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NARRATIVE REVIEW

Preclinical and Clinical Evidence for Semax

OC Wellness Clinical Education

OC Wellness, Newport Beach, California

ARTICLE TYPE	SOURCES	HUMAN STUDIES	U.S. STATUS
Narrative review	55 · PMID linked	13 reports (N = 847 where stated)	Not FDA approved

ABSTRACT

Background. Semax (Met Glu His Phe Pro Gly Pro) is a synthetic heptapeptide built from the ACTH(4 to 7) sequence and a C terminal Pro Gly Pro tripeptide. It is registered in Russia as nasal drops, is not approved in the United States, and since 30 October 2026 may be compounded in the United States as semax free base for intranasal use under a temporary federal enforcement discretion policy.

Methods. Narrative review. Europe PMC was searched from inception to 3 November 2026 with seven queries, yielding 327 unique records; ClinicalTrials.gov and public regulatory documents from the FDA, HHS and the World Anti Doping Agency were also reviewed. For publications in Russian, only the English abstract was used.

Results. Preclinical work, conducted largely by the developing institutions, showed that intranasal semax increased hippocampal BDNF protein and TrkB phosphorylation in rats, bound specific sites in rat basal forebrain, reduced infarct size in a rat cortical ischemia model, and shifted ischemic gene expression toward lower inflammatory transcription. Thirteen indexed human reports were identified, with 847 participants where numbers were stated. Most were open label or nonrandomized Russian studies in ischemic stroke, cerebrovascular insufficiency and optic nerve disease; two placebo controlled imaging studies in healthy volunteers measured network connectivity only. No human pharmacokinetic study, formal toxicology program or randomized blinded efficacy trial with a clinical primary endpoint was found. FDA reviewers judged effectiveness evidence insufficient and raised concerns about anticoagulant activity, potentiation of amphetamine induced dopamine release in rodents and immunogenicity.

Conclusions. The mechanistic rationale for semax is coherent in rodents, but human evidence remains preliminary and geographically concentrated. Use outside Russia rests on low certainty evidence, and the federal policy covers only intranasal semax free base.

Keywords: semax; ACTH(4 to 10) analogue; brain derived neurotrophic factor; ischemic stroke; intranasal peptide; compounding

1 Introduction

Semax was developed by researchers of the Russian Academy of Sciences, whose 1997 review described 15 years of work on its design and study, as a stabilized analogue of ACTH(4 to 10), a fragment of adrenocorticotropic hormone that retains the neurobehavioral activity of the parent hormone without its corticotropic and melanotropic effects.[12] The three C terminal residues of ACTH(4 to 10) are replaced in semax by Pro Gly Pro,[1] and in rat serum semax proved more resistant than the native fragment to the other enzymes that took part in their degradation.[3] The developing group described semax as one of the few regulatory peptide analogues to have passed from basic research into clinical use, and it is now registered in Russia as 0.1% and 1% nasal drops.[21]

In the United States, semax is marketed by wellness clinics and online vendors for indications ranging from anxiety and attention to stroke, optic atrophy and neurodegenerative disease, often as an injection and sometimes combined with selank.[1] The FDA reviewed it for the 503A bulks list in July 2026, and on 30 October 2026 HHS adopted an enforcement discretion policy that permits compounding of semax free base for intranasal use only.[145] Clinicians are therefore being asked about a peptide whose evidence base is extensive, mostly Russian in origin, and difficult to appraise from outside that literature.

