FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

July 23 - 24, 2026

The attached package contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Semax – Related Bulk Drug Substances (Semax (free base) and Semax acetate)

Table of Contents

FDA Evaluation of Semax–Related Bulk Drug Substances (Semax (free base) and Semax acetate)

DATE: 5/11/2026

FROM: Jamiele Mattocks, PharmD, BCACP
Consumer Safety Officer (CSO), Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

Tracy Rupp, PharmD, MPH, BCPS
Lead Consumer Safety Officer, OCQC, OC

Jing Li, PhD
Office of Product Quality Assessment II (OPQAII), Office of Pharmaceutical Quality (OPQ)

Edna Albuquerque, PhD
Senior Pharmacology/Toxicology Reviewer, Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM), Office of New Drugs (OND)

Andrea Benedict, PhD
Nonclinical Supervisor, DPT-RPURM/SM, OND

Marianne San Antonio, DO
Physician, Pharmacy Compounding Review Team (PCRT), Office of Specialty Medicine (OSM), OND

Suhail Kasim, M.D. MPH
Lead Physician, PCRT, OSM, OND

THROUGH: Russell Wesdyk, B.S., MBA
ADRA, OPQA2, OPQ

Alex Gorovets, M.D.
Deputy Director, OSM, OND

Matt Lash, JD
Acting Director, OCQC, OC
Deputy Director, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Semax-related Bulk Drug Substances for Inclusion on the 503A Bulk Drug Substances List

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

List of Abbreviations

Abbreviation	Term
AE	adverse event
ACTH	adrenocorticotropic hormone
ADHD	attention deficit hyperactivity disorder
ALS	amyotrophic lateral sclerosis
API	active pharmaceutical ingredient
BDS	bulk drug substance
BET	bacterial endotoxins test
CAS	Chemical Abstracts Service
CoA	Certificate of Analysis
CQA	critical quality attributes
FAERS	FDA Adverse Event Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
IN	intranasal
INN	International Nonproprietary Names
IUPAC	International Union of Pure and Applied Chemistry
IP	intraperitoneal
IV	intravenous
MF	Molecular formula
MW	Molecular weight
MPST	modified pain sensitivity test
NF	National Formulary
OTC	over-the-counter
REG	rhoencephalogram
ROA	route of administration
SC	subcutaneous
TSEP	trigeminal somatosensory evoked potentials
UNII	Unique Ingredient Identifier
USAN	United States Adopted Name
USP	United States Pharmacopeia

I. INTRODUCTION

The Food and Drug Administration (FDA, the Agency, or we) received nominations for semax-related bulk drug substances for inclusion on the list of bulk drug substances (BDS) that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] The nominators provided inconsistent information in the nomination packages regarding the specific BDS proposed. Specifically, it is unclear in both packages whether the nomination was for semax acetate or semax (free base). Semax acetate and semax (free base) are different active pharmaceutical ingredients and hence are considered different BDSs. Please see additional information in section II.A. The nominations were withdrawn[2] and FDA is evaluating the substances at its discretion.

Although it is unclear whether the nominators intended to nominate semax acetate or semax (free base), FDA has decided to evaluate both on its own initiative.

Semax acetate and semax (free base) were evaluated for the following use(s): cerebral ischemia, migraine and trigeminal neuralgia[3,4]. The semax-related drug products proposed in the nominations are intranasal spray or subcutaneous injection in 7,500 µg/mL or 1,000 µg/mL dosage strengths.

---

[1] The nomination from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0284) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0284. The nomination from LDT Health Solutions (Document ID: FDA-2018-N-2973-0002 attachment 1) can be accessed at: https://www.regulations.gov/document/FDA-2018-N-2973-0002. These nominations were withdrawn, but because FDA is evaluating semax acetate and semax (free base) on its own initiative, FDA considered information submitted in these nominations as part of this evaluation.

[2] Document IDs: FDA-2015-N-3534-0484 and FDA-2015-N-3534-0485.

[3] Semax-related BDSs were nominated for "analgesia", but because the reference submitted by the nominator that discussed analgesia was in subjects with migraine and trigeminal neuralgia, we evaluated the Semax-related BDSs for these uses. Semax was also nominated for "ADHD" and "nootropic". ADHD was not evaluated because supporting literature for this use was not found. "Nootropic" does not have an ICD-10 code and no professional society treatment guidelines could be found for this use. Dorland Medical Dictionary 29th Edition defines it as "having positive effects on organically impaired cognition or nervous system function." Therefore, this use will be considered as part of the evaluation for cerebral ischemia.

[4] We have explained that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance, though we acknowledge that inclusion of a substance on the 503A Bulks List may not be limited to a specific use. See 84 FR 4696, 4701.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for semax (free base) or semax acetate, and neither is a component of an FDA-approved drug.

We have evaluated publicly available data on the physicochemical characteristics, historical use, effectiveness, and safety in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing both semax (free base) and semax acetate on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

II. EVALUATION CRITERIA

A. Is the Substance Well-Characterized, Physically and Chemically?[5]

Semax is a common name and not a United States Adopted Name (USAN)[6]. FDA has encountered multiple salts, and derivatives, including different active moieties, sold commercially under the same common name for similarly situated products. Inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN[7], IUPAC[8], USAN) represent a safety risk for patients as they may be dosed with a different BDS than the physician ordered. From a chemical analysis standpoint, inconsistent naming conventions for semax-related BDSs also introduce risks because of the inability to determine which BDS a particular reference standard is referencing.

[5] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid Certificate of Analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

[6] United States Adopted Name (USAN) is a unique, nonproprietary name for a drug sold in the United States. The USAN Council, which is sponsored by several organizations, assigns USANs.

[7] International Nonproprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

[8] The International Union of Pure and Applied Chemistry (IUPAC) is an international federation of National Adhering Organizations working for the advancement of the chemical sciences, especially by developing nomenclature and terminology.

A BDS or active pharmaceutical ingredient (API)[9] used in a drug product may be a free base (i.e., the native molecule) or a salt or an ester of the free base, all of which share the same active moiety.[10] Different active moieties are not interchangeable because they can have different safety and efficacy profiles. A free base or the various salts or ester forms of an active moiety are distinct APIs, each with a different chemical structure and unique physical/chemical, or pharmacokinetic/pharmacodynamic characteristics. As a result, each may offer distinct properties (e.g., different solubilities, permeability, melting points, stability, or flow characteristics) and may also have different safety and/or efficacy profiles. All distinct active moieties, as well as free bases, salts, or esters of any given active moiety, are distinct BDSs for these reasons.

This evaluation pertains to semax acetate and semax (free base).

Table 1 below summarizes available identifying information obtained from public domain for each BDS.

[9] The terms BDS and API are used interchangeably in the compounding context. See 21 CFR 207.3 ("Bulk drug substance, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."). An API is defined in FDA regulations at 21 CFR 207.1, which states "Active pharmaceutical ingredient means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."

[10] "Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."21 CFR 314.3.

Table 1. Summary of Basic Information on Semax (Free Base) and Semax Acetate.

Characteristic	Semax (Free Base)	Semax Acetate
UNII[11] Code	I5FAL2585H	Not available
CAS No.*	80714-61-0	2828433-33-4 or use the CAS number same as free base
MF/MW (g/mol)	$C_{37}H_{51}N_9O_{10}S$/813.93	$C_{39}H_{55}N_9O_{12}S$/874.0
Peptide sequence	H-Met-Glu-His-Phe-Pro-Gly-Pro-OH	H-Met-Glu-His-Phe-Pro-Gly-Pro-OH.CH_3CO_2H
Supplier[12]	Yes	Yes
Active moiety	Semax (free base)	Semax (free base)

* CAS: Chemical Abstracts Service; MF/MW: molecular formula/molecular weight; UNII: Unique Ingredient Identifier

Two nominations were submitted, which, as discussed above, were later withdrawn. They provided inconsistent information about the different semax-related BDSs in their nominations. Due to inconsistencies in the nomination packages, the nominated BDS is unclear from both nominators of semax-related BDSs. For example, the Certificate of Analysis (CoA) submitted with the nomination refers to one BDS by name in the title and a different BDS by the CAS number and molecular formula. All chemistry-related information about the BDSs provided by both nominators is summarized in Table 2.

Table 2. Summary of Information Submitted in Two Withdrawn Nominations.

Nominator	**1**	**2**
Nominated BDS	Semax	Semax
BDS per UNII code	I5FAL2585H *(matches semax free base)*	I5FAL2585H *(matches semax free base)*
CoA	CoA provided for Semax Acetate	CoA provided for Semax Acetate
CAS No.	80714-61-0 *(matches semax free base)*	80714-61-0 *(matches semax free base)*
MF	$C_{37}H_{51}N_9O_{10}S$ *(provided in the nomination and CoA, matches semax free base)*	$C_{37}H_{51}N_9O_{10}S$ *(provided in the CoA, matches semax free base)*
MW	813.93 *(provided in the CoA, matches semax free base)*	813.93 *(provided in the CoA, matches semax free base)*
Chemical name	H-Met-Glu-His-Phe-Pro-Gly-Pro-OH *(provided in the CoA, matches semax free base)*	H-Met-Glu-His-Phe-Pro-Gly-Pro-OH *(provided in the CoA, matches semax free base)*

Italics in the table above represents the information identified by FDA.

[11] The Unique Ingredient Identifier (UNII) is an alphanumeric identifier linked to a substance's molecular structure or descriptive information and is generated by the Global Substance Registration System (GSRS) of the Food and Drug Administration (FDA).

[12] The existence of a supplier of BDS may be relevant to FDA's characterization analysis because it indicates that consistent production of the BDS according to a standard may be possible. BDSs with suppliers are also frequently accompanied by COAs associated with their production, which can help FDA to identify and characterize BDSs.

FDA chose to concurrently evaluate both BDSs (semax free base and semax acetate) in this section under two different sub-sections of this evaluation (II.A.1 and II.A.2) and will provide a separate conclusion for each of the two BDSs.

The nominators proposed to compound the BDSs into the following dosage forms:

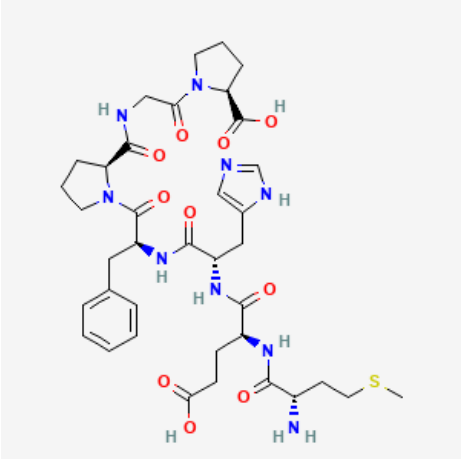
- Injection/subcutaneous injection
  - For an injection product, in general, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET), and foreign particulates are critical safety factors. For this reason, microbial bioburden load (i.e., microbial enumeration test) and BET are critical for the BDSs to be used in compounding injections. Evaluation of the solubility of the BDS is also critical to ensure that no BDS precipitates are formed in the compounded drug product.
- Nasal spray solution
  - The container closer system including container, closer, and pump are considered critical components of metered-dose nasal spray solution products. The CQAs for nasal spray device include pump delivery, spray content uniformity, spray pattern and plume geometry, and droplet size distribution. However, there is a lack of information about what type of device (e.g., metered-dose nasal spray container closer system) would be used to deliver semax, nor any information for a control strategy to assure the product CQAs which are critical for the safety and effectiveness of the compounded product. Other CQAs for solution-based nasal spray products include microbial quality, foreign particulates, and leachables. As such, the microbial quality of the BDSs to be used in compounding the nasal spray solution formulation, and suitability/compatibility of the device components with the formulation are critical quality considerations. Evaluation of the solubility of the BDS is also considered to ensure complete dissolution upon formulation.

There is no USP drug substance monograph for semax (free base) or its acetate salt. We reviewed physical and chemical characterization-related information provided by the nominator and performed a literature search for additional information on semax (free base) and its acetate salt. Databases searched for information on semax (free base) and its acetate salt in preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. Semax (Free Base)

Semax (free base) is reported to be a heptapeptide and synthetic analogue of adrenocorticotropic hormone (ACTH) 4-10 fragment with the following amino acid sequence: Met-Glu-His-Phe-Pro-Gly-Pro (Deigin et al., 2022). The molecular formula of semax (free base) is $C_{37}H_{51}N_9O_{10}S$ and its molecular weight is 813.93 g/mol. Its chemical structure and peptide sequence are shown in Figure 1.

Figure 1. The Chemical Structure of Semax (Free Base).[13]



a. Stability of the Active Pharmaceutical Ingredient and Likely Dosage Forms

It is reported that lyophilized semax (free base) is stable for 4 years when stored at -20°C in a tightly closed container.[14] Upon reconstitution, keep solution at +4°C for up to 2-7 days.[15]

FDA notes that peptides can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Hence, peptides may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation, especially for semax (free base) with 7 amino acids. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

[13] Semax | C37H51N9O10S | CID 9811102 - PubChem (nih.gov). Accessed 12/12/24.
[14] https://cdn.caymanchem.com/cdn/insert/27719.pdf. Accessed 12/12/24.
[15] https://www.prospecbio.com/semax. Accessed 12/12/24.

b. Probable Routes of API Synthesis

Semax (free base) was reported to be synthesized via the steps described below by sequentially producing the compounds from I to VII to obtain the final substance, semax (free base) (Ponomareva-Stepnaya et al., 1984).

1. Boc-Pro-Gly-ProOBzl (I)
2. Boc-His-Phe-OBzl (II)
3. Boc-His-Phe (Ill)
4. Boc-His-Phe-Pro-Gly-Pro-OBzl (IV)
5. Boc-y-Bzl-Glu-His-Phe-Pro-Gly-Pro-OBzl (V)
6. Boc-Met-y-Bzl-Glu-His-Phe-Pro-Gly-Pro-OBzl (VI)
7. Boc-Met-Glu-His-Phe-Pro-Gly-Pro (VII)
8. H-Met-Glu-His-Phe-Pro-Gly-Pro (VIII)

However, we do not know what synthetic method was used to manufacture the nominated semax (free base).

c. Likely Impurities[16]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including semax (free base). For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may be derived from impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids) and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. Drug substance and its proposed product-related impurities may also include peptide-related aggregates, especially for a peptide like semax (free base) with 7 amino acids that may have an inherent tendency to aggregate.

There is no CoA for semax (free base) in the nomination. We conducted literature searches and found a CoA for semax (free base) that only contains ID, amino acid analysis, and purity testing results shown below as an example (Figure 2).[17] However, there is no information on the

---

[16] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section C.I. as part of the safety assessment of the substance.

[17] https://documents.tocris.com/pdfs/tocris_coa/7712_1_coa.pdf?1715792499. Accessed 12/12/24.

impurity limits/testing results as key attribute control in the CoA to demonstrate quality control of impurity profile of semax (free base).

Because there is lack of information regarding potential impurities that can be present in semax (free base) and the lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide related aggregates.

Figure 2. Example of a CoA for Semax.

