Semax — Basic Review Questions

1. What is Semax, and what is the rationale behind its structure?

Answer: 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 and classified as a melanocortin-derived neuropeptide/nootropic. The structural rationale is to keep ACTH's central, neurotrophic, melanocortin effects while shedding the hormone's endocrine actions: by using only the short ACTH(4-10)-scaffold fragment rather than the whole 39-amino-acid hormone, Semax produces cognitive/neurotrophic effects with no HPA-axis or cortisol stimulation at nootropic doses. The glyproline tail adds metabolic stability and itself contributes anti-inflammatory activity. It is approved in Russia and Ukraine for stroke, cognitive disorders, and optic-nerve disease.

2. What is the central tension a practitioner must understand about Semax?

Answer: Semax has a genuine clinical pedigree — it is approved in Russia and Ukraine and sits on Russia's Vital & Essential Drugs list, with real clinical-trial support (strongest in stroke), and Dr. Seeds regards it as a very good, possibly underutilized intranasal peptide. But all of the randomized controlled trials are Russian: there are no Western RCTs, no head-to-head trials against standard care, no GLP-compliant toxicology data in the English-language literature, and no long-term safety data (studies are largely ≤14-day courses). It is not FDA- or EMA-approved and is research use only in the West. A real regional approval and a coherent multi-target mechanism are not the same as Western-validated, FDA-grade evidence, and that gap must be disclosed.

3. What are Semax's three main mechanisms of action?

Answer: Semax is a multi-target neuroprotectant working through three converging routes. (1) BDNF/TrkB neurotrophin system: it rapidly upregulates BDNF (~3-fold mRNA, ~1.4-fold protein), TrkB (~2-fold mRNA, ~1.6-fold phosphorylation), peaking around 3 hours, with basal-forebrain binding (KD 2.4 nM) and, after ischemia, upregulation of NGF, NT-3, TrkA, and TrkC in the ischemic cortex — driving learning, memory, and neuroprotection. (2) Melanocortin MC4R signaling: derived from the ACTH(4-10) scaffold, it engages MC4 receptors for cognitive/nootropic and selective-attention effects (with proposed dopamine augmentation), without HPA-axis stimulation. (3) Copper chelation: it binds Cu(II) (albumin-like affinity, N4 geometry anchored by its histidine), stripping copper from amyloid-beta to prevent Aβ:Cu^{2+} complexes, reduce aggregation, and silence copper-catalyzed ROS — cutting Aβ(1-42) toxicity up to ~90% in vitro. Layered over these is a broad anti-inflammatory, anti-ischemic effect (suppressed IL-1/IL-6/chemokines; CREB up; JNK, c-Fos, and MMP-9 down, protecting the blood-brain barrier).

4. Where is the evidence strongest, and where is it weakest?

Answer: Strongest: acute ischemic stroke and cerebrovascular insufficiency, supported by Russian clinical trials (Gusev 1997, n=30, showing motor-deficit regression; Gusev 2005, n=187, showing disease stabilization and reduced stroke/TIA risk). Moderate:

optic-nerve neuroprotection and glaucoma (Polunin 2000, 74 patients/98 eyes, with improved acuity, visual fields, and color vision; Kurysheva 2001 in glaucoma). Emerging: Alzheimer's disease — the copper-amyloid axis and an APP/PS1 plaque-reduction model — but this is in-vitro and animal data needing human validation. Hypothesis only: ADHD/Rett syndrome (mechanistic rationale). Weakest/absent: there are no Western RCTs, no GLP toxicology in English, no formal human pharmacokinetics, and no long-term safety data; the mechanistic data are largely animal, and the copper/amyloid data are in vitro.

5. How is Semax dosed, and why is the dosing distinction a safety issue?

Answer: Intranasal is the validated route, and the dosing differs enormously by indication — a roughly 1000-fold difference that Dr. Seeds stresses must not be confused. Acute ischemic stroke uses MILLIGRAMS: 12–18 mg/day intranasally for 5–10 days (12 mg for moderate, 18 mg for severe strokes). All other indications use MICROGRAMS: cerebrovascular insufficiency and cognitive/nootropic use at 200–600 mcg/day for 10–14 days, and optic-nerve disease at 600–1200 mcg/day (drops) or 400–600 mcg/day (electrophoresis) for 8–10 days. Preclinical animal work used 50–250 mcg/kg. Confusing a microgram protocol for a milligram one (or vice versa) would be a serious dosing error. In Western compounding, nasal sprays are typically formulated so one spray delivers roughly 500–750 mcg.

6. What is Dr. Seeds's practice approach, and how might Semax be combined with Selank?

Answer: Dr. Seeds favors the intranasal 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 he prefers intermittent dosing (about 2–3 times per week) rather than daily, in short courses (up to ~2 weeks, mirroring the trials), with rotation/cycling, and he emphasizes that dosing is highly patient-specific — "the art of using Semax" — starting conservatively, especially where anxiety is a concern. For stroke/cerebrovascular use, the milligram-range, daily, short-course trial protocols apply as an adjunct to standard care. He 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 — so one peptide supports cognition while the other manages anxiety. All combinations are practice-derived and lack human combination-trial data.

7. What is the safety profile, and what are the key contraindications and cautions?

Answer: Within its evidence base Semax is well tolerated, with no serious adverse events reported even at the high (12–18 mg/day) stroke doses, no organ toxicity, and no tolerance or dependence. Minor effects: transient nasal irritation (common, mild), occasional mild headache (rare, higher doses), mild anxiety/restlessness (rare, higher doses), and rare glucose fluctuation. Two practical cautions: anxiety/restlessness is more likely with Semax than with Selank — because Semax is mildly stimulating (its nootropic/dopaminergic character), often related to too-high dosing — so for anxiety- or panic-prone patients Selank is the better choice; and glucose can move in either direction, so diabetics warrant monitoring. Contraindications/precautions: avoid in

pregnancy/lactation (insufficient data); use caution in anxiety/panic disorders (start low, or use Selank); monitor glucose in diabetes; and use caution with hepatic/renal impairment (altered peptide metabolism). The hard limits remain limited long-term safety data and no GLP toxicology in English.

8. What is the appropriate practitioner posture toward Semax?

Answer: Measured optimism with a few specific disciplines. 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 (tPA, thrombectomy, intraocular-pressure control, rehabilitation), never a replacement. 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-versus-milligram dosing; favor intermittent rather than daily nootropic use; be cautious in anxiety-prone and diabetic patients (and prefer Selank where anxiety dominates); 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.