This review summarizes the preclinical and clinical evidence for semax as published through 3 November 2026, describes what is known about its pharmacokinetics and safety, sets out its regulatory status in the United States and under the World Anti Doping Agency (WADA) Prohibited List, and identifies the gaps that limit clinical inference. Selank (Thr Lys Pro Arg Pro Gly Pro) and N acetylated semax derivatives are distinct molecules and

are excluded; acetylation of the semax N terminus alone altered its copper coordination and abolished its protection against copper toxicity in neuroblastoma cells.[67]

2 Methods

This is a narrative review. Europe PMC, which indexes all MEDLINE records with their PubMed identifiers, was searched through its REST interface on 3 November 2026 (Pacific time) from database inception, restricted to MEDLINE sourced records. Seven queries were run: semax in title or abstract (199 records); semax or its sequence or the synonym ACTH(4 to 7)PGP in any field (320); semax with patients, humans, volunteers, stroke or clinical (154); synonyms for ACTH(4 to 10) analogues (41); semax with melanocortin receptor terms (20); semax with safety, adverse, toxicity or tolerability (67); and semax with pediatric, attention or mood terms (76). The union comprised 327 unique records, most of them unrelated full text matches, which were screened by title and, where relevant, abstract. ClinicalTrials.gov was searched for the term semax on the same date and returned no registered studies.[8]

Primary reports of semax (Met Glu His Phe Pro Gly Pro) in humans, animals or cells were eligible, together with reviews used for context. Reports concerning selank, N acetyl semax, semax amidate or other ACTH derived peptides were excluded unless they included a semax arm. Records without an abstract were not used for findings unless the FDA had summarized them, in which case the FDA summary is cited. For publications in Russian, only the English abstract indexed in PubMed was used, and no statement goes beyond it. Regulatory information was obtained directly from the FDA briefing document and meeting page for the July 2026 Pharmacy Compounding Advisory Committee, the FDA Category 2 page, the HHS policy and its Appendix B, and the WADA 2026 Prohibited List.[19104511] Fifty five sources are cited. No formal risk of bias assessment or quantitative synthesis was performed, and study quality is described qualitatively from the information available in each abstract, which is a limitation of this review.

3 Structure, origin and pharmacology

Semax free base has the molecular formula C37H51N9O10S and a molecular weight of 813.93 g/mol; the acetate salt (C39H55N9O12S, 874.0 g/mol) shares the same active moiety.[1] Semax is a common name and not a United States Adopted Name, and the FDA noted that naming conventions for semax related substances do not follow established standards such as INN, IUPAC or USAN; in both withdrawn nominations the certificate of analysis was titled for semax acetate while the CAS number, molecular formula and chemical name matched the free base.[1] None of the clinical reports reviewed by the FDA specified whether the free base or a salt was administered.[1]

No receptor for semax has been identified. Tritium labelled semax bound rat basal forebrain membranes in a time dependent, specific, reversible and calcium dependent manner, with a dissociation constant of 2.4 nM and a maximal binding capacity of 33.5 fmol/mg protein.[12] In vitro, semax inhibited enkephalin degrading enzymes of human serum with a half maximal inhibitory concentration of 10 µM.[6] Its most consistently reported action is induction of neurotrophins. In glial cultures from newborn rat basal forebrain, BDNF mRNA rose eightfold and NGF mRNA fivefold 30 minutes after exposure.[13] A single intranasal dose of 50 µg/kg in rats produced a maximal 1.4 fold increase in hippocampal BDNF protein, a 1.6 fold increase in TrkB tyrosine phosphorylation, and threefold and twofold increases in exon III BDNF and TrkB mRNA, accompanied by more conditioned avoidance reactions.[14] The time course is region specific: hippocampal and retinal BDNF and NGF expression fell 20 minutes after dosing while frontal cortex expression rose, and retinal BDNF expression was increased at 90 minutes.[15]