TOCRIS
a biotechne brand

Print Date: Sep 13th 2022

Certificate of Analysis

www.tocris.com

Product Name: Semax **Catalog No.:** 7712 **Batch No.:** 1
CAS Number: 80714-61-0

1. PHYSICAL AND CHEMICAL PROPERTIES

Batch Molecular Formula:	$C_{37}H_{51}N_9O_{10}S$
Batch Molecular Weight:	813.93
Physical Appearance:	White lyophilised solid
Counter Ion:	TFA
Solubility:	Soluble to 2 mg/ml in water
Storage:	Store at -20°C

2. ANALYTICAL DATA

HPLC:	Shows 96.1% purity
Mass Spectrum:	Consistent with structure

3. AMINO ACID ANALYSIS DATA

Amino Acid	Theoretical	Actual	Amino Acid	Theoretical	Actual
Ala			Lys		
Arg			Met	1.00	0.97
Asx			Phe	1.00	1.01
Cys			Pro	2.00	2.05
Glx	1.00	1.00	Ser		
Gly	1.00	1.01	Thr		
His	1.00	0.97	Trp		
Ile			Tyr		
Leu			Val		

d. Physicochemical Characteristics Pertinent to Product Performance, Such as Particle Size and Polymorphism

Semax (free base) is white lyophilized powder. Based on reports in most publicly available literature semax (free base) is soluble in water up to 2 mg/mL[18] and approximately 10 mg/mL in phosphate-buffered saline.[19]

[18] https://documents.tocris.com/pdfs/tocris_coa/7712_1_coa.pdf?1715792499. Accessed 12/12/24.
[19] https://cdn.caymanchem.com/cdn/insert/27719.pdf. Accessed 12/12/24.

Because the BDS is soluble in water and would be solubilized prior to administration, particle size and polymorphism are not considered critical quality attributes that affect performance for the proposed injectable dosage forms with the concentration of 1,000 µg/mL.

However, due to lack of information on the formulation for the proposed dosage forms (injection and intranasal spray) with the concentration of 7,500 µg/mL, we cannot evaluate how the physicochemical characteristics of semax (free base) will impact the performance of the proposed final products (7,500 µg/mL).

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the API Is Poorly Characterized or Difficult to Characterize

Because there is lack of CoA for semax (free base), we do not know if microbial bioburden and/or bacterial endotoxin tests are in place to control the BDS proposed for compounding injectable dosage form. Endotoxin test is considered a critical quality control attribute for an injection product. However, endotoxin testing was not identified from publicly available scientific literature, either.

As mentioned at the beginning of Section IIA, for a metered dose nasal spray solution product, the information about the container closer system (including container, closer, and pump) is relevant to the CQAs (pump delivery, spray content uniformity, spray pattern and plume geometry, and droplet size distribution) for the proposed product and would affect how the BDS is delivered. However, no such information is available either in the nomination or the publicly available scientific literature.

Conclusions: Semax (free base) is reported to be a heptapeptide. As reported in the literature, semax (free base) is expected to be stable under reported storage conditions (below -20°C).

Semax (free base) is considered to be not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) BDS-specific quality control attributes, including impurities, aggregates, bacterial endotoxins, and microbial bioburden testing, were not found in the publicly available scientific literature and lack of CoA in the nomination which are offered as evidence to establishing identity, purity, and impurity profiles of the substance of semax (free base) delivered via the subcutaneous (SC) and intranasal spray routes of administration (ROAs). The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.D.2.d., FDA is concerned about the potential for immunogenicity of semax (free base) when formulated in an injectable or intranasal spray dosage forms due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the Section II.A.1.c. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

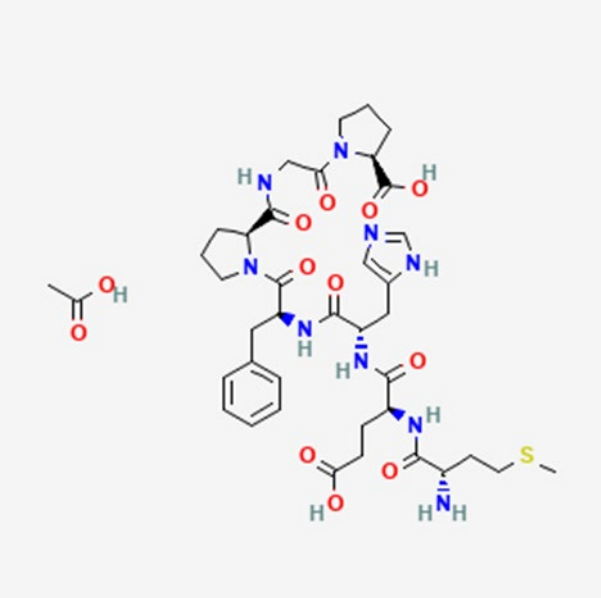
In addition, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about the container closer system, including container, closer, and pump – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

2. *Semax Acetate*

Semax acetate is reported to be an acetate salt form of semax (free base). The molecular formula of semax acetate is $C_{39}H_{55}N_9O_{12}S$ and its chemical structure is shown in Figure 3. One of the withdrawn nominators provided an example of a CoA for semax acetate with the quality control attribute testing results, including identification, amino acid composition, peptide purity, related substances, water content, acetate content and residual solvents (Figure 4A). There are no testing results for the quality control attribute on aggregates, microbial bioburden and bacterial endotoxin levels.

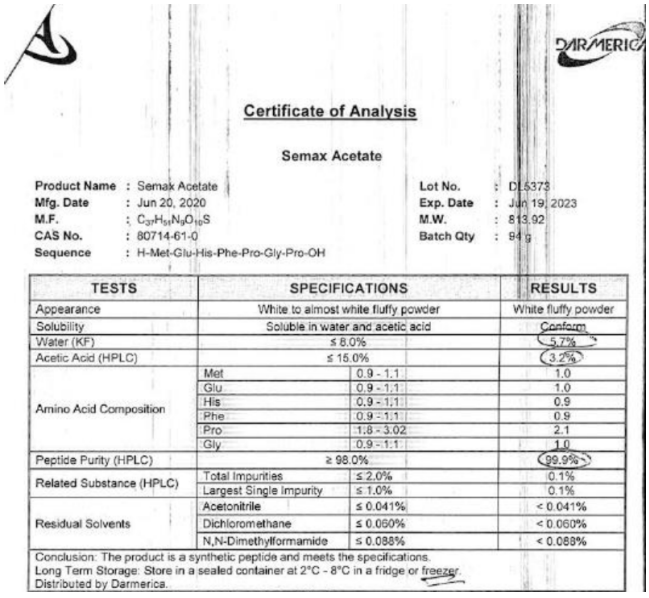
The CoAs provided by the nominators include the quality control attribute testing results for identification, amino acid composition, peptide purity, single impurity or total impurities, water content, and acetate content (Figure 4B). There are no testing results for the quality control attribute on aggregates, and microbial levels.

Figure 3. The Structure of Semax Acetate.[20]



[20] https://pubchem.ncbi.nlm.nih.gov/compound/Semax-acetate. Accessed 12/12/24.

Figure 4. Nominator-Provided Examples of CoAs for Semax Acetate.



Certificate of Analysis

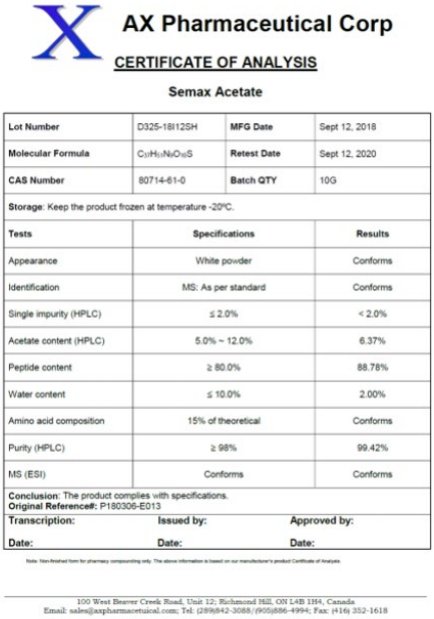
Semax Acetate

Product Name : Semax Acetate
Mfg. Date : Jun 20, 2020
M.F. : $C_{37}H_{51}N_9O_{10}S$
CAS No. : 80714-61-0
Sequence : H-Met-Glu-His-Phe-Pro-Gly-Pro-OH

Lot No. : DL5373
Exp. Date : Jun 19, 2023
M.W. : 813.92
Batch Qty : 94 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to almost white fluffy powder		White fluffy powder
Solubility	Soluble in water and acetic acid		Conform
Water (KF)	≤ 8.0%		5.7%
Acetic Acid (HPLC)	≤ 15.0%		3.2%
Amino Acid Composition	Met	0.9 - 1.1	1.0
	Glu	0.9 - 1.1	1.0
	His	0.9 - 1.1	0.9
	Phe	0.9 - 1.1	0.9
	Pro	1.8 - 3.02	2.1
	Gly	0.9 - 1.1	1.0
Peptide Purity (HPLC)	≥ 98.0%		99.9%
Related Substance (HPLC)	Total Impurities	≤ 2.0%	0.1%
	Largest Single Impurity	≤ 1.0%	0.1%
Residual Solvents	Acetonitrile	≤ 0.041%	< 0.041%
	Dichloromethane	≤ 0.060%	< 0.060%
	N,N-Dimethylformamide	≤ 0.088%	< 0.088%

Conclusion: The product is a synthetic peptide and meets the specifications.
Long Term Storage: Store in a sealed container at 2°C - 8°C in a fridge or freezer.
Distributed by Darmerica.



AX Pharmaceutical Corp

CERTIFICATE OF ANALYSIS

Semax Acetate

Lot Number	D325-18I12SH	MFG Date	Sept 12, 2018
Molecular Formula	$C_{37}H_{51}N_9O_{10}S$	Retest Date	Sept 12, 2020
CAS Number	80714-61-0	Batch QTY	10G

Storage: Keep the product frozen at temperature -20°C.

Tests	Specifications	Results
Appearance	White powder	Conforms
Identification	MS: As per standard	Conforms
Single impurity (HPLC)	≤ 2.0%	< 2.0%
Acetate content (HPLC)	5.0% ~ 12.0%	6.37%
Peptide content	≥ 80.0%	88.78%
Water content	≤ 10.0%	2.00%
Amino acid composition	15% of theoretical	Conforms
Purity (HPLC)	≥ 98%	99.42%
MS (ESI)	Conforms	Conforms

Conclusion: The product complies with specifications.
Original Reference#: P180306-E013

Transcription: Issued by: Approved by:
Date: Date: Date:

100 West Beaver Creek Road, Unit 12, Richmond Hill, ON L4B 1H4, Canada
Email: sales@axpharmaceutical.com; Tel: (289)842-3088/(905)886-4994; Fax: (416) 352-1618

A. Provided by withdrawn nominator **1** **B.** Provided by withdrawn nominator **2**

a. Stability of the Active Pharmaceutical Ingredient and Likely Dosage Forms

Based on the CoA provided by withdrawn nominator 1, long-term storage conditions for semax acetate are "in a sealed container at 2°C to 8°C." Additionally, semax acetate is reported to be stable at -80°C for 2 years and at -20°C for 1 year under sealed storage away from moisture and light. The aliquot solution of semax acetate is stable at -80°C for 6 months and at -20°C for 1 month.[21]

FDA notes that peptides can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Hence, peptides may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation, especially for semax acetate containing 7 amino acids that may have an inherent tendency to aggregate. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the

[21] https://www.medchemexpress.com/semax-acetate.html?srsltid=AfmBOoqS1WDZwkh3sDswlqWGV8EP_jXzC1mhO5DSf0TDJRz0kq4gq-oj. Accessed 12/12/24.

quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

b. Probable Routes of API Synthesis

Semax (free base) can be synthesized using the method mentioned in A.1.b. Then, the semax (free base) can be converted into its acetate salt.

c. Likely Impurities[22]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including semax acetate. For most synthetic peptides, the solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid-phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may be derived from impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids) and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. Drug substance and its proposed product-related impurities may also include peptide-related aggregates, especially for a peptide like semax acetate with 7 amino acids that may have an inherent tendency to aggregate.

In the CoAs the withdrawn nominators provided there is no information regarding the nature of individual impurities that can be present at up to 1.0% (withdrawn nominator 1) or 2.0% (withdrawn nominator 2) level. Such information also cannot be found from publicly available scientific literature.

Because there is lack of information regarding the nature of potential impurities that can be present in semax acetate and the lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide related aggregates.

d. Physicochemical Characteristics Pertinent to Product Performance, Such as Particle Size and Polymorphism

Semax acetate is a white powder. It is soluble in water based on the CoA provided by withdrawn nominator 1. However, there are no water solubility data available in both withdrawn

[22] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the *Nonclinical Assessment* (Section C.I.) as part of the safety assessment of the substance.

nominations and publicly available scientific literature. The only solubility data we can find is that semax acetate is soluble in DMSO with 100 mg/mL.[23] However, the data is not helpful for our evaluation of the proposed dosage forms.

Because the nominator did not provide any information on how to compound proposed injectable and intranasal spray products with the strengths proposed, we cannot evaluate how the physicochemical characteristics of semax acetate, especially the water solubility of semax acetate, will impact the performance of the proposed injectable and intranasal spray products due to lack of the water solubility data for semax acetate.

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the API Is Poorly Characterized or Difficult to Characterize

In the CoA provided by withdrawn nominator 1, there is no testing result for microbial bioburden and/or bacterial endotoxin levels. Bacterial endotoxin test is considered a critical quality control attribute for an injection product. However, endotoxin testing was not identified from publicly available scientific literature, either.

As mentioned at the beginning of Section IIA, for a metered dose nasal spray solution product, the information about the container closer system (including container, closer, and pump) is relevant to the CQAs (pump delivery, spray content uniformity, spray pattern and plume geometry, and droplet size distribution) for the proposed product and would affect how the BDS is delivered. However, no such information is available either in the nominations or the publicly available scientific literature.

Conclusions: Semax acetate is reported to be an acetate salt of semax (free base). As reported in the literature, semax acetate is expected to be stable under reported storage conditions.

Semax acetate is considered not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) certain critical characterization data specific to semax acetate (including impurities, aggregates, microbial bioburden and/or bacterial endotoxin) were not found in the publicly available scientific literature, and the CoAs provided, which were offered as evidence to establishing identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, microbial and bacterial endotoxins). The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.D.2.d., FDA is concerned about the potential for immunogenicity of semax acetate when formulated in an injectable dosage form for SC administration as well as in intranasal spray dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.2.c. The nominations did not include, and FDA has not identified, information about semax acetate to suggest that this substance does not present these risks. Therefore, we cannot rule out potential immunogenicity issues associated with peptide and peptide-related impurities aggregates. In addition, it is difficult to evaluate how the physicochemical characteristics of semax acetate, especially the water solubility of semax acetate, will impact on the performance of the proposed injectable and intranasal spray products

[23] https://www.abmole.com/products/semax-acetate.html. Accessed 12/12/24.

due to lack of water solubility data for semax acetate. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

In addition, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about container closer system, including container, closer, and pump – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

B. Has the Substance Been Used Historically in Compounding?

This evaluation focuses on semax (free base) and semax acetate for intranasal and subcutaneous administration and their use in cerebral ischemia and analgesia for migraine and trigeminal neuralgia; however, FDA searched generally on the historical use of semax-related BDSs in compounding. Information about use may not specify specific attributes of the product, such as route of administration. Databases searched for this evaluation included PubMed, EMBASE, Registration of Medicines in Russia[24], European Pharmacopoeia (11.8 Edition)[25], Japanese Pharmacopoeia (18th Edition)[26], International Pharmacopoeia (12th Edition)[27], NatMed Pro database[28], GlobalEdge[29], USP-NF[30], FDA Adverse Event Reporting System (FAERS) public dashboard[31], Compounding Today[32], Google/Google Scholar, and the Outsourcing Facility Product Reporting Database[33]. It is often unclear which form of semax is being discussed in information from these sources. Therefore, FDA will consider the information discussed in this section in its evaluation of all forms of semax as appropriate.

