulation, acting through three targets — BDNF/TrkB upregulation (≈3× BDNF mRNA), MC4R cognitive signaling, and Cu(II) chelation that cuts amyloid aggregation and ROS (−90% Aβ toxicity in vitro) — plus broad anti-ischemic, anti-inflammatory, BBB protection. APPROVED in Russia/Ukraine (stroke, cognition, optic nerve; essential-medicines list) with real clinical trials, but NO Western RCTs, NO GLP toxicology (English), and NO long-term safety data; NOT FDA/EMA-approved. Strongest evidence: stroke and optic nerve; emerging: copper-amyloid/Alzheimer's. DOSING: stroke = 12–18 MG/day; cognitive/cerebrovascular/optic = 200–1200 MCG/day — never confuse them. Mildly stimulating (can cause anxiety — use Selank instead, or pair Semax AM + Selank PM). A genuinely promising, Russia-approved neuroprotective adjunct — still investigational and unvalidated in the West.**

Selected References & Source Note

This guide was prepared from the recorded SSRP lecture on Semax by William Seeds, MD, and the accompanying slide deck. The 18 references below are reproduced from the lecture's bibliography (PMIDs as listed); the human clinical data are from Russian trials, with the remainder animal, in-vitro, review, or mechanistic-rationale sources. Readers should consult the primary sources directly.

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For educational and research purposes only. Not medical advice. Semax is approved in Russia/Ukraine (stroke, cognitive disorders, optic-nerve disease) but is not FDA/EMA-approved; all RCTs are Russian, with no GLP toxicology in English and no long-term safety data. Acute-stroke dosing is in milligrams; all other indications use micrograms. Prepared from lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.