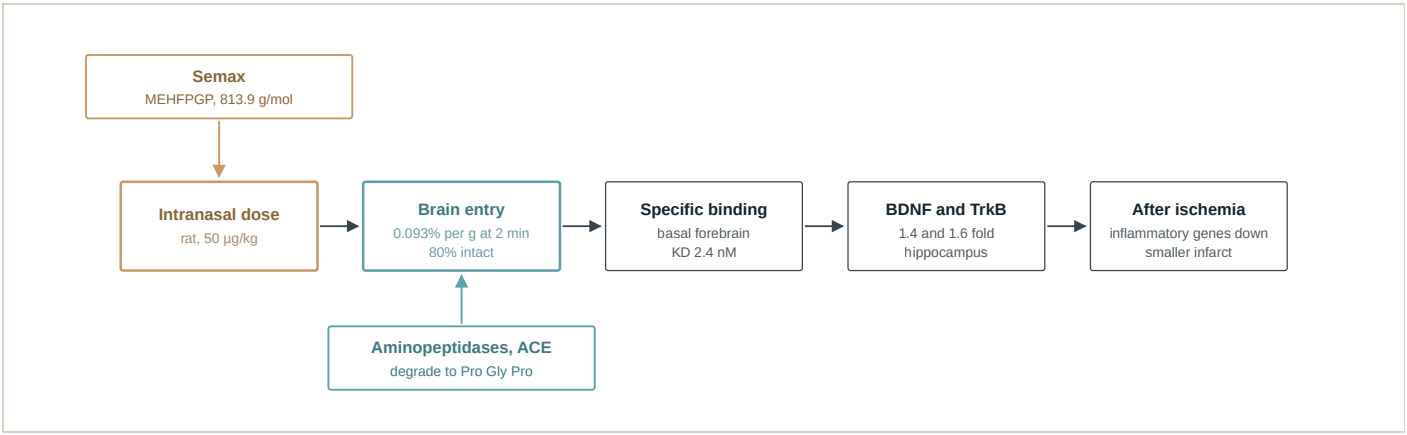


Figure 1. Proposed mechanism of semax, assembled from rat and cell studies. Values are from single studies in rats.[161214171819] No step has been measured directly in humans; plasma BDNF has been reported in stroke patients only as an indirect marker. ACE, angiotensin converting enzyme; KD, dissociation constant.

Semax also acts on monoaminergic transmission. In rodents, 0.15 mg/kg intraperitoneally raised striatal tissue 5 hydroxyindoleacetic acid by 25 percent and extracellular 5 hydroxyindoleacetic acid to 180 percent of baseline over 1 to 4 hours without changing dopamine, yet semax given 20 minutes before D amphetamine markedly enhanced amphetamine induced striatal dopamine release and locomotion.[20] In rats, intranasal semax under acute and chronic immobilization stress

stimulated anticoagulant, fibrinolytic and antiplatelet activity.[21] The FDA characterized semax as a pleiotropic substance acting through poorly understood mechanisms, with neuroprotective, neurotrophic, anticoagulant, analgesic and antidepressant like effects in rodents.[1]

4 Preclinical evidence

4.1 Cerebral ischemia

Cerebral ischemia is the most extensively studied indication. In rats with photothrombotic infarction of the prefrontal cortex, intranasal semax for 6 days reduced infarct volume and improved retention of a passive avoidance response; the FDA review described the infarcts as approximately 20 percent smaller with 250 µg/kg intranasally.[181] In incomplete global ischemia, semax prevented the rise in cortical nitric oxide and restored neurological function, whereas glycine did not.[22] In the same model, semax reduced histological ischemic damage and increased proliferation of neuroglia, endothelium and subventricular progenitor cells.[23]

Transcriptomic work from a single research group has characterized the response in detail. After permanent middle cerebral artery occlusion (pMCAO) in rats, semax increased transcription of Bdnf, TrkC and TrkA at 3 hours and of Nt 3 and Ngf at 24 hours, effects the authors described as selective for ischemic cortex.[24] Genome wide analysis after pMCAO found that immune response genes made up more than half of the genes whose expression semax altered at 24 hours, and that 24 vascular system genes at 3 hours and 12 at 24 hours were affected.[2526] After transient occlusion (tMCAO), RNA sequencing identified 394 differentially expressed genes at 24 hours in semax treated relative to saline treated rats, with suppression of inflammatory and activation of neurotransmission related transcripts.[17] Quantitative PCR confirmed reductions in Il1a, Il1b, Il6, Ccl3 and Cxcl2 mRNA, and protein studies showed increased active CREB with reduced MMP 9, c Fos and active JNK.[2728]