1. Length of Time the Substance Has Been Used in Compounding

The nominator states that semax has been used to compound drug products but did not provide any additional information regarding the historical use of semax in compounding. The nominators submitted 38 articles but none of the articles discussed the use of a compounded formulation of semax.

The extent to which semax has been used in compounding is unclear. A Google search did not identify any pharmacies that market drug products containing any form of semax. Based on a press release from the office of the U.S. Attorney for the Eastern District of Kentucky, a

---

[24] Available at https://grls.rosminzdrav.ru/default.aspx (available in Russian; translation required). Accessed 12/4/25.
[25] Available at https://pheur.edqm.eu/home (subscription required). Accessed 12/4/25.
[26] Available at https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0029.html. Accessed 12/4/25.
[27] Available at https://digicollections.net/phint/2025/index.html#d/b.1. Accessed 12/4/25.
[28] Available at https://naturalmedicines.therapeuticresearch.com/ (subscription required). Accessed 12/4/25.
[29] Available at https://globaledge.msu.edu/industries/healthcare/regulatory-agencies.
[30] Available at https://www.uspnf.com/ (subscription required). Accessed 12/4/25.
[31] Available at https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. Accessed 12/4/25.
[32] Available at https://compoundingtoday.com (subscription required). Accessed 12/4/25.
[33] Available at https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/. Accessed 12/4/25.

pharmacy compounded and distributed products containing semax from 10/25/18 to 4/1/20, but it is unclear which form of semax was being used to compound the products.[34] No studies were found in which semax was used as a compounded drug product.

2. The Medical Condition(s) It Has Been Used to Treat

A literature search revealed that semax has been studied as a therapy for peptic ulcer, chronic ischemic brain disease, migraine, and trigeminal neuralgia. One article discusses the use of intranasal semax (1%, 2-4 drops 3 times a day for 10 days) in addition to basic therapy (omeprazole 20 mg twice a day, "denol" 120 mg 2 times a day, and "solcoseril" 2.0 intramuscularly) versus basic therapy without semax for peptic ulcer. The study authors note that the semax used in this study was synthesized at the Laboratory of Regulatory Peptides, Institute of Molecular Genetics, Russian Academy of Sciences (Ivanikov et al. 2002). Semax has also been studied as a therapy for chronic ischemic brain disease (Cherkasova et al. 2002) and for migraine and trigeminal neuralgia (Koroleva et al. 1996).

One article hypothesizes that a possible use for semax, based on animal models and studies in healthy adults, might be attention deficit hyperactivity disorder (ADHD) and Rett syndrome (Tsai 2006).

Semax is marketed online for a variety of conditions: anxiety, depression, attention/memory improvement, ischemic events/stroke, nerve regeneration, diabetic neuropathy, ADHD, opioid withdrawal, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, dys-circulatory encephalopathy, optic nerve atrophy, pain, and gastric protection.[35]

3. How Widespread Its Use Has Been

No outsourcing facility has reported compounding drug products containing semax since 2019.[36] An online search identified websites of health/wellness clinics, medical concierge services, functional and regenerative medicine clinics, and online retailers in the United States that are

---

[34] See https://www.justice.gov/usao-edky/pr/nicholasville-compounding-pharmacy-and-its-owner-sentenced-unlawful-distribution. Accessed 12/4/25.

[35] See https://rwacenter.com/product/semax/, https://www.eternityhealthpartners.com/semax-selank/, https://neuronmedical.com/peptide-therapy-selank-semax-thousand-oaks/, https://stemedix.com/peptides/, https://www.transformyou.com/semax-peptide, https://www.biltmorerestorativemedicine.com/health-wellness/peptide-therapy-in-asheville-nc/, https://www.limitlesslifenootropics.com/product/semax-10ml-nasal-spray-30mg/. Accessed 12/4/25.

[36] Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act. Under section 503B, a compounder can become an outsourcing facility. Outsourcing facilities are required to provide FDA with a list of drugs they compounded during the previous 6-month period upon initial registration and in June and December each year. This retrospective information does not identify drugs that outsourcing facilities intend to produce in the future. The outsourcing facility product report is available at: https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility. Accessed 12/4/25.

marketing semax injection and intranasal products.[37] Many of the websites do not describe or clearly state whether the semax products marketed are compounded.

Semax products are marketed as single ingredient formulations and in combination with selank. One website offers a semax single ingredient 2.5 mg/mL injectable product and a 1.25 mg/mL nasal spray; the website also offers a "50:50" combination of semax and selank as a 2.5 mg/mL injectable product and 1.25 mg/mL nasal spray.[38] One online retail website offers a semax 30 mg nasal spray product.[39] Another online retail website offers semax 30 mg "for research purposes only" and lists nasal spray and subcutaneous injection as common methods of administration.[40]

None of the websites searched indicate whether their marketed products contain the base or a salt or ester of semax.

4. Recognition of the Substance in Other Countries or Foreign Pharmacopeias

There is no monograph for semax in the European Pharmacopoeia (11th Edition, 11.8), the Japanese Pharmacopoeia (18th Edition), or the International Pharmacopoeia (12th Edition). Semax is a registered drug in Russia and is available as 0.1% and 1% nasal drops.[41]

Conclusions: It is often unclear whether the semax discussed in the sources considered for this section is the salt formulation or the free base. Semax injection and intranasal products are widely marketed in the United States through health/wellness clinics, medical concierge services, functional and regenerative medicine clinics, and online retailers for anxiety, depression, attention/memory improvement, ischemic events/stroke, nerve regeneration, diabetic neuropathy, ADHD, opioid withdrawal, ALS, Parkinson's disease, Alzheimer's disease, dys-circulatory encephalopathy, optic nerve atrophy, pain, and gastric protection. The extent to which semax has been used in compounding is unclear. Semax is a registered drug in Russia and is available as 0.1% and 1% nasal drops.

---

[37] See https://rwacenter.com/product/semax/, https://www.eternityhealthpartners.com/semax-selank/, https://neuronmedical.com/peptide-therapy-selank-semax-thousand-oaks/ https://stemedix.com/peptides/, https://www.transformyou.com/semax-peptide, https://www.biltmorerestorativemedicine.com/health-wellness/peptide-therapy-in-asheville-nc/, https://pharmagradepeptides.is/product/semax-30mg-2/ , https://pinnacleintegrative.com/peptides/, https://www.limitlesslifenootropics.com/product/semax-10ml-nasal-spray-30mg/. Accessed 12/4/25.

[38] See https://rwacenter.com/product/semax/, https://rwacenter.com/product/semax-selank/. Accessed 12/4/25.

[39] See https://www.limitlesslifenootropics.com/product/semax-10ml-nasal-spray-30mg/. Accessed 12/4/25.

[40] See https://pharmagradepeptides.is/product/semax-30mg-2/. Accessed 12/4/25.

[41] See https://grls.rosminzdrav.ru/GRLS.aspx?RegNumber=&MnnR=&lf=&TradeNmR=%d1%81%d0%b5%d0%bc%d0%b0%d0%ba%d1%81&OwnerName=&MnfOrg=&MnfOrgCountry=&isfs=0&regtype=1%2c6&pageSize=10&order=Registered&orderType=desc&pageNum=1 (available in Russian; translation required). Accessed 12/4/25.

C. Available Evidence of Effectiveness or Lack of Effectiveness of Drug Products Compounded With the Substance

In addition to the references submitted by the nominator, the following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites. In addition to a comprehensive review of pertinent information from these databases, this section provides a brief overview of cerebral ischemia, migraine, and trigeminal neuralgia and a discussion of the proposed use(s) of semax-related BDSs.

We evaluated semax-related BDSs for cerebral ischemia, migraine and trigeminal neuralgia[42] and considered available data to support effectiveness. The clinical references discuss an active moiety the authors call semax, but these references do not specify whether the substance used was a free base or a salt. Therefore, when discussing these references, the substance will be referred to as semax (the term that was used by the authors).

1. Cerebral Ischemia

Cerebral ischemia is a common mechanism of acute brain injury that results from impaired blood flow to the brain. Cerebral ischemia can be global or focal. The most common cause of global brain ischemia is systemic hypotension. Focal brain ischemia most commonly arises from obstruction of arterial blood flow to the brain, often as a result of thrombosis, embolism or vascular stenosis. The management of this condition is targeted at correcting the underlying cause and minimizing risk factors, such as diabetes mellitus, hypertension, and hyperlipidemia, to decrease the risk of recurrence (DeSai and Shapshack 2023).

Studies for the acute treatment of cerebral ischemia generally evaluate endpoints such as neurological improvement based on clinical outcomes that measure clinical disability at three months after stroke based on the modified Rankin Scale score.[43] Studies for the prevention of cerebral ischemia have evaluated endpoints such as reduction in the occurrence of stroke, reduction in risk of stroke, time to first occurrence of new ischemic stroke, and reduction in blood pressure.

Professional society guidelines for the treatment and prevention of cerebral ischemia do not discuss semax-related BDSs (Powers et al. 2019; Johnston et al. 2006; Kleindorfer et al. 2021).

---

[42] Semax-related BDSs were nominated for "analgesia", but because the reference submitted by the nominator that discussed analgesia was in subjects with migraine and trigeminal neuralgia, we evaluated the Semax-related BDSs for these uses. Semax was also nominated for "ADHD" and "nootropic". ADHD was not evaluated because supporting literature for this use was not found. "Nootropic" does not have an ICD-10 code and no professional society treatment guidelines could be found for this use. Dorland Medical Dictionary 29th Edition defines it as "having positive effects on organically impaired cognition or nervous system function". Therefore, this use will be considered as part of the evaluation for cerebral ischemia.

[43] Modified Rankin Score (Broderick et al. 2017). https://pmc.ncbi.nlm.nih.gov/articles/PMC5552200/pdf/nihms875857.pdf Accessed 12/5/25.

a. Reports of Trials, Clinical Evidence, and Anecdotal Reports of Effectiveness, or Lack of Effectiveness, of the Bulk Drug Substance

- Cherkasova et al. 2002 (meeting abstract)

  This reference was submitted by the nominators and is an abstract from a professional society meeting. No full published article could be located for this reference. The abstract describes a study in which semax was given to both rats and humans. An unknown number of human subjects with chronic ischemic brain disease received intranasal semax 600 mg daily for 10 days. The authors discuss lab values that were measured but do not specify if these labs were done in the animal or human subjects. The authors do not discuss how long the human subjects had ischemia or if they had received other medications for the prevention or treatment of this condition. Although the authors measured labs related to blood clotting (such as plasmin, antithrombin III, and protein C), the authors do not provide full results for these lab values, nor do they discuss clinical function before and after receiving semax.

References regarding the use of semax-related BDSs for cerebral ischemia found by FDA were articles published in Russian[44], some of which had English abstracts. Because the full references were not available in English, these references were not considered as part of this evaluation[45]. Although several review articles hypothesize that semax might be used in the treatment of cerebral ischemia, the information referenced in these review articles is based on data from studies completed in animals[46], and do not provide additional references in humans with cerebral ischemia. One review[47] provided some human references, but the references regarding cerebral ischemia are written in Russian[48] and those studies regarding neuroprotective and nootropic effects are in healthy adults[49] or are written in Russian[50].

b. Whether the Product Compounded With This Bulk Drug Substance Is Intended To Be Used in a Serious or Life-Threatening Disease

Cerebral ischemia is a serious disease that, if untreated, can result in death or permanent disability (DeSai and Shapshak 2023).

---

[44] Miasoedova et al. 1999, Gusev et al. 1997, Gusev et al. 2005, Gusev et al. 2018.
[45] See 21 CFR 10.20(c)(2) ("If a part of the material submitted is in a foreign language, it must be accompanied by an English translation verified to be complete and accurate, together with the name, address, and a brief statement of the qualifications of the person making the translation. A translation of literature or other material in a foreign language is to be accompanied by copies of the original publication.")
[46] Deigin et al. 2022; Tarasov et al. 2017.
[47] Kolomin et al. 2013.
[48] Shmyrev et al. 1998; Gusev et al. 1997; Gusev et al. 1996; Gusev et al. 2005.
[49] Kaplan et al. 1996.
[50] Kaplan et al. 1992; Alekseeva et al. 1999.

c. Therapies That Have Been Used for the Condition(s) Under Consideration

There are many FDA-approved drug products that prevent and treat the same medical condition as that proposed for the semax-related compounded drug product(s).[51] These drug products are listed in Table A located in Appendix 1.[52]

d. Conclusion for Cerebral Ischemia

There is insufficient evidence of effectiveness to support use of semax (free base) or semax acetate for cerebral ischemia. The only available information was in the form of a meeting abstract that lacked information about relevant clinical endpoints. Professional society guidelines on the treatment of cerebral ischemia do not discuss semax-related BDSs. Cerebral ischemia is a serious condition and there are FDA-approved drug products for the prevention and treatment of this condition.

2. Migraine

Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting, and, frequently, cutaneous allodynia (Ailani et al. 2021).

Studies for the acute treatment of migraine generally evaluate endpoints such as reduction to no pain within 2 hours of receiving a treatment, freedom from most bothersome symptoms such as nausea, phonophobia, or photophobia following treatment, and the use of rating scales to assess changes in daily functioning following treatment. Studies for the preventive treatment of migraine have evaluated endpoints such as change from baseline in the mean monthly migraine days, change from baseline in the need for acute migraine treatments, and the use of rating scales to assess changes in daily functioning following treatment.

Professional society guidelines for the treatment of migraine do not discuss semax-related BDSs (Ailani et al. 2021).

a. Reports of Trials, Clinical Evidence, and Anecdotal Reports of Effectiveness, or Lack of Effectiveness, of the Bulk Drug Substance

- Koroleva et al. 1996

  This reference was submitted by the nominator. This study evaluated adults with migraine, trigeminal neuralgia, or dental plexalgia. The data for the study populations related to trigeminal neuralgia are discussed below in Section II.C.3.a. In the migraine group, 12 subjects (10 women and 2 men aged 19-56 years) received one dose (0.5 mg/kg) of intranasal semax. Pain severity was measured using the modified pain sensitivity test (MPST) rating scales. The authors did not describe this rating scale and

[51] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

[52] Labels for the drug products listed in this table can be found at https://nctr-crs.fda.gov/fdalabel/ui/search. Accessed 8/4/25.

there was no information referenced about the scale and we did not identify additional information about the MPST rating scale. Rhoencephalogram (REG) was recorded before and 5, 15, and 30 minutes after administration of semax. The article provided insufficient information on REG recordings and its relevance to clinical outcomes in subjects experiencing migraine headaches; changes in REG recordings appeared to have been used as a measure of vasodilatory effect and vascular tone to identify two types of responders to semax administration.
The authors reported that total MPST score decreased from 78% before semax to 32% after semax administration. Four subjects out of twelve (33%) reported cessation of headache pain 90-120 minutes after semax administration, whereas in 8 subjects the authors reported that "the effect of semax was weaker; "pain was not eliminated but became less severe." There was no information about migraine headache characteristics at baseline such as headache intensity or severity, presence or absence of associated symptoms, unilaterality or bilaterality of the headache, etc. Additional limitations of this study include the small sample size, no blinding, no control group, the absence of reporting of the actual scores or standard deviations for the scores of the rating scales, and there were insufficient details provided on the design and the conduct of this study. A minority of the subjects had resolution of their pain and it is unclear from the rating scales used how much the pain interfered with daily functioning and how semax may have affected that.