4.2 Other models

In rats with MPTP lesions of the dopaminergic system, daily intranasal semax at 0.2 mg/kg reduced behavioral disturbances,[29] although in the 6 hydroxydopamine model it did not affect motor activity or passive defensive behavior.[30] In male rats exposed to chronic unpredictable stress, daily intraperitoneal semax at 60 nmol/kg reversed or attenuated anhedonia, adrenal hypertrophy and the fall in hippocampal BDNF, with no effect in the forced swim test.[31] In female mice with spinal cord contusion, semax improved functional recovery and inhibited pyroptosis.[32] Analgesic effects depended on route: intraperitoneal semax reduced pain sensitivity in rats, whereas intranasal doses that improved learning did not.[33] In culture, semax increased survival of rat basal forebrain cholinergic neurons approximately 1.5 to 1.7 fold and improved survival of cerebellar granule cells exposed to glutamate by an average of 30 percent.[3435]

Table 1. Selected preclinical studies of semax.

STUDY	SPECIES AND MODEL	DOSE AND ROUTE	PRINCIPAL FINDING
Shadrina 2001[13]	Rat basal forebrain glial cultures	In vitro	BDNF mRNA 8 fold, NGF mRNA 5 fold at 30 min
Dolotov 2006a[12]	Rat, basal forebrain	50 and 250 µg/kg IN; membrane binding	KD 2.4 nM; BDNF increased at 3 h in basal forebrain, not cerebellum
Dolotov 2006b[14]	Rat, hippocampus	50 µg/kg IN, single	BDNF protein 1.4 fold; TrkB phosphorylation 1.6 fold; more avoidance reactions
Romanova 2006[18]	Rat, photothrombotic cortical infarct	IN for 6 days	Smaller infarct; passive avoidance retained
Bashkatova 2001[22]	Rat, incomplete global ischemia	Not stated in abstract	Prevented cortical NO rise; neurological function restored
Dmitrieva 2010[24]	Rat, pMCAO	Not stated in abstract	Bdnf, TrkC, TrkA up at 3 h; Nt 3, Ngf up at 24 h
Medvedeva 2014[25]	Rat, pMCAO	Not stated in abstract	Immune genes over 50% of altered genes at 24 h
Filippenkov 2020[17]	Rat, tMCAO	Not stated in abstract	394 DEGs at 24 h; inflammatory genes down
Eremin 2005[20]	Rodents, striatum	0.15 mg/kg IP	Extracellular 5 HIAA to 180%; amphetamine effects enhanced
Grigorjeva 2010[21]	Rat, immobilization stress	Repeated IN	Anticoagulant and antiplatelet activity stimulated
Levitskaya 2004[29]	Rat, MPTP lesion	0.2 mg/kg IN daily	Fewer behavioral disturbances
Slominsky 2017[30]	Rat, 6 OHDA lesion	Not stated in abstract	No effect on motor activity
Inozemtseva 2024[31]	Male rat, chronic unpredictable stress	60 nmol/kg IP daily	Anhedonia and hippocampal BDNF loss reversed or attenuated
Liu 2025[32]	Female mouse, spinal cord injury	Not stated in abstract	Better functional recovery; less pyroptosis

5 HIAA, 5 hydroxyindoleacetic acid; 6 OHDA, 6 hydroxydopamine; DEG, differentially expressed gene; IN, intranasal; IP, intraperitoneal; KD, dissociation constant; MPTP, 1 methyl 4 phenyl 1,2,3,6 tetrahydropyridine; NO, nitric oxide; pMCAO and tMCAO, permanent and transient middle cerebral artery occlusion.

Nearly all of these studies came from a small network of Russian institutes connected with the peptide's development. The FDA noted that ischemia studies were generally restricted to 100 µg/kg intraperitoneally or 250 µg/kg intranasally, that dose response relationships had not been established for any route, and that systemic exposure was not measured.[1]

5 Clinical evidence in humans

Because semax is synthetic, there are no observational studies of endogenous levels. All human data come from interventional reports, summarized in Table 2. The full texts of most are in Russian, and several PubMed records carry publication type tags that do not match the design described in the abstract; the motor neuron disease study, for example, is indexed as a randomized controlled trial but its abstract describes an open label trial in sequential groups.[36]

5.1 Cerebrovascular disease

In acute hemispheric ischemic stroke, 30 patients received semax in addition to intensive therapy and were compared with 80 patients of similar severity on conventional therapy. The authors reported some influence on the rate of recovery of general cerebral, focal and especially motor deficits, and identified 12 mg daily for moderate and 18 mg daily for severe stroke, over 5 and 10 days, as the most effective doses.[37] A retrospective immunobiochemical analysis from the same group reported a shift toward antiinflammatory mediators.[38] In 187 patients with cerebrovascular insufficiency, semax was reported to produce significant clinical improvement and a reduced risk of stroke and transient ischemic attack, with a minor percentage of side effects.[39] In 2018, 110 patients undergoing early or late rehabilitation after ischemic stroke were divided into subgroups with and without semax, given as two 10 day courses of 6,000 µg/day separated by 20 days; semax was associated with higher plasma BDNF throughout the study period and with faster improvement in the Barthel index.[40] None of these abstracts describes randomization, allocation concealment or blinding. FDA reviewers did not consider these Russian language reports because no English translations were available, and found the only English language evidence for cerebral ischemia, a meeting abstract, insufficient.[1]

5.2 Other indications

In 73 patients with posthypoxic encephalopathy, semax was described as effective for mnestic disorders, and some patients showed paroxysmal EEG activity after administration.[41] Ophthalmology groups reported improved visual acuity, visual fields and optic nerve electrophysiology when semax drops or endonasal electrophoresis were added to treatment of optic nerve disease, glaucomatous optic neuropathy and nonproliferative diabetic retinopathy.[42][43][44] In 27 patients with motor neuron disease, semax 12 mg daily intranasally did not

alter chronic partial denervation or clinical rating scales but improved quality of life scores, maximally on day 10.[36] In refractory peptic ulcer, healing by day 14 was observed in 89.5 percent of patients receiving intranasal semax with standard therapy and 30.8 percent of controls.[45] In 118 patients with psoriasis and metabolic syndrome, adding intranasal 0.1% semax was associated with lower total cholesterol, triglycerides and LDL cholesterol and higher HDL cholesterol; the abstract states the dose as 600 mg/day, which cannot be reconciled with a 0.1% solution and should be treated as unverified.[46]

Two placebo controlled imaging studies were conducted in healthy volunteers. In 24 adults, intranasal 1% semax (14 participants) produced a larger rostral default mode network component on resting state functional MRI 5 and 20 minutes after dosing than placebo (10 participants).[47] In 52 adults given semax, selank or placebo, both peptides altered connectivity between the right amygdala and right temporal cortex.[48] The FDA noted that the semax groups in these two studies may have overlapped.[1] Neither study measured cognition.

5.3 Reports known only through secondary sources

The FDA briefing document summarized several reports without usable PubMed abstracts. In an uncontrolled study of single intranasal doses of 0.5 mg/kg, headache resolved in 4 of 12 patients with migraine and pain characteristics did not change in 16 patients with typical trigeminal neuralgia.[1] The FDA also listed a study in 19 healthy men and meeting abstracts describing 120 adolescents with depression and 331 children with tics or Tourette syndrome treated with semax alongside other therapies.[1] A 2026 Russian expert council on adjunctive treatment of pediatric attention deficit hyperactivity disorder placed semax in its group with a limited evidence base.[49]

Table 2. Human interventional studies of semax indexed in PubMed, as described in their English abstracts.