FDA was unable to find additional references regarding the use of semax-related BDSs for migraine.

b. Whether the Product Compounded With This Bulk Drug Substance Is Intended To Be Used in a Serious or Life-Threatening Disease

Migraine can be a serious condition and can significantly impair functional ability and may increase the risk for other serious medical conditions, such as depression and epilepsy (Ailani et al. 2021).

c. Therapies That Have Been Used for the Condition(s) Under Consideration

There are many FDA-approved drug products and over-the-counter (OTC) drug products that treat the same medical condition as that proposed for the semax-related compounded drug product(s).[53] These drug products are listed in Tables B and C in Appendix 2.[54]

d. Conclusion for Migraine

There is insufficient evidence of effectiveness to support use of semax (free base) or semax acetate for headache pain (analgesia) in subjects with migraine headache. The results from only one small, uncontrolled, open label study showed that semax was not effective in resolving

[53] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[54] Labels for the drug products listed in this table can be found at https://nctr-crs.fda.gov/fdalabel/ui/search. Accessed 8/4/25.

headache pain for the majority of subjects with migraine. Professional society guidelines on the treatment of migraine do not discuss semax-related BDSs. Migraine is a serious condition and there are FDA-approved drug products for the prevention and treatment of this condition.

3. Trigeminal Neuralgia

Trigeminal neuralgia is a condition causing severe, unilateral, episodic facial pain. Patients typically report brief, lancinating attacks triggered by eating, drinking, talking, or touching the face. There is a distinction between typical trigeminal neuralgia paroxysms where there is no pain between episodic attacks and trigeminal neuralgia with concomitant pain where there is background pain between attacks. Chong et al. (2023) discusses three etiologic classifications for trigeminal neuralgia:

- Classic—vascular contact on the trigeminal nerve.
- Secondary—possible underlying pathology such as schwannoma or multiple sclerosis.
- Idiopathic—no apparent structural cause.

Professional society guidelines for treatment and prevention of trigeminal neuralgia do not discuss semax-related BDSs (Chong et al. 2023).

a. Reports of Trials, Clinical Evidence, and Anecdotal Reports of Effectiveness, or Lack of Effectiveness, of the Bulk Drug Substance

- Koroleva et al. 1996

This reference was submitted by the nominator. This study evaluated adults with migraine, trigeminal neuralgia, or dental plexalgia. The data for study populations related to migraine was described above in Section II.C.2.a. The authors defined dental plexalgia as a subtype of trigeminal neuralgia. There was a total of 25 adult subjects with trigeminal neuralgia in the study. The typical trigeminal neuralgia group consisted of 16 subjects (12 women and 4 men aged 45-65 years) and the dental plexalgia group consisted of 9 subjects (3 women and 6 men aged 15-52 years). Subjects in both groups received one dose (0.5 mg/kg) of intranasal semax. Pain severity and frequency were measured using the modified pain sensitivity test (MPST) rating scales. The authors did not describe this rating scale and there was no information referenced about the scale and we did not identify additional information about the MPST rating scale. Thresholds of sensation and pain in response to electrostimulation of the skin in symmetrical areas of the face on healthy and affected sides as well as trigeminal somatosensory evoked potentials (TSEP) before and 5, 15, and 30 minutes after semax administration were recorded.

The authors report that in the subjects with typical trigeminal neuralgia, there were no changes in the characteristics of pain in the MPST nor changes in sensation or pain thresholds and TSEP after administration of semax. In subjects with dental plexalgia, pain resolved in 6 subjects and 3 subjects reported a decrease in pain severity, with change in their perception of pain. However, MPST results showed that overall, there was no reduction in frequency of pain attacks, duration of pain attacks, and differences in sensory characteristics of pain. Although there were some differences in patient reports of pain severity pre- and post- semax, the authors do not provide quantitative changes in

TSEP after semax administration, and its clinical relevance is unclear. Authors concluded that "no significant changes in TSEP were observed after a single intranasal administration of semax. This observation indicates that semax does not exhibit analgesic activity by itself. Additionally, limitations of this study include the small sample size, no blinding, no control, the absence of reporting of the actual scores or standard deviations for the scores of the MPST rating scales or TSEP. There was insufficient information for the MPST rating scales or TSEP that were used to inform the study endpoints in a population with trigeminal neuralgia. Furthermore, it appears that the authors assigned arbitrary units when they discussed their findings.

FDA was unable to find other references that discuss the use of semax-related BDSs for trigeminal neuralgia.

b. Whether the Product Compounded With This Bulk Drug Substance Is Intended To Be Used in a Serious or Life-Threatening Disease

Trigeminal neuralgia is a serious condition that causes pain that is severe and distressing and that interferes with daily activity. It was reported that patients with trigeminal neuralgia experienced an increased risk of anxiety and depression (Chong et al. 2023).

c. Therapies That Have Been Used for the Condition(s) Under Consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the semax-related compounded drug product(s).[55]

Carbamazepine (Equetro), oral (NDA 021710) is indicated for the treatment of the pain associated with trigeminal neuralgia. (https://nctr-crs.fda.gov/fdalabel/ui/spl-summaries/criteria/579097). There are several oral carbamazepine dosage formulations, and the above product and reference is an example of one of these formulations.

Professional society treatment guidelines also recommend the off-label use of FDA-approved drug products, such as oxcarbazepine, lamotrigine, baclofen, gabapentin, and pregabalin for the treatment of trigeminal neuralgia if carbamazepine is not effective. For patients who are hospitalized with acute relapses, lidocaine nerve block, botulinum toxin, sumatriptan, phenytoin or fosphenytoin might also be used (Chong et al. 2023).

d. Conclusion for Trigeminal Neuralgia

There is insufficient evidence of effectiveness to support use of semax (free base) or semax acetate for analgesia in patients with trigeminal neuralgia pain that is severe and distressing. The results from only one small, uncontrolled, open-label study showed that semax was not effective in resolving pain for the majority of subjects with trigeminal neuralgia in the study. Professional society guidelines on the treatment of trigeminal neuralgia do not discuss semax-related BDSs.

[55] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

Trigeminal neuralgia is a serious condition and there are FDA-approved drug products for the treatment of this condition.

Overall Conclusions on Effectiveness: There is insufficient evidence to support the effectiveness for semax (free base) or semax acetate for cerebral ischemia, migraine, or trigeminal neuralgia. Only two available references were available with insufficient details on the design and conduct of the studies, and the available references demonstrated lack of effectiveness and were limited by small sample size and lack of information about some relevant clinical endpoints. Cerebral ischemia, migraine and trigeminal neuralgia are all serious conditions and FDA-approved therapies for the acute treatment and prevention of these conditions exist.

D. Are There Concerns About the Safety of the Substance for Use in Compounding?

1. Nonclinical Assessment

The nominations included nonclinical information. Specifically, the nominations included a list of 35 articles published in English describing pharmacological studies of semax.[56] In addition, the nominations included an article describing some of the pharmacokinetic properties of semax delivered via the intranasal ROA to rats (Shevchenko et al. 2006a). Although the article is written in a foreign language, FDA identified in the publisher site (https://link.springer.com/) the English version of the same article, which is also indexed in the Google Scholar database (Shevchenko et al. 2006b). The nominations included an article describing the analgesic effects of a different peptide, selank (Meshavkin et al. 2006), which is out of the scope of this evaluation and is, therefore, not further discussed.

The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemicals Agency, FDA's Generally Recognized as Safe (GRAS) Notice Inventory, Google, Google Scholar, National Institutes of Health's dietary supplement label database, National Toxicology Program website, Pharmapendium, PubMed, Society of Toxicology, USP, and Web of Science.

a. General Pharmacology of the Drug Substance

Semax is a synthetic heptapeptide analog of the ACTH 4-10 fragment ($ACTH_{4-10}$), which is devoid of the hormonal corticotropic and melanotropic properties but retains the neurobehavioral properties of the full-length ACTH protein (Kolomin et al. 2013). The amino acid sequences of $ACTH_{4-10}$ and semax differ with respect to the three amino acids in the C-terminal domain

[56] Agapova et al. 2007a; Agapova et al. 2007b; Bakaeva et al. 2009; Bakhmet and Koplik 2012; Boyarshinova et al. 2008; Cherkasova et al. 2002; Eremin et al. 2004; Eremin et al. 2005; Glazova et al. 2005; Grigorjeva and Lyapina 2010; Inozemtsev et al. 2013; Inozemtsev et al. 2016; Ivanova et al. 2003; Ivanova et al. 2004; Ivanova et al. 2005; Ivanova et al. 2007; Kolik et al. 2014; Kopylova et al. 2003; Koroleva et al. 1996; Lebedeva et al. 2018; Levitskaya et al. 2010; Lyapina et al. 2006; Malyshev et al. 2013; Manchenko et al. 2012; Medvedeva et al. 2014; Orlov et al. 1999; Romanova et al. 2006; Safarova et al. 2002; Shevchenko et al. 2013; Slominsky et al. 2017; Solov'ev et al. 2016; Stavchansky et al. 2011; Vlasova et al. 2009.

(Figure 5). The C-terminal sequence Pro-Gly-Pro in semax is thought to increase the heptapeptide stability to hydrolysis catalyzed by peptidases (Potaman et al. 1991a).

Figure 5. Amino Acid Sequences of Semax and $ACTH_{4-10}$.

Semax	Met – Glu – His – Phe – Pro – Gly – Pro
$ACTH_{4-10}$	Met – Glu – His – Phe – Arg – Trp – Gly

Left to right: Amino acid sequences from the N- to the C-terminus of the peptides. Arg: arginine; Glu: glutamic acid; Gly: glycine; His: histidine; Phe: phenylalanine; Pro: proline; Trp: tryptophan. All are L-amino acids.

According to nonclinical studies, semax, like $ACTH_{4-10}$, has multiple pharmacological properties. In addition to acting as an analgesic, a neuroprotectant, and a neurotrophic agent, semax also induces antidepressant- and anxiolytic-like effects in rodents (Bashkatova et al. 2001; Dolotov et al. 2006; Severyanova et al. 2020; Silachev et al. 2009; Volodina et al. 2012). The paragraphs that follow focus on the pharmacological properties of semax that are most closely associated with the nominated clinical indications of cerebral ischemia and analgesia.

Semax and Cerebral Ischemia in Animal Models

In a study conducted in a rat model of focal cerebral ischemia, semax reduced the ischemic damage and prevented the development of cognitive deficits (Romanova et al. 2006). Specifically, in this study, focal photothrombotic ischemia was induced in anesthetized rats that received an intravenous (IV) injection of the photosensitizing dye Bengal rose and had their surgically exposed cranial surface exposed to a cold light beam for 15 minutes. At 15 minutes and 1 hour after the photostimulation, half of the rats were treated with semax (250 µg/kg, intranasal [IN]) and the other half with vehicle (water; 7 µL, IN). The treatments were repeated once a day for 6 more days. The control group consisted of untreated sham-operated rats. Eight days after the photothrombosis, the infarcted brain areas were approximately 20% smaller in semax-treated rats than vehicle-treated rats. Although semax-treated rats and vehicle-treated rats had significantly reduced locomotor activity compared to control rats, semax-treated rats did not present memory retention deficit in a passive avoidance task whereas water-treated rats did (Romanova et al. 2006).

In a different study conducted in adult male rats with global cerebral ischemia induced by bilateral carotid artery occlusion, semax also reduced the ischemic damage (Stavchansky et al. 2011). In this study, rats were treated via the intraperitoneal (IP) route with semax (100 µg/kg) or saline 15 minutes, 1, 4, and 8 hours after the carotid occlusion. Half of the animals were euthanized at 30 minutes and the other half at 24 hours post-occlusion. Histological assessment revealed that vehicle-treated rats presented marked ischemic damage in the frontoparietal cortex at 30 minutes post-occlusion and in the cerebral cortex, thalamus, mesencephalon, hippocampus, cerebellum, and pons at 24 hours post-occlusion. Ischemic damage was characterized by large numbers of neurons with nuclear condensation and shrinking of the cytoplasm. In addition to reducing the ischemic damage, the treatment with semax increased the number of cells expressing proliferating cell nuclear antigen, a DNA repair protein that is generally associated with cell division, in the fourth ventricle and other brain regions (Stavchansky et al. 2011). These findings led the authors to conclude that semax may be neuroprotective and may promote stem cell neurodifferentiation (Stavchansky et al. 2011).

Stavchansky and colleagues further reported that the capillaries in the cerebral cortex of semax (100 μg/kg, IP)-treated ischemic rats appeared moderately dilated and filled by erythrocytes but did not have the signs of stasis seen in the cerebral cortical blood vessels of saline-treated rats 30 minutes and 24 hours post-occlusion (Stavchansky et al. 2011). Considering these findings, the authors proposed that the antithrombotic properties of semax might contribute to its effectiveness in suppressing cerebral ischemic damage. However, the authors did not provide direct evidence for semax-induced antithrombotic effects in ischemic rats. Direct evidence that semax has anticoagulant and antithrombotic properties has been provided by studies conducted in non-ischemic rats (Cherkasova et al. 2002; Cherkasova et al. 2001; Grigorjeva and Lyapina 2010; Lyapina et al. 2006).

Cherkasova and colleagues reported that intranasal administration of semax (1 mg/kg/day) compared to saline to adult male rats for 5 days increased the anticoagulant and fibrinolytic activities of the plasma (Cherkasova et al. 2002; Cherkasova et al. 2001). The increased levels of total fibrinolytic activity, plasmin, and plasminogen were pharmacologically relevant as semax-treated rats compared to saline-treated rats developed smaller thrombi in response to 1.5-hour clamping of the jugular vein (Cherkasova et al. 2002; Cherkasova et al. 2001).

Grigorjeva and colleagues assessed the effects of semax on coagulation endpoints in rats exposed to acute or chronic stress (Grigorjeva and Lyapina 2010). In this study, adult male rats treated with saline (0.05 mL/day, 0.85% NaCl solution, IP) for 4 days and subjected to acute or chronic immobilization stress presented a hypercoagulating phenotype characterized by shorter activated partial thromboplastin time, shorter fibrinolytic activity, lower activity of plasminogen tissue activator, and lower platelet aggregation compared to non-stressed rats. By contrast, adult male rats treated with semax (1 mg/kg/day, IP) for 4 days and subjected to acute or chronic immobilization stress presented a hypocoagulating phenotype characterized by longer partial thromboplastin time, higher fibrinolytic activity, higher activity of plasminogen tissue activator, and lower platelet aggregation compared to non-stressed rats (Grigorjeva and Lyapina 2010).

Considering the results of their study, Grigorjeva and Lyapina concluded that semax protected the rats from the hypercoagulating effects of acute and repeated stress (Grigorjeva and Lyapina 2010). However, we note that semax-treated rats presented a hypocoagulating phenotype when compared to control (non-stressed) rats. Because the study did not evaluate the dose-response relationship for the effects of semax, it is unclear whether it would be possible to titrate semax doses to reverse a hypercoagulating condition without creating a condition that could favor the development of a bleeding event.