STUDY	DESIGN	N	POPULATION	DOSE AND DURATION	PRINCIPAL FINDING
Gusev 1997[37]	Controlled; allocation not described	110 (30 semax)	Acute hemispheric ischemic stroke	12 or 18 mg/day, 5 or 10 days; route not stated	Some faster recovery, especially motor
Miasoedova 1999[38]	Retrospective comparison	Not stated	Acute ischemic stroke	Not stated	Shift toward antiinflammatory mediators
Gusev 2005[39]	Comparative; allocation not stated	187	Cerebrovascular insufficiency	Not stated	Clinical improvement; fewer strokes and TIAs; well tolerated
Gusev 2018[40]	Subgroups with and without semax	110	Rehabilitation after ischemic stroke	6,000 µg/day, two 10 day courses	Higher plasma BDNF; faster Barthel gains
Alekseeva 1999[41]	Comparative	73	Posthypoxic encephalopathy	Not stated	Benefit in mnestic disorders; paroxysmal EEG activity in some
Polunin 2000[42]	Three groups including control	Not stated	Optic nerve disease	Nasal drops or endonasal electrophoresis	Better acuity, fields, color vision
Kurysheva 2001[43]	Comparative	Not stated	Glaucomatous optic neuropathy	Not stated	Advantage over traditional neuroprotective therapy
Ivanikov 2002[45]	Controlled, add on	32 (per FDA)	Refractory peptic ulcer	1%, 2 to 4 drops IN three times daily, 10 days	Healing at day 14: 89.5% vs 30.8%
Serdiuk 2007[36]	Open label, sequential groups	27	Motor neuron disease	12 mg/day IN, two 10 day courses	No effect on denervation or clinical scales; better quality of life
Nazarova 2013[44]	Three groups including control	114	Nonproliferative diabetic retinopathy	0.1% by electrophoresis or IN drops	Improved visual and electrophysiological measures
Dontsova 2015[46]	Two group comparison	118	Psoriasis with metabolic syndrome	0.1% IN, 10 days; dose as stated "600 mg/day"	Lipid profile improved vs standard care
Lebedeva 2018[47]	Placebo controlled	24	Healthy adults	1% IN, single dose	Larger rostral default mode network component
Panikratova 2020[48]	Placebo controlled, three arm	52	Healthy adults	Single dose	Altered amygdala and temporal connectivity

Totals include control participants. IN, intranasal; TIA, transient ischemic attack. All abstracts except Ivanikov 2002, Lebedeva 2018 and Panikratova 2020 accompany Russian language full texts.

6 Pharmacokinetics, formulation and doses studied

The FDA found no pharmacokinetic study of semax in humans by any route and no study of subcutaneous administration in any species.[1] Animal data are limited to tracer studies in rats. After

intravenous injection of tritiated semax, labelled peptide was detected in brain extracts at no more than 0.01 percent of the injected dose.[50] After intranasal administration of 50 µg/kg, 0.093 percent of total radioactivity per gram was found in brain at 2 minutes, of which 80 percent was intact semax; degradation was rapid, and Pro Gly Pro predominated among metabolites.[16] In rat serum, aminopeptidases and angiotensin converting enzyme accounted for most hydrolysis, with bestatin inhibiting up to 66 percent and lisinopril about 15 percent of total activity.[19] Because Pro Gly Pro has its own transcriptional and anticoagulant activity in rats, effects observed after dosing may reflect metabolites as well as the parent peptide.[241]

The registered Russian products are 0.1% and 1% nasal drops; the withdrawn U.S. nominations proposed an intranasal spray or subcutaneous injection at 7,500 or 1,000 µg/mL.[1] Human doses reported in abstracts include 12 to 18 mg daily in acute stroke, 6,000 µg daily in two 10 day courses during rehabilitation, 12 mg daily intranasally in motor neuron disease, and 2 to 4 drops of a 1% solution three times daily for 10 days in peptic ulcer.[37403645] The FDA additionally recorded single doses of 0.5 mg/kg and 0.25 mg, and 1 mg daily for 2 days.[1] No dose has been established for any indication outside Russia, and none is recommended here.

7 Safety and tolerability

Human safety data are sparse. The 2005 study in cerebrovascular insufficiency reported a minor percentage of side effects and good tolerability in older patients,[39] and the developers wrote in 1997 that no negative side effects or complications had been associated with administration.[2] A 2022 narrative overview by Russian authors described semax as having low toxicity and as causing no dependence or withdrawal syndrome.[51] Against this, the FDA identified exposure in 33 to 47 healthy adults, 69 adults with medical conditions and 451 children, with adverse events reported as absent in one study and not discussed in the others. FAERS contained one report, of ocular pain and burning with hospitalization after use of semax 0.1% nasal drops bought online, unresolved a year later.[1] HHS, by contrast, characterized the intranasal human record as several hundred subjects with no reported adverse outcome.[5] The paroxysmal EEG activity described after semax in posthypoxic encephalopathy led the authors to recommend EEG monitoring at first administration in that population.[41]

The FDA found no acute toxicity, repeat dose toxicity, genotoxicity or developmental and reproductive toxicity studies, and judged the only long term tumor study, in tumor bearing female SHK mice treated for less than 3 months, inadequate to assess carcinogenic potential.[1] Its specific concerns were bleeding risk, given anticoagulant and antiplatelet effects in rats, particularly with concomitant antithrombotic drugs;[121] unknown abuse potential, given potentiation of amphetamine induced striatal dopamine release;[201] and immunogenicity related to aggregates and peptide impurities, for which no data exist.[1] Product quality outside regulated supply is an additional risk, since forensic analysis of seized preparations identified semax and selank, and such peptides are sold online as lyophilized powder for injection and as nasal sprays.[52]

8 Regulatory and anti doping status

Semax is not approved by the FDA for any indication, has no USP or National Formulary monograph and is not a component of any FDA approved drug.[1] It has no monograph in the European, Japanese or International Pharmacopoeias; the FDA briefing document states that "Semax is a registered drug in Russia and is available as 0.1% and 1% nasal drops."[1] Semax was placed in Category 2 of the FDA interim list of bulk substances that may present significant safety risks on 29 September 2023 and was withdrawn from that category on 22 April 2026.[510] On 24 July 2026 the Pharmacy Compounding Advisory Committee considered semax free base and semax acetate for cerebral ischemia, migraine and trigeminal neuralgia and voted 8 to 5 in favor of inclusion on the 503A bulks list, although FDA staff had recommended against both forms on grounds of inadequate characterization, insufficient evidence of effectiveness and unresolved safety concerns.[91] The vote is advisory, and neither form is on the final list.

The HHS enforcement discretion policy published on 30 October 2026 applies to semax free base for intranasal use only; semax acetate is not named, and injectable forms are not covered.[5] Conditions include a patient specific prescription under section 503A, a single active ingredient, bulk substance from an FDA registered manufacturer with a valid certificate of analysis, the label statement "This is a compounded drug product. Not for resale.", and reporting of serious adverse events and quality problems to MedWatch and the state.[4] The policy is temporary, does not extend to 503B outsourcing facilities, and states that compounded drugs are not FDA approved.[4] HHS justified its departure from FDA staff advice on the grounds that certificates of analysis now address the testing gaps CDER identified, that historical use is documented, and that CDER's safety concerns were mechanistic.[5]

Semax is not named on the WADA 2026 Prohibited List. Section S0 prohibits pharmacological substances not addressed elsewhere on the List and with no current approval by any governmental regulatory health authority for human therapeutic use, a criterion that registration in Russia may not meet. The introductory sentence of section S2 extends the class to substances with similar chemical structure or similar biological effects, and S2.2.2 lists corticotrophins and their releasing factors, with tetracosactide as an example.[111] A 2025 review of brain doping substances classified semax as of unclear status and presumed to meet WADA criteria by similarity to tetracosactide under S2.[53] Athletes subject to testing should obtain a ruling from their anti doping organization.