In a separate study, Lyapina and collaborators reported that, in vitro, semax was devoid of anticoagulant effects (Lyapina et al. 2006). However, in line with previous findings, the authors reported that in-vivo treatment of rats with semax (1 mg/kg, IN or IV) significantly increased fibrin depolymerizing activity and tissue plasminogen activator and reduced (by ~35%) platelet aggregation (Lyapina et al. 2006). In the same study, the shorter peptide segment Pro-Gly-Pro, which is recognized as a semax metabolite (see the *Pharmacokinetics* section), was shown to have anticoagulant properties both in vivo and vitro. It is possible that, in vivo, the anticoagulant and antithrombotic effects of semax are due to its metabolites. The molecular mechanisms accounting for the anticoagulant effects of semax and its metabolites remain unknown.

It has been proposed that the effectiveness of semax in suppressing ischemic cerebral damage could also be related to its antioxidant properties (Vlasova et al. 2009) and its ability to rapidly modulate gene expression (Agapova et al. 2007a; Agapova et al. 2007b; Medvedeva et al. 2014). In adult male rats treated with semax (50 µg/kg, IN), expression of nerve growth factor and brain-derived neurotrophic factor increased significantly in different brain regions, including the hippocampus, as early as 60 minutes after the treatment (Agapova et al. 2007a). The expression of genes encoding growth factors was also found to be upregulated in the hippocampus at 3 and 24 hours after the induction of ischemia by middle carotid artery occlusion in rats treated with semax (100 µg/kg, IP injection at 15 minutes, 1, 4, and 8 hours after the occlusion) compared to saline (Medvedeva et al. 2014). Upregulation of brain-derived neurotrophic factor and nerve growth factor could be beneficial in the context of cerebral ischemia because both factors are known for their antiapopotic and anti-inflammatory properties and for their ability to induce neurogenesis and promote synaptic plasticity (Sims et al. 2022). The molecular mechanisms by which semax regulates gene expression are unknown.

We note that nonclinical studies assessing the pharmacological effects of semax in cerebral ischemia are limited in that they are generally restricted to a fixed dose of semax (100 µg/kg, IP, in some studies or 250 µg/kg, IN, in others). As such, dose-response relationships for semax delivered via different ROAs have not been established. Those studies also lacked an assessment of the systemic exposure to semax needed to reduce cerebral ischemia. In addition, studies assessing the antithrombotic effects of semax in vivo have been conducted with a fixed IN dose of semax (1 mg/kg) that is 4 times higher than the IN dose shown to suppress ischemic brain damage. In the absence of direct evidence that coagulation endpoints are reduced by semax in animal models of ischemia, it is difficult to establish the relevance of the antithrombotic properties of semax to the suppression of cerebral ischemia.

Semax and Pain

In rodents, semax administered via some ROAs has been shown to induce analgesia. For instance, in one study, treatment of adult male rats with semax (1.5, 15, 50, or 500 µg/kg, IP) dose dependently increased the pain threshold of the animals (measured as the pressure the animals tolerated in their leg prior to withdrawing it). As the IP semax dose increased from 1.5 to 500 µg/kg, the magnitude and duration of the semax-induced analgesic effect increased and the time for onset of the effect decreased (Manchenko et al. 2012). In the same study, the same semax doses delivered intranasally were unable to induce analgesia (Manchenko et al. 2012).

In separate studies, the same research group assessed the analgesic effects of semax (50 µg/kg or 500 µg/kg, IP) in rats subjected to each of the following tests: (i) tail flick test, (ii) hind leg compression, (iii) hot plate test, and (iv) paw-withdrawal test (Ivanova et al. 2003; Ivanova et al. 2007; Ivanova et al. 2004; Ivanova et al. 2005). In all studies, control groups consisted of rats treated with an equivalent volume of vehicle. In all tests, rats treated with the highest IP dose of

semax (500 μg/kg) consistently presented higher pain thresholds than saline-treated rats.[57] In the four tests, the analgesic effects of semax were evident starting at approximately 15 minutes and lasted for at least 60 minutes after the treatment.

In the study published in 2003, Ivanova and colleagues also assessed the analgesic effect of semax in the acetic acid-induced writhing test in mice. In this test, mice were treated with semax (50 μg/kg or 500 μg/kg, IP) or vehicle before receiving an IP injection of acetic acid (0.6%; 0.1 mL/10 g). Number of acetic acid-induced contractions of the abdominal wall (writhing), a measure of pain, was significantly lower at 40-50 minutes after the semax treatment compared to vehicle treatment (Ivanova et al. 2003). No dose-response relationship was noted in this test, as the magnitude of the analgesic effect induced by the IP semax doses of 50 μg/kg and 500 μg/kg was comparable (Ivanova et al. 2003).

The molecular mechanisms underlying the analgesic effects of semax are poorly understood. In vitro, semax has been shown to inhibit the activity of enkephalinases, enzymes that catalyze the hydrolysis of the endogenous opioids enkephalins, with an apparent potency of 10 μM (Kost et al. 2001). Since enkephalinases are membrane-bound enzymes, they could represent the molecular targets to which radiolabeled semax delivered intranasally to rats was shown to bind with a dissociation constant (K_d) of approximately ~ 2.4 nM (Dolotov et al. 2006). Enkephalinase inhibition leading to an increase in the concentrations of endogenous opioids could contribute to the analgesic effect of semax. However, Ivanova and colleagues reported that the opioid receptor antagonist naloxone (1 mg/kg, IP) did not prevent the analgesic effect of semax, as assessed in the paw-withdrawal test in rats (Ivanova et al. 2005). Instead, the authors provided evidence that the analgesic effect semax (50 or 500 μg/kg, IP) could not be detected in rats that were pretreated with cyproheptadine (1 mg/kg, IP, 15 minutes before semax). Considering that cyproheptadine acts as an antagonist at the serotonin 5-HT1a and 5-HT2a receptors, the authors proposed that semax-induced analgesia is mediated, at least in part, via an increase of serotoninergic signaling in the brain (Ivanova et al. 2005).

The proposal that semax-induced analgesia may be mediated by semax-induced increase of serotoninergic signaling in the brain is supported by the finding that semax (0.15 or 0.6 mg/kg, IP) administered to adult male C57/BL6 mice dose dependently increased extracellular striatal levels of the serotonin metabolite 5-hydroxyindoleacetic acid (Eremin et al. 2004; Eremin et al. 2005). However, semax does not appear to act selectively on the serotoninergic system because treatment of mice with semax also potentiated amphetamine-induced dopamine release in the striatum and amphetamine-induced locomotor activity (Eremin et al. 2005). This finding is concerning because increased dopaminergic tone in the striatum is a response typically induced by drugs of abuse such as cocaine (Volkow et al. 2006). At the time of this evaluation, the

[57] In the tail flick test, 4 cm of the end tail of the rats was submersed in hot water at 56°C, and the time it took for animals to flick their tail was taken as a measure of pain threshold. In the hindleg compression and the paw-withdrawal tests, pressure of defined force was applied to the leg or paw of the rats, and the pressure force at which the rats withdrew their limb or paw was taken as a measure of pain threshold. In the hot plate test, rats were placed on a hot plate warmed to 53°C, and the time for the animals to lick one of their hind legs for the first time was taken as a measure of pain threshold.

nominator did not submit, and FDA did not identify nonclinical studies to demonstrate whether semax has reinforcing and addictive properties to inform its abuse potential.

b. Pharmacokinetics/Toxicokinetics

An in-vivo study assessed the blood and brain concentrations of semax in adult male Wistar rats treated with radioactively labeled semax ([^{3}H]-semax; 50 µg/kg, IV) (Potaman et al. 1991b). The highest concentrations of semax measured in the brain represented approximately 0.005% of the administered dose. The highest ratio of brain-to-blood semax concentrations was 0.24 and was measured 10 minutes after the IV injection of [^{3}H]-semax (Potaman et al. 1991b). The authors hypothesized that an active transport mechanism and/or passive transmembrane diffusion through the vascular epithelium, particularly in the circumventricular organs where the endothelial is leaky, could contribute to the entry of semax in the brain (Potaman et al. 1991b).

A separate in-vivo study assessed the blood and brain concentrations of semax in rats (unidentified sex, age, and strain) treated with [^{3}H]-semax (50 µg/kg, IN) (Shevchenko et al. 2006b). The highest concentrations of semax in the brain were measured at 2 minutes after the treatment (the first time point of blood collection and brain harvesting) and represented approximately 0.072% of the administered dose [^{3}H]-semax. The highest ratio of brain-to-blood semax concentrations in rats treated intranasally with [^{3}H]-semax was approximately 0.67 (Shevchenko et al. 2006b).

Both the percentage of the semax dose that reached the rat brain and the ratio of brain-to-blood semax concentrations were considerably higher in rats treated intranasally than in rats treated intravenously with [^{3}H]-semax (Potaman et al. 1991b; Shevchenko et al. 2006b). The brain delivery of peptides administered intranasally is thought to be facilitated, at least in part, by their axonal transport through the direct pathway established by the olfactory receptor cells that are in contact with both the nasal cavity and the olfactory bulb, the main olfactory relay center in the brain (Lin et al. 2016; Spetter and Hallschmid 2015).

In-vitro studies reported that semax is quickly hydrolyzed in rat blood and brain tissue (Potaman et al. 1991a; Shevchenko et al. 2013). In-vivo studies reported that the metabolites identified in the blood of [^{3}H]-semax-treated rats were generated by the sequential proteolytic removal of amino acids from the N-terminal domain of semax (Potaman et al. 1991a; Shevchenko et al. 2006b). Figure 6 shows the amino acid sequences of semax metabolites identified in the brain and serum of [^{3}H]-semax-treated rats (Shevchenko et al. 2006b). The tripeptide proline-glycine-proline was the main metabolite identified in the blood and brain taken from [^{3}H]-semax-treated rats (Shevchenko et al. 2006b). In rat serum, aminopeptidases and angiotensin-converting enzyme are the main enzymes that catalyze the proteolytic degradation of semax (Potaman et al. 1993).

Figure 6. Amino Acid Sequences of Semax and Its Metabolites [Adapted From Shevchenko et al. 2006].

Semax	Met – Glu – His – Phe – Pro – Gly – Pro
Sem-6	Glu – His – Phe – Pro – Gly – Pro
Sem-5	His – Phe – Pro – Gly – Pro
Sem-4	Phe – Pro – Gly – Pro
Sem-3	Pro + Gly – Pro + Pro – Gly – Pro

Left to right: Amino acid sequences from the N- to the C-terminus of the peptides. Glu: glutamic acid; Gly: glycine; His: histidine; Phe: phenylalanine; Pro: proline. All are L-amino acids.

At the time of this evaluation, the nominator did not submit, and FDA did not identify studies assessing the pharmacokinetic profile of semax delivered via the SC ROA.

c. Acute Toxicity[58]

At the time of this evaluation, the nominator did not submit, and FDA did not identify acute toxicity studies of semax.

d. Repeat-Dose Toxicity[59]

At the time of this evaluation, the nominator did not submit, and FDA did not identify repeat-dose toxicity studies of semax.

e. Genotoxicity[60]

At the time of this evaluation, FDA did not identify additional studies assessing the genotoxic potential of semax.

---

[58] Acute toxicity refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). For more information on general approaches for acute toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

[59] Repeat-dose toxicity studies consist of in-vivo animal studies that seek to evaluate the toxicity of the test substance when it is repetitively administered daily for an extended period. For more information on general approaches for repeat-dose toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

[60] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems. For more information on general approaches for genotoxicity studies, please refer to FDA's guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012), available at https://www.fda.gov/media/71980/download.

f. Developmental and Reproductive Toxicity[61]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical developmental and reproductive studies of semax.

g. Carcinogenicity[62]

The effects of long-term treatment with semax on the frequency and size of spontaneous mammary tumors have been assessed in female SHK mice (Meshavkin et al. 2013). SHK mice are reported to develop a high frequency of mammary tumors and have a considerably shorter mean lifespan (~12.5 months) than other mouse strains, including CBA and C3HA (~21 months) (Emanuel et al. 1976).

In the study by Meshavkin and collaborators, SHK female mice already had pronounced mammary gland tumors when they were assigned to treatment with vehicle (saline, 0.2 mL/day, IP; n=27) or semax (3 mg/kg/day, IP; n=16) 5 days/week until the end of their natural life. The authors did not provide the age of the mice at start of treatment. However, it is likely that mice were ~11 months old when their treatments started because: (i) the mean lifespan of saline-treated mice in the study by Meshavkin and colleagues was ~44 days (Meshavkin et al. 2013), and (ii) the mean lifespan of SHK mice is reported to be ~12.5 months (Emanuel et al. 1976).

The late-life treatment of SHK mice with semax significantly reduced the size of their mammary gland tumors. Specifically, at end of life, the sizes of mammary gland tumors were 7.4±1.6 cm^3 in semax-treated mice and 15.0±2.0 cm^3 in saline-treated mice. The semax treatment also prolonged the mean lifespan of SHK mice by ~68%. Although the authors concluded that semax may have anticarcinogenic properties (Meshavkin et al. 2013), the data should be interpreted with caution because: (i) the study tested a fixed dose of semax, and, as such, did not provide an assessment of dose-response relationships, (ii) the study assessed the effects of semax only in female (not male) mice, and (iii) the semax treatment was short lived with respect to the lifespan of the animals.

---

[61] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects of a substance within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of a substance on pre-, peri-, and postnatal development. Developmental toxicity or teratogenicity refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth. For more information on general approaches for reproductive and developmental toxicity studies, please refer to FDA's guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021), available at https://www.fda.gov/media/148475/download.

[62] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to cause tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life. For more information on general approaches for carcinogenicity studies, please refer to FDA's guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* (July 1997), available at https://www.fda.gov/media/71935/download.

The study by Meshavink and colleagues is not adequately designed to assess the carcinogenic potential of semax. In a typical nonclinical carcinogenic study, male and female rodents are treated daily with the test article for a minimum of 2 years. As discussed by Haseman and colleagues, rodent carcinogenicity studies in which treatments only last 12 to 18 months (instead of ≥24 months) would be equivalent to evaluating human cancer in 30- to 50-year-old subjects and would, therefore, result in markedly reduced sensitivity to detect the carcinogenic potential of an exposure (Haseman et al. 2001). Considering the finding that female SHK mice with growing mammary tumors lived for 73.7±10.5 days following the start of the semax treatment, the mean duration of the treatment was shorter than 3 months.

In November 2022, FDA published the guidance entitled *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals*, which discusses the use of a weight-of-evidence analysis to assess the human carcinogenic potential of pharmaceuticals.[63] This analysis, which takes into account the primary and off-target mechanisms of action as well the potential genetic, hormonal, and immunomodulatory effects of the test article in addition to its metabolic profile, may be used in lieu of nonclinical carcinogenicity studies to inform the carcinogenic potential of the article.

At the time of this evaluation, the nominator did not submit, and FDA did not identify weight-of-evidence analyses or nonclinical 2-year carcinogenicity studies to inform the carcinogenic potential for semax.

Conclusions: From the nonclinical pharmacological perspective, semax is a substance that exhibits pleiotropism. Acting through poorly understood mechanisms of action, semax in rodents: (i) has neuroprotective and neurotrophic properties, (ii) acts as an anticoagulant and antithrombotic, (iii) has analgesic properties, and (iv) induces antidepressant- and anxiolytic-like effects. The nonclinical finding that the serotoninergic antagonist cyproheptadine inhibited semax-induced analgesia in mice led to the proposal that the analgesic effect of semax depends, at least in part, on semax-induced activation of the serotoninergic system. It is concerning, however, that, in mice, semax also potentiated amphetamine-induced dopamine release in the striatum because increased dopaminergic tone in the striatum is a response typically induced by drugs of abuse such as cocaine. At the time of this evaluation, the nominator did not submit, and FDA did not identify published nonclinical toxicity studies to assess the pharmacokinetic profile of semax via the nominated SC ROA and to inform the abuse potential and other safety considerations for possible clinical uses of semax.

2. Human Safety

In addition to the references submitted by the nominator, the following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FAERS, ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites. The clinical references discuss an active moiety the authors call semax but these references do not specify whether the substance used was a free base or a salt.

---

[63] *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals: Guidance for Industry* (November 2022), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s1br1-addendum-s1b-testing-carcinogenicity-pharmaceuticals.

Therefore, when discussing these references, the substance will be referred to as semax (the term that was used by the authors).

a. Pharmacokinetic Data

We were not able to find pharmacokinetic studies in humans following exposure to semax (free base) or semax acetate via any ROA.

b. Reported Adverse Reactions (FAERS, Case Reports and Anecdotal Cases Assessing Safety)

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for semax-related BDSs, through December 3, 2025[64]. The search retrieved one FAERS report (#25343150). This was a direct report from a consumer. The consumer reported that in May 2024 she experienced ocular pain and eye burning after using Semax 0.1% nasal drops purchased online from a company called CosmicNootropic. The consumer reported hospitalization following the exposure and that the eye pain had not resolved as of the time of the report in May 2025. OSE also conducted two literature searches of PubMed through February 27, 2024, and from February 27, 2024 through December 3, 2025, and did not identify literature case reports of AEs in humans.

c. Clinical Studies Assessing Safety

We were unable to find literature that discussed administration via subcutaneous injection ROA. The only ROA discussed in the literature was intranasal. Therefore, assessment of safety for semax was limited to the intranasal ROA. Based on two references submitted by the nominator and six references found by FDA, semax has been administered to 33-47 healthy adults[65], 69 adults with medical conditions (including chronic ischemic brain disease, pain due to migraine and trigeminal neuralgia, and peptic ulcer), and 451 children with either depression or tics/Tourette Syndrome. The references do not discuss the type of device that was used to administer the substance via this ROA. Additional information regarding critical attributes of the device to assess product safety and effectiveness are discussed in Section II.A.1.e and Section I.A.2.e. Doses were 0.5 mg/kg once, 1 mg daily for 2 days, 600 mg daily for 10 days, or 2-4 drops per nostril three times a day for 10 days. Three of the references were professional society meeting abstracts and details of the full studies conducted in all the pediatric subjects and in adults with chronic ischemic brain disease were not available. In one reference the authors report that no AEs were observed[66] and in the other references AEs were not discussed.[67] One reference (Cherkasova et al. 2002) discussed possible anti-thrombotic properties of semax and this raises concern about the risk of bleeding, particularly in certain populations at risk for

---

[64] Compounders under section 503A of the FD&C Act generally do not report adverse events to FDA. FDA encourages compounders, health care professionals, and consumers to report adverse events and product quality concerns associated with compounded drugs to FDA's MedWatch Adverse Event Reporting program. Unless an adverse event report is submitted to FDA, the Agency may not be aware of adverse events associated with a product compounded under section 503A.

[65] It is unclear if the same subjects were used in Lebedeva et al. 2018 and Panikratova et al. 2020.

[66] Koroleva et al. 1996.

[67] Cherkasova et al. 2002, Kaplan et al. 1996, Ivanikov et al. 2002, Proskurina et al. 2018, Aminova et al. 2016, Lebedeva et al. 2018, Panikratova et al. 2020.

bleeding or if combined with other medications that increase bleeding risk. In several of the references, semax was administered concomitantly with other medications or therapies[68], making it difficult to determine the contribution of semax to any effects seen. Details of the individual studies can be found in Table 3 below.

Table 3. Summary of References With Safety Information.

Reference	Population	Intervention	AE
Cherkasova et al. 2002[a, b]	Subjects with chronic ischemic brain disease[d]	IN semax 600 mg daily for 10 days	AEs not discussed
Koroleva et al. 1996[b]	37 adults with pain (trigeminal neuralgia, dental plexalgia, and migraine)	IN semax 0.5 mg/kg given once	Authors reported no AEs
Kaplan et al.1996	19 healthy adult males	IN semax 1 mg (16 mcg/kg) daily for 2 days or IN semax 0.25 mg given once	AEs not discussed
Ivanikov et al. 2002	32 adults with peptic ulcer	Semax 1% solution, 2-4 drops per nostril TID for 10 days + basic therapy (omeprazole 20 mg BID + denol 20 mg TID + socolseril 2 IM) vs. basic therapy only	AEs not discussed
Proskurina et al. 2018[a]	120 children ages 12-14 years with depression	Semax 0.1% + cognitive behavioral therapy + low-power physiotherapy (electromagnetic radiation of millimeter range)	AEs not discussed
Aminova et al. 2016[a]	331 children with tics and Tourette Syndrome	Encephabol + semax + neuroleptics	AEs not discussed
Lebedeva et al. 2018	14 healthy adults	IN semax (1.2 mg)	AEs not discussed
Panikratova et al. 2020[c]	14 healthy adults	IN semax (1.2 mg)	AEs not discussed

[a] These references were meeting abstracts and full information about the studies were not available.
[b] These references were submitted by the nominators.
[c] The subjects who received semax treatment in this study appear to be very similar to those subjects who received semax in Lebedeva et al. 2018. It is unclear if the same subjects were used in both studies.
[d] The authors did not specify the number of subjects in this abstract.

d. Other Safety Information (e.g., Relevant Safety Information From Other Regulatory Agencies as Appropriate)

No additional safety information from other regulatory agencies was found.

Immunogenicity and Aggregation Concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[69] The guidance describes immunogenicity as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins including endogenous

[68] Ivanikov et al. 2002, Proskurina et al. 2018, Aminova et al. 2016.
[69] See FDA's guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) at https://www.fda.gov/media/85017/download.

proteins or peptides, or to induce immunologically related adverse clinical events. Although this guidance addresses therapeutic protein products, the concerns about immunogenicity are also relevant to peptides (such as semax (free base) and semax acetate), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via the SC or nasal spray ROA.

The consequences of triggering an immune response may range from antibody responses with no apparent clinical manifestations to life-threatening and catastrophic reactions. Such outcomes are often unpredictable in patients administered therapeutic protein or peptide products. One possible consequence of the development of an immune response is the development of neutralizing antibody activity that may lead to loss of efficacy or even result in the neutralization of the activity of the endogenous peptide counterpart.

In addition, compared to small molecule APIs, peptides are distinct because they may have an inherent tendency to aggregate. Aggregation refers to the processes through which peptides associate into larger species consisting of multiple peptide chains. Aggregates can be highly ordered or amorphous and the formation can be reversible or irreversible (Zapadka et al. 2017). Peptides with as few as two amino acids have been shown to aggregate (Frederix et al. 2011). Aggregates can impact the pharmacology of the peptide. In addition, aggregation is a risk factor in immunogenicity and for decreased pharmacotherapeutic effect of the drug product due to effects on bioavailability, formation of precipitates, or anti-drug antibody production (Ratanji et al. 2014).

The nominators did not provide, and FDA did not identify clinical studies assessing immunogenicity or aggregation of semax (free base) or semax acetate. Although semax (free base) and semax acetate consist of seven amino acids, FDA is concerned about their potential for immunogenicity when administered by an injection ROA as proposed due to the potential for aggregation as well as potential peptide-related impurities. Based on available information there are insufficient data to conclude that semax (free base) or semax acetate does not present these risks.

e. Therapies That Have Been Used for the Condition(s) Under Consideration

There are FDA-approved drug products and/or OTC monograph drug products that treat the same medical condition as that proposed for the semax-related compounded drug product(s)[70]. See the lists of FDA-approved products for each proposed use in Sections II.C.1.c, II.C.2.c, and II.C.3.c.

Conclusions: There is insufficient clinical information to characterize the safety profile of semax (free base) or semax acetate. We were not able to find pharmacokinetic studies in humans following exposure to semax (free base) or semax acetate via any ROA. There are no safety data for semax (free base) and semax acetate administered by the proposed SC ROA. The only ROA discussed in the literature was intranasal. It is not clear which BDS was used in the clinical

[70] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling. See 84 FR 4696.

studies as the references do not specify whether the semax used was a free base or a salt form (such as semax acetate).

Based on available clinical information for semax (free base) and semax acetate, the use of semax-related bulk drug substances in compounding may raise safety concerns. Most of the references did not discuss safety. One reference (Cherkasova et al. 2002) discussed possible anti-thrombotic properties of semax and this raises concern about the risk of bleeding, particularly in certain populations at risk for bleeding or if combined with other medications that increase bleeding risk. Compounded drugs do not include labeling that would adequately warn physicians and patients of such risks.

The nominators did not provide, and FDA did not identify clinical studies assessing immunogenicity or aggregation of semax (free base) or semax acetate. Although semax (free base) and semax acetate consists of seven amino acids, FDA is concerned about their potential for immunogenicity when administered by an injection ROA as proposed due to the potential for aggregation as well as potential peptide-related impurities.Based on available information there are insufficient data to conclude that semax (free base) or semax acetate does not present these risks.

There are currently available FDA-approved drugs for treatment and prevention of cerebral ischemia, migraine, and trigeminal neuralgia.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate semax (free base) and semax acetate for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** semax (free base) or semax acetate being placed on that list based on the following:

1. Conclusions on the physical and chemical characterization for each semax-related BDS, semax (free base) and semax acetate, are included in subsections 1.1 and 1.2.

   1.1.

   Semax (free base) is reported to be a heptapeptide. As reported in the literature, semax (free base) is expected to be stable under reported storage conditions (below -20°C)

   Semax (free base) is considered to be not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) BDS specific quality control attributes, including impurities, aggregates, bacterial endotoxins and microbial bioburden testing, were not found in the publicly available scientific literature and lack of CoA in the nominations which are offered as evidence to establishing identity, purity, and impurity profiles of the substance of semax (free base) delivered via the SC and intranasal spray ROAs. The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.D.2.d., FDA is concerned about the potential for immunogenicity of semax (free base) when formulated in an injectable or intranasal spray dosage forms due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.1.c. We also note that the

stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

In addition, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about container closer system, including container, closer, and pump – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

1.2.

Semax acetate is reported to be an acetate salt of semax (free base). As reported in the literature, semax acetate is expected to be stable under reported storage conditions.

Semax acetate is not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) certain critical characterization data specific to semax acetate (including impurities, aggregates, microbial bioburden and/or bacterial endotoxin) were not found in the publicly available scientific literature, and the CoAs provided, which were offered as evidence to establishing identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, microbial and bacterial endotoxins). The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.D.2.d., FDA is concerned about the potential for immunogenicity of semax acetate when formulated in an injectable dosage form for SC administration as well as in intranasal spray dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.2.c. The nominations did not include, and FDA has not identified, information about semax acetate to suggest that this substance does not present these risks. Therefore, we cannot rule out potential immunogenicity issues associated with peptide and peptide-related impurities aggregates. In addition, it is difficult to evaluate how the physicochemical characteristics of semax acetate, especially the water solubility of semax acetate, will impact on the performance of the proposed injectable and intranasal spray products due to lack of water solubility data for semax acetate. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

In addition, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about container closer system, including container, closer, and pump – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

2. It is often unclear whether the semax discussed in the sources considered for an understanding of historical use in compounding is the salt form or the free base. Semax injection and intranasal products are widely marketed in the US through health/wellness clinics, medical concierge services, functional and regenerative medicine clinics, and online retailers for anxiety, depression, attention/memory improvement, ischemic events/stroke, nerve regeneration, diabetic neuropathy, ADHD, opioid withdrawal, ALS, Parkinson's disease, Alzheimer's disease, dys-circulatory encephalopathy, optic nerve atrophy, pain, and

gastric protection. The extent to which semax has been used in compounding is unclear. Semax is a registered drug in Russia and is available as 0.1% and 1% nasal drops.

3. From the nonclinical pharmacological perspective, semax is a substance that exhibits pleiotropism. Acting through poorly understood mechanisms of action, semax in rodents: (i) has neuroprotective and neurotrophic properties, (ii) acts as an anticoagulant and antithrombotic, (iii) has analgesic properties, and (iv) induces antidepressant- and anxiolytic-like effects. The nonclinical finding that the serotoninergic antagonist cyproheptadine inhibited semax-induced analgesia in mice led to the proposal that the analgesic effect of semax depends, at least in part, on semax-induced activation of the serotoninergic system. It is concerning, however, that, in mice, semax also potentiated amphetamine-induced dopamine release in the striatum because increased dopaminergic tone in the striatum is a response typically induced by drugs of abuse such as cocaine. At the time of this evaluation, the nominator did not submit, and FDA did not identify published nonclinical toxicity studies to assess the pharmacokinetic profile of semax via the nominated SC ROA and to inform the abuse potential and other safety considerations for possible clinical uses of semax.

   There is insufficient clinical information to characterize the clinical safety profile of semax (free base) or semax acetate. We were not able to find pharmacokinetic studies in humans following exposure to semax (free base) or semax acetate via any ROA. There are no safety data for semax (free base) and semax acetate administered by the proposed SC ROA. The only ROA discussed in the literature was intranasal. It is not clear which BDS was used in the clinical studies as the references do not specify whether the semax used was a free base or a salt form (such as semax acetate).

   Based on available clinical information for semax (free base) and semax acetate, the use of semax-related bulk drug substances in compounding may raise safety concerns. Most of the references did not discuss safety. One reference (Cherkasova et al. 2002) discussed possible anti-thrombotic properties of semax and this raises concern about the risk of bleeding, particularly in certain populations at risk for bleeding or if combined with other medications that increase bleeding risk. Compounded drugs do not include labeling that would adequately warn physicians and patients of such risks.

   The nominators did not provide, and FDA did not identify clinical studies assessing immunogenicity or aggregation of semax (free base) or semax acetate. Although semax (free base) and semax acetate consists of seven amino acids, FDA is concerned about their potential for immunogenicity when administered by an injection ROA as proposed due to the potential for aggregation as well as potential peptide-related impurities. Based on available information there are insufficient data to conclude that semax (free base) or semax acetate does not present these risks.

   There are currently available FDA-approved drugs for treatment and prevention of cerebral ischemia, migraine, and trigeminal neuralgia.

4. There is insufficient evidence to support the effectiveness for semax (free base) or semax acetate for cerebral ischemia, migraine, or trigeminal neuralgia. Only two available references with insufficient details on the design and conduct of the studies were available,

and the available references demonstrated lack of effectiveness and were limited by small sample size, and lack of information about some relevant clinical endpoints. Cerebral ischemia, migraine and trigeminal neuralgia are all serious conditions and FDA-approved therapies for the acute treatment and prevention of these conditions exist.

On balance, the physicochemical characterization, information on historical use, lack of evidence of effectiveness, and safety information identified for both semax (free base) and semax acetate weigh against them being added to the 503A Bulks List. In particular, FDA's proposal is based on the fact that semax (free base) and semax acetate are not well characterized from a physiochemical perspective due to lack of certain critical characterization data specific to semax forms regarding lack of endotoxin data for injectable routes of administration and information to indicate how an appropriate container and pump for an intranasal spray product would be selected and qualified. There is a lack of information on the safety profile for semax (free base) and semax acetate where the use of semax-related bulk drug substances in compounding may raise safety concerns as discussed above. In addition, FDA also did not identify information that addresses additional concerns related to potential immunogenicity risk. We have insufficient evidence of effectiveness to support the use of semax-related BDSs as a treatment for cerebral ischemia, migraine and trigeminal neuralgia. The lack of evidence of effectiveness discussed above and the existence of FDA-approved drugs to treat most of these conditions weighs against semax-related BDSs being added to the 503A Bulks List. Accordingly, we propose not adding semax (free base) or semax acetate to the 503A Bulks List.

IV. REFERENCES

Agapova, TY, YV Agniullin, M Shadrina, S Shram, P Slominsky, S Lymborska and N Myasoedov, 2007a, Neurotrophin Gene Expression in Rat Brain under the Action of Semax, an Analogue of ACTH4-10, Neurosci Lett, 417(2):201-205.

Agapova TY, YV Agniullin, D Silachev, M Shadrina, P Slominsky, S Shram, S Limborskaya and N Myasoedov, 2007b, Expression Changes Caused by the Peptide Semax in the Intracellular Signal Pathway Genes in Rat Hippocampus, Dokl Biochem Biophys, 417(1):334-336.

Ailani, J, R Burch and M Robbins, 2021, The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice, Headache, 61(7):1021-1039.

Aminova, D, 2016, Cognitive Impairments in Children with Tic Disorders and Tourette Syndrome, Mov Dis, 31, Supp 2, Abstract # 966:S1-S697

Bakaeva, Z, K Baglikova, P Klimova, L Andreeva and G Samonina, 2009, The Comparison of Gastroprotective Properties of Semax and Its Metabolites, Mosc Univ Biol Sci Bull, 64:137-140.

Bakhmet, A and E Koplik, 2012, Antistress Effect of Semax in the Course of Recovery of Spleen Lymphoid Structures after the Stress in Rats with Different Behavioral Activity, Bull Exp Biol Med (USSR) (Engl Transl), 153:661-663.

Bashkatova, VG, VB Koshelev, OE Fadyukova, AA Alexeev, AF Vanin, KS Rayevsky, IP Ashmarin and DM Armstrong, 2001, Novel Synthetic Analogue of ACTH 4-10 (Semax) but Not Glycine Prevents the Enhanced Nitric Oxide Generation in Cerebral Cortex of Rats with Incomplete Global Ischemia, Brain Res, 894(1):145-149.

Boyarshinova, O, O Perepelkina, N Markina and I Poletaeva, 2008, Audiogenic Epilepsy in Young Mice of Different Strains after Neonatal Semax Treatment, Bull Exp Biol Med (USSR) (Engl Transl), 146(1):86.

Broderick, J, O Adeoye, J Elm, 2017, The Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials, Stroke, 48(7):2007-2012.

Cherkasova, K, I Ashmarin, A Kubatiev and V Skvortsova, 2002, Neuropeptide Semax – Effective Antithrombotic Drug, Eur Neuropsychopharmacol, 12(Supp 3):406-407.

Cherkasova, K, L Lyapina and I Ashmarin, 2001, Comparative Study of Modulatory Effects of Semax and Primary Proline-Containing Peptides on Hemostatic Reactions, Bull Exp Biol Med (USSR) (Engl Transl), 132:625-626.

Chong M, A Bahra and J Zakrzewsja, 2023, Guidelines for the Management of Trigeminal Neuralgia, Cleveland Clin J Med, 90(6):355-362.

Deigin, VI, EA Poluektova, AG Beniashvili, SA Kozin and YM Poluektov, 2022, Development of Peptide Biopharmaceuticals in Russia, Pharmaceutics, 14(4): 716.

DeSai, C and A Shapshack, 2023, Cerebral Ischemia, StatPearls, NCBI Bookshelf, National Library of Medicine, National Institute of Health: 1-12.

Dolotov, OV, EA Karpenko, LS Inozemtseva, TS Seredenina, NG Levitskaya, J Rozyczka, EV Dubynina, EV Novosadova, LA Andreeva and LY Alfeeva, 2006, Semax, an Analog of ACTH (4-10) with Cognitive Effects, Regulates BDNF and TRKb Expression in the Rat Hippocampus, Brain Res, 1117(1):54-60.

Emanuel, N, L Obukhova, T Bunto and V D'yakova, 1976, Kinetics of Survival and Experimental Determination of the Aging Rate, Biol Bull Acad Sci USSR, 3(4-6):653-657.

Eremin, K, V Kudrin, I Grivennikov, N Miasoedov and K Rayevsky, 2004, Effects of Semax on Dopaminergic and Serotoninergic Systems of the Brain, Dokl Biol Sci, 394(1):1-3.

Eremin, KO, VS Kudrin, P Saransaari, SS Oja, IA Grivennikov, NF Myasoedov and KS Rayevsky, 2005, Semax, an ACTH (4-10) Analogue with Nootropic Properties, Activates Dopaminergic and Serotoninergic Brain Systems in Rodents, Neurochem Res, 30(12):1493-1500.

Frederix, PW, RV Ulijn, NT Hunt and T Tuttle, 2011, Virtual Screening for Dipeptide Aggregation: Toward Predictive Tools for Peptide Self-Assembly, J Phys Chem Lett, 2(19):2380-2384.

Glazova, NY, N Levitskaya and L Andreeva, 2005, P. 5.013 Study of Neurotropic Effects Ofsemax Analogues Depending on Their Structure, Eur Neuropsychopharmacol, (15):S207.

Grigorjeva, M and L Lyapina, 2010, Anticoagulation and Antiplatelet Effects of Semax under Conditions of Acute and Chronic Immobilization Stress, Bull Exp Biol Med (USSR) (Engl Transl), 149(1):44-47.

Gusev, E, M Martynov, E Kostenko, L Petrova and S Bobyreva, 2018, The Efficacy of Semax in the Treatment of Patients at Different Stages of Ischemic Stroke, Zh Nevrol Psikhiatr Im S S Korsakova, 118 (3. Vyp.2): 61.

Gusev, E, V Skvortsova and E Chukanova, 2005, Semax in Prevention of Disease Progress and Development of Exacerbations in Patients with Cerebrovascular Insufficiency, Zh Nevrol Psikhiatr Im S S Korsakova, 105(2):35-40.

Gusev, E, V Skvortsova, N Miasoedov, V Nezavibat'ko, E Zhuravleva and A Vanichkin, 1997, Effectiveness of Semax in Acute Period of Hemispheric Ischemic Stroke (A Clinical and Electrophysiological Study) Zh Nevrol Psikhiatr Im S S Korsakova / Ministerstvo zdravookhraneniia i meditsinskoĭ promyshlennosti Rossiĭskoĭ Federatsii, Vserossiĭskoe obshchestvo nevrologov [i] Vserossiĭskoe obshchestvo psikhiatrov. 15:26–34.

Inozemtsev, A, A Agapitova, S Bokieva, N Levitskaya, A Kamenskii and N Myasoedov, 2013, Semax Prevents Functional Impairments of Avoidance Response in Rats, Dokl Biol Sci, 448(1):1.

Inozemtsev, A, S Bokieva, O Karpukhina, K Gumargalieva, A Kamensky and N Myasoedov, 2016, Semax Prevents Learning and Memory Inhibition by Heavy Metals, Dokl Biol Sci, 468:112-114.

Ivanikov I, M Brekhova, G Samonina, N Myasoedov and I Ashmarin, 2002, Therapy of Peptic Ulcer with Semax Peptide, Bull Exp Biol Med, 134 (1): 73-74.

Ivanova, D, N Levitskaya, L Andreeva, LY Alfeeva, A Kamenskii and N Myasoedov, 2003, The Effect of Semax on Animal Pain Sensitivity in Various Experimental Models, Dokl Biol Sci, 388:5-8.

Ivanova, D, N Levitskaya, L Andreeva, A Kamenskii and N Myasoedov, 2007, Comparative Study of Analgesic Potency of ACTH 4-10 Fragment and Its Analog Semax, Bull Exp Biol Med (USSR) (Engl Transl), 143:5-8.

Ivanova, D, D Vilensky, N Levitskaya, L Andreeva and A Kamensky, 2004, P. 2.16 ACTH (4-10) Analogue Semax Attenuates Opioid-Induced Analgesia, Eur Neuropsychopharmacol, (14):S32-S33.

Ivanova, D, D Vilensky, N Levitskaya, L Andreeva and A Kamensky, 2005, P. 4.037 Study of Mechanisms of the ACTH (4-10) Analogue Semax Analgesic Activity, Eur Neuropsychopharmacol, (15):S192-S193.

Johnston, S, M Nguyen-Huynh, M Schwarz, K Fuller, C Williams and S Josephson, 2006, National Stroke Association Guidelines for the Management of Transient Ischemic Attacks, Ann Neurol, 60:301-313.

Kaplan, A, A Kochetovaa, V Nezavibathko, T Rjasina and I Ashmarin, 1996, Synthetic ACTH Analogue Semax Displays Nootropic-Like Activity in Humans, Neurosci Res Comm, 19(2): 115-123.

Kleindorfer, D, A Towfighi, S Chaturvedi, K Cockroft, J Gutierrez, D Lombardi-Hill, H Kamel, W. Kernan, S Kittner, E Leira, O Lennon, J Meschia, T Nguyen, P Pollak and P Santangeli, 2021, 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack, Stroke, 52(7):e364-467.

Kolik, L, A Nadorova and M Kozlovskaya, 2014, Efficacy of Peptide Anxiolytic Selank During Modeling of Withdrawal Syndrome in Rats with Stable Alcoholic Motivation, Bull Exp Biol Med (USSR) (Engl Transl), 157:52-55.

Kolomin, T, M Shadrina, P Slominsky, S Limborska and N Myasoedov, 2013, A New Generation of Drugs: Synthetic Peptides Based on Natural Regulatory Peptides, Neurosci Med, 4(04):223.

Kopylova, G, E Smirnova, LT Sanzhieva, B Umarova, T Lelekova and G Samonina, 2003, Glyprolines and Semax Prevent Stress-Induced Microcirculatory Disturbances in the Mesentery, Bull Exp Biol Med (USSR) (Engl Transl), 136:441-443.

Koroleva, M, E Meizerov, V Nezavibat'ko, A Kamenskii, V Dubynin and YB Yakovlev, 1996, Analgesic Action of the New Drug Semax, Bull Exp Biol Med (USSR) (Engl Transl), 122:1107-1109.

Kost, N, OY Sokolov, M Gabaeva, I Grivennikov, L Andreeva, N Myasoedov and A Zozulya, 2001, Semax and Selank Inhibit the Enkephalin-Degrading Enzymes of Human Serum, Russian J Bioorg Chem, 27(3):156-159.

Lebedeva, I, YR Panikratova, OY Sokolov, D Kupriyanov, A Rumshiskaya, N Kost and N Myasoedov, 2018, Effects of Semax on the Default Mode Network of the Brain, Bull Exp Biol Med (USSR) (Engl Transl), 165(5):653-656.

Levitskaya, N, D Vilenskii, E Sebentsova, L Andreeva, A Kamensky and N Myasoedov, 2010, Influence of Semax on the Emotional State of White Rats in the Norm and against the Background of Cholecystokinin-Tetrapeptide Action, Biol Bull, 37:186-192.

Lin, T, E Liu, H He, MC Shin, C Moon, VC Yang and Y Huang, 2016, Nose-to-Brain Delivery of Macromolecules Mediated by Cell-Penetrating Peptides, Acta Pharm Sin B, 6(4):352-358.

Lyapina, L, V Pastorova, TY Obergan, G Samonina, I Ashmarin and N Myasoedov, 2006, Comparison of Anticoagulant Effects of Regulatory Proline-Containing Oligopeptides. Specificity of Glyprolines, Semax, and Selank and Potential for Their Practical Application, Biol Bull, 33:153-161.

Malyshev, A, E Razumkina, V Dubynin and N Myasoedov, 2013, Semax Corrects Brain Dysfunction Caused by Prenatal Introduction of Valproic Acid, Dokl Biochem Sci, 450(1):126.

Manchenko, D, NY Glazova, N Levitskaya, L Andreeva, A Kamenskii and N Myasoedov, 2012, The Nootropic and Analgesic Effects of Semax Given Via Different Routes, Neurosci Behav Physiol, 42:264-270.

Medvedeva, EV, VG Dmitrieva, OV Povarova, SA Limborska, VI Skvortsova, NF Myasoedov and LV Dergunova, 2014, The Peptide Semax Affects the Expression of Genes Related to the Immune and Vascular Systems in Rat Brain Focal Ischemia: Genome-Wide Transcriptional Analysis, BMC Genomics, 15:1-12.

Meshavkin, V, N Kost, OY Sokolov, YA Zolotarev, N Myasoedov and A Zozulya, 2006, Naloxone-Blocked Depriming Effect of Anxiolytic Selank on Apomorphine-Induced Behavioral Manifestations of Hyperfunction of Dopamine System, Bull Exp Biol Med (USSR) (Engl Transl), 142:598-600.

Meshavkin, VK, NV Kost, OY Sokolov, LA Andreeva and NF Myasoedov, 2013, The Influence of Oligopeptides on Spontaneous Carcinogenesis in Mice, Dokl Biol Sci, 449:79-81.

Miasoedova, N, V Skvortsova, E Nasonov, E Zhuravleva, I Grivennikov, E Arsen'eva and I Sukhanov, 1999, Investigation of Mechanisms of Neuroprotective Effect of Semax in Acute Period of Ischemic Stroke, Zhurnal nevrologii i psikhiatrii imeni SS Korsakova / Ministerstvo zdravookhraneniia i meditsinskoĭ promyshlennosti Rossiĭskoĭ Federatsii, Vserossiĭskoe obshchestvo nevrologov [i] Vserossiĭskoe obshchestvo psikhiatrov, 15:15-19.

Orlov, A, A Khomutov, I Mukhina, YB Zimin, S Parin and D Kozin, 1999, Effect of Semax and Semax-Heparin Mixture on Isolated Heart Activity after Total Ischemia in Rats, Bull Exp Biol Med (USSR) (Engl Transl), 128:1084-1086.

Panikratova, YR, IS Lebedeva, OY Sokolov, AD Rumshiskaya, DA Kupriyanov, NV Kost and NF Myasoedov, 2020, Functional Connectomic Approach to Studying Selank and Semax Effects, Dok Biol Sci: Proc Acad Sci USSR, Biol Sci Sec, 490(1): 9-11.

Ponomareva-Stepnaya, MA, VN Nezavibat'ko, LV Antonova, LA Andreeva, LY Alfeeva, VN Potaman, AA Kamenskii and IP Ashmarin, 1984, An Analog of $ACTH_{4-10}$ – A Long-Action Stimulator of Learning, Pharm Chem J, 18: 445-450.

Potaman, V, L Alfeeva, A Kamensky, N Levitzkaya and V Nezavibatko, 1991a, N-Terminal Degradation of ACTH (4–10) and Its Synthetic Analog Semax by the Rat Blood Enzymes, Bioch Biophys Res Comm, 176(2):741-746.

Potaman, VN, LY Alfeeva, AA Kamensky and VN Nezavibatko, 1993, Degradation of ACTH/MSH(4-10) and Its Synthetic Analog Semax by Rat Serum Enzymes: An Inhibitor Study, Peptides, 14(3):491-495.

Potaman, V, L Antonova, V Dubynin, D Zaitzev, A Kamensky, N Myasoedov and V Nezavibatko, 1991b, Entry of the Synthetic ACTH (4-10) Analogue into the Rat Brain Following Intravenous Injection, Neurosci Lett, 127(1):133-136.

Powers W, A Rabinstein, T Ackerson, O Adeoye, N Bambakidis, K Becker, J Biller, M Brown, B Demaerschalk, B Hoh, E Jauch, C Kidwell, T Leslie-Mazwi, B Ovboagele, P Scott, K Sheth, A Southerland, D Summers and D Tirschwell, 2019, Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association, Stroke, 50 (12): e344-e418.

Proskurina, T, E Mykhailova and T Matkovska, 2018, Some Questions of Therapy of Vegetative Disorders in Children and Adolescents with Depression, 26th European Congress of Psychiatry, E-Poster, 48S:S359–S566.

Ratanji, KD, JP Derrick, RJ Dearman and I Kimber, 2014, Immunogenicity of Therapeutic Proteins: Influence of Aggregation, J Immunotoxicol, 11(2):99-109.

Romanova, G, D Silachev, F Shakova, YN Kvashennikova, I Viktorov, S Shram and N Myasoedov, 2006, Neuroprotective and Antiamnesic Effects of Semax During Experimental Ischemic Infarction of the Cerebral Cortex, Bull Exp Biol Med (USSR) (Engl Transl), 142:663-666.

Safarova, E, S Shram, I Grivennikov and N Myasoedov, 2002, Trophic Effects of Nootropic Peptide Preparations Cerebrolysin and Semax on Cultured Rat Pheochromocytoma, Bull Exp Biol Med (USSR) (Engl Transl), 133:401-403.

Severyanova, L, A Kryukov, D Plotnikov and M Dolgintsev, 2020, Peptide ACTH4-7-Pgp: Effects on Various Types of Pain and Pain-Induced Behavior in Rats after Systemic and Central Administration, Bull Exp Biol Med (USSR) (Engl Transl), 170(2):185-190.

Shevchenko, KV, I Nagaev, L Alfeeva, LA Andreeva, AA Kamenskiĭ, NG Levitskaia, VP Shevchenko, IA Grivennikov and NF Miasoedov, 2006a, [Kinetics of Semax Penetration into the Brain and Blood of Rats after Its Intranasal Administration], Bioorg Khim, 32(1):64-70.

Shevchenko, K, IY Nagaev, LY Alfeeva, L Andreeva, A Kamenskii, N Levitskaya, V Shevchenko, I Grivennikova and N Myasoedov, 2006b, Kinetics of Semax Penetration into the Brain and Blood of Rats after Its Intranasal Administration, Russ J Bioorg Chem, 32:57-62.

Shevchenko, K, IY Nagaev, L Andreeva, V Shevchenko and N Myasoedov, 2013, Stability of Semax Acetyl to Proteolysis in Various Biological Media, Dokl Biol Sci, 449(1):110.

Silachev, D, S Shram, F Shakova, G Romanova and N Myasoedov, 2009, Formation of Spatial Memory in Rats with Ischemic Lesions to the Prefrontal Cortex; Effects of a Synthetic Analog of ACTH (4-7), Neurosci Behav Physiol, 39(8):749-756.

Sims, SK, B Wilken-Resman, CJ Smith, A Mitchell, L McGonegal and C Sims-Robinson, 2022, Brain-Derived Neurotrophic Factor and Nerve Growth Factor Therapeutics for Brain Injury: The Current Translational Challenges in Preclinical and Clinical Research, Neural Plast, 2022:3889300.

Slominsky, P, M Shadrina, T Kolomin, A Stavrovskaya, E Filatova, L Andreeva, S Illarioshkin and N Myasoedov, 2017, Peptides Semax and Selank Affect the Behavior of Rats with 6-OHDA Induced PD-Like Parkinsonism, Dokl Biol Sci, 474:106-109.

Solov'ev, V, M Gengin, A Stolyarov, O Solov'eva, M Begutov and O Lyubchenko, 2016, The Activities of Basic Carboxypeptidases in the Nervous System of Rats During Exercise Stress and in Response to Semax and Selank, Neurochem J, 10:59-63.

Spetter, MS and M Hallschmid, 2015, Intranasal Neuropeptide Administration to Target the Human Brain in Health and Disease, Mol Pharm, 12(8):2767-2780.

Stavchansky, VV, VV Yuzhakov, AY Botsina, VI Skvortsova, LN Bondurko, MG Tsyganova, SA Limborska, NF Myasoedov and LV Dergunova, 2011, The Effect of Semax and Its C-End Peptide PGP on the Morphology and Proliferative Activity of Rat Brain Cells During Experimental Ischemia: A Pilot Study, J Mol Neurosci, 45:177-185.

Tarasov VV, NV Kudryashov, VN Chubarev, TS Kalinina, GE Barreto, GM Ashraf, G Aliev, 2018, Pharmacological Aspects of Neuro-Immune Interactions, Curr Pharmac Des, 24(1):15-21.

Tsai SJ, 2007, Semax, An Analogue of Adrenocorticotropin (4-10), is a Potential Agent for the Treatment of Attention-deficit Hyperactivity Disorder and Rett Syndrome, Med Hyp, 68(5): 1144-1146.

Vlasova, I, D Buravtcov and A Saletsky, 2009, Luminescence Analysis of Blood Components in Studies of the Neuroprotective Properties of the Drug "Semax" in Cerebral Ischemia, J Appl Spec, 76:121-126.

Volkow, ND, G-J Wang, F Telang, JS Fowler, J Logan, A-R Childress, M Jayne, Y Ma and C Wong, 2006, Cocaine Cues and Dopamine in Dorsal Striatum: Mechanism of Craving in Cocaine Addiction, J Neurosci, 26(24):6583-6588.

Volodina, M, E Sebentsova, NY Glazova, N Levitskaya, L Andreeva, D Manchenko, A Kamensky and N Myasoedov, 2012, Semax Attenuates the Infl Uence of Neonatal Maternal Deprivation on the Behavior of Adolescent White Rats, Bull Exp Biol Med (USSR) (Engl Transl), 152(5):560-563.

Zapadka, KL, Becher FJ, Gomes Dos Santos AL and Jackson SE, 2017, Factors Affecting the Physical Stability (Aggregation) of Peptide Therapeutics, Interface Focus, 7(6).

V. APPENDICES

APPENDIX 1: TREATMENTS FOR STROKE

Table A. FDA-Approved Drug Products for Stroke.

Treatment Type	Class	Name of Product	ROA
Acute	Tissue plasminogen activator (tPA)	Alteplase	IV
Prevention	Aldosterone antagonist	Spironolactone	Oral
Prevention	Aldosterone antagonist	Carospir	Oral
Prevention	Aldosterone antagonist	Eplerenone	Oral
Prevention	Alpha-adrenergic blocker	Doxazosin mesylate	Oral
Prevention	Alpha-adrenergic blocker	Doxazosin	Oral
Prevention	Angiotensin 2 receptor blocker	Azilsartan kamedoxomil	Oral
Prevention	Angiotensin 2 receptor blocker	Candesartan	Oral
Prevention	Angiotensin 2 receptor blocker	Cadesartan Cilexetil	Oral
Prevention	Angiotensin 2 receptor blocker	Irbesartan	Oral
Prevention	Angiotensin 2 receptor blocker	Losartan	Oral
Prevention	Angiotensin 2 receptor blocker	Losartan potassium	Oral
Prevention	Angiotensin 2 receptor blocker	Olmesartan medoxomil	Oral
Prevention	Angiotensin 2 receptor blocker	Prexxartan	Oral
Prevention	Angiotensin 2 receptor blocker	Telmisartan	Oral
Prevention	Angiotensin 2 receptor blocker	Valsartan	Oral
Prevention	Angiotensin-converting enzyme inhibitor	Benazepril hydrochloride	Oral
Prevention	Angiotensin-converting enzyme inhibitor	Enalapril	Oral
Prevention	Angiotensin-converting enzyme inhibitor	Enalapril maleate	Oral
Prevention	Angiotensin-converting enzyme inhibitor	Lisinopril	Oral
Prevention	Angiotensin-converting enzyme inhibitor	Ramipril	Oral
Prevention	Beta-adrenergic blocker	Metoprolol	Oral
Prevention	Beta-adrenergic blocker	Metoprolol succinate	Oral
Prevention	Beta-adrenergic blocker	Metoprolol tartrate	Oral
Prevention	Beta-adrenergic blocker	Nebibolol	Oral
Prevention	Beta-adrenergic blocker	Nebivolol	Oral
Prevention	Beta-adrenergic blocker	Nebivolol hydrochloride	Oral
Prevention	Beta-adrenergic blocker	Propranolol hydrochloride	Oral
Prevention	Biguanide; sodium-glucose cotransporter 2 inhibitor	Canagliflozin and metformin hydrochloride	Oral
Prevention	Calcium channel blocker	Diltiazem hydrochloride	Oral
Prevention	Calcium channel blocker	Verapamil hydrochloride	Oral
Prevention	Calcium channel blocker	Amlodipine	Oral
Prevention	Dihydropyridine calcium channel blocker	Amlodipine besylate	Oral
Prevention	Direct thrombin inhibitor	Dabigatran etexilate	Oral
Prevention	Direct thrombin inhibitor	Dabigatran etexilate mesylate	Oral
Prevention	Factor Xa inhibitor	Apixaban	Oral
Prevention	Factor Xa inhibitor	Edoxaban tosylate	Oral
Prevention	Factor Xa inhibitor	Rivaroxaban	Oral
Prevention	GLP-1 receptor agonist	Dulaglutide	SC
Prevention	GLP-1 receptor agonist	Liraglutide	SC
Prevention	GLP-1 receptor agonist	Semaglutide	SC

Treatment Type	Class	Name of Product	ROA
Prevention	HMG-CoA reductase inhibitor	Atorvaliq	Oral
Prevention	HMG-CoA reductase inhibitor	Atorvastatin calcium	Oral
Prevention	HMG-CoA reductase inhibitor	Pravastatin sodium	Oral
Prevention	HMG-CoA reductase inhibitor	Rosuvastatin	Oral
Prevention	HMG-CoA reductase inhibitor	Rosuvastatin calcium	Oral
Prevention	HMG-CoA reductase inhibitor	Simvastatin	Oral
Prevention	Loop diuretic	Torsemide	Oral
Prevention	NSAID; platelet aggregation inhibitor	Acetylsalicylic acid	Oral
Prevention	NSAID; platelet aggregation inhibitor	Aspirin and dipyridamole	Oral
Prevention	P2Y12 platelet inhibitor	Clopidogrel	Oral
Prevention	P2Y12 platelet inhibitor	Clopidogrel Bisulfate	Oral
Prevention	P2Y12 platelet inhibitor	Prasugrel	Oral
Prevention	P2Y12 platelet inhibitor	Prasugrel hydrochloride	Oral
Prevention	P2Y12 platelet inhibitor	Ticagrelor	Oral
Prevention	PCSK9 inhibitor	Alirocumab	SC
Prevention	PCSK9 inhibitor	Evolocumab	SC
Prevention	Protease-activated receptor antagonist	Vorapaxar	Oral
Prevention	Renin inhibitor	Aliskirin	Oral
Prevention	Renin inhibitor	Aliskirin hemifumarate	Oral
Prevention	Sodium-glucose cotransporter 2 inhibitor	Canagliflozin	Oral
Prevention	Vitamin K antagonist	Warfarin	Oral
Prevention	Vitamin K antagonist	Warfarin sodium	Oral

APPENDIX 2: TREATMENTS FOR MIGRAINE

Table B. FDA-Approved Prescription Drug Products for Migraine.

Treatment Type	Class	Name of Product	ROA
Acute	Nonsteroidal anti-inflammatory drug	Celecoxib	Oral
Acute	Nonsteroidal anti-inflammatory drug	Diclofenac potassium	Oral
Acute	Opioid agonist	Fentanyl	Buccal, sublingual
Acute	Opioid agonist	Fentanyl Citrate	Oral, buccal, sublingual, transmucosal, nasal
Acute	Serotonin 1b and 1d receptor agonists	Almotriptan	Oral
Acute	Serotonin 1b and 1d receptor agonists	Almotriptan malate	Oral
Acute	Serotonin 1b and 1d receptor agonists	Almotriptan malate	Oral
Acute	Serotonin 1b and 1d receptor agonists	Eletriptan hydrobromide	Oral
Acute	Serotonin 1b and 1d receptor agonists	Frovatriptan succinate	Oral
Acute	Serotonin 1b and 1d receptor agonists	Naratriptan	Oral
Acute	Serotonin 1b and 1d receptor agonists	Rizatriptan	Oral
Acute	Serotonin 1b and 1d receptor agonists	Rizatriptan benzoate	Oral
Acute	Serotonin 1b and 1d receptor agonists	Sumatriptan	Oral, SC, nasal
Acute	Serotonin 1b and 1d receptor agonists	Sumatriptan succinate	Oral, SC
Acute	Serotonin 1b and 1d receptor agonists	Zolmitriptan	Oral, nasal
Acute	Ergotamine derivative	Dihydroergotamine mesylate	Nasal
Acute	Calcitonin gene-related peptide receptor antagonist	Atogepant	Oral
Acute	Calcitonin gene-related peptide receptor antagonist	Rimegepant sulfate	Oral
Acute	Calcitonin gene-related peptide receptor antagonist	Ubrogepant	Oral
Acute	Calcitonin gene-related peptide receptor antagonist	Zavegepant	Nasal
Acute	Serotonin (5-HT) 1F receptor agonist	Lasmiditan	Oral
Preventative	Anti-epileptic	Divalproex sodium	Oral
Preventative	Anti-epileptic	Topiramate	Oral
Preventative	Anti-epileptic	Valproate sodium	IV
Preventative	Anti-epileptic	Valproic acid	Oral
Preventative	Beta blocker	Propranolol hydrochloride	Oral

Treatment Type	Class	Name of Product	ROA
Preventative	Calcitonin gene-related peptide antagonist	Eptinezumab-JJMR	IV
Preventative		Erenumab-AOOE	SC
Preventative	Calcitonin gene-related peptide antagonist	Fremanezumab-VFRM	SC
Preventative	Calcitonin gene-related peptide antagonist	Galcanezumab-GNLM	SC
Preventative	Acetylcholine release inhibitor; neuromuscular blocker	Onabotulinumtoxina	Intradermal, IM

Table C. Non-Prescription Drugs for Migraine.

Product Type	Name of Product	ROA
Single API	Ibuprofen (e.g., Advil Migraine, Motrin IB migraine)	Oral
Combination of APIs	Acetaminophen + Aspirin + Caffeine (e.g., Excedrin migraine)	Oral

Semax – Related Bulk Drug Substances (Semax (free base) and Semax acetate) Nominations

International Peptide Society Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Semax
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	H-Met-Glu-DL-His-Phe-Pro-Gly-Pro-OH or L-methionyl-L-alpha-glutamyl-DL-histidyl-L-phenylalanyl-L-prolyl-glycyl-L-proline
Common Name(s)	Pro-Gly-Pro-ACTH (4-7), ACTH (4-7), prolyl-glycyl-proline-, ACTH (4-7)
UNII Code	I5FAL2585H
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of AX Pharmacueticals Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	Russian Pharmacopoeia
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Intranasal Spray
Compounded Strengths	7,500 mcg/ml, 1,000 mcg/ml
Anticipated Routes of Administration	Intranasal Spray
Saftey & Efficacy Data	Koroleva, M.V. et al., 1996. Analgesic action of the new drug Semax. Bulletin of Experimental Biology and Medicine, 122(5), pp.1107–1109. Available at: http://dx.doi.org/10.1007/bf02447659
	Grigorjeva, M.E. & Lyapina, L.A., 2010. Anticoagulation and Antiplatelet Effects of