9 Discussion

The preclinical case for semax is internally consistent. Neurotrophin induction, specific binding in rat forebrain and attenuation of inflammatory transcription after experimental ischemia have been reported repeatedly, and functional outcomes in rodent stroke models point in the same direction.[14121718] Independent replication is lacking, however. Most of the cited animal work came from institutes associated with the peptide's development, few studies tested more than one dose, and none measured brain or plasma exposure alongside effect.[1] Groups outside that network have so far contributed chiefly metal binding chemistry and spinal cord injury models in mice and rats.[543255]

The clinical evidence is weaker still. Thirteen indexed reports describe about 850 participants where numbers are given, but the largest stroke studies did not report randomization or blinding, outcome scales and effect sizes cannot be extracted from the abstracts, and the full texts are in Russian. The only placebo controlled studies measured imaging connectivity in small groups of healthy volunteers.[4748] Plasma BDNF, the most frequently cited human mechanistic marker, is an indirect measure of central neurotrophin activity.[40] Where a randomized design was claimed in indexing, as in motor neuron disease, the abstract reported no effect on disease measures.[36] The FDA reached a comparable judgment on effectiveness for its three evaluated indications.[1]

Translation to current U.S. use raises separate problems. Clinical experience exists only for nasal drops and electrophoresis, whereas much U.S. marketing is for subcutaneous injection, for which there are no human or animal pharmacokinetic or safety data.[1] The salt form used in Russian studies is unspecified, and the federal policy covers only the free base.[15] Nasal delivery device performance, which determines dose, has not been characterized for compounded products.[1]

This review has limitations. It relied on a single bibliographic platform, used only English abstracts for Russian publications, included no formal risk of bias assessment, and was prepared by a single team with a stated competing interest. Records without abstracts were not assessed except through FDA summaries. Priorities for research include an independent randomized, blinded trial of intranasal semax with a clinically meaningful endpoint, human pharmacokinetic studies by the intranasal route, standard nonclinical toxicology, and evaluation of bleeding and abuse liability signals.

CLINICAL CONSIDERATIONS

- Human efficacy evidence consists of small, mostly open label Russian studies; benefit in healthy adults has not been tested.[1]
- Only intranasal semax free base falls within the HHS policy; injectable use has no human data.[51]
- Animal anticoagulant activity is relevant to patients with bleeding risk or on antithrombotic therapy.[21]
- Amphetamine potentiation in rodents and paroxysmal EEG activity in one patient series warrant caution with stimulants and seizure history.[2041]
- Findings for selank and N acetyl semax derivatives do not apply to semax.[7]

10 Conclusions

Semax is a registered nasal medicine in Russia with a coherent rodent mechanism centered on neurotrophin induction and modulation of the transcriptional response to ischemia. The human evidence consists of small, mostly open label or nonrandomized studies reported in Russian, with no human pharmacokinetic data, no formal toxicology program and no independent randomized trial with a clinical endpoint.

For U.S. clinicians, the certainty of benefit for any indication is low, the safety profile is incompletely characterized, and the federal enforcement discretion policy extends only to intranasal semax free base prepared under specified conditions. Its anti doping status is unresolved.

DECLARATIONS

Purpose. Internal evidence review prepared for clinicians at OC Wellness. It has not been externally peer reviewed.

Funding. None.

Competing interests. OC Wellness provides clinical services that may include prescribing compounded preparations of the peptide reviewed.

Data availability. All sources are listed in the references.

Use of sources. Findings are reported as stated in the cited abstracts or full texts. For Russian language publications, only the English abstract indexed in PubMed was used.

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ABOUT THIS REVIEW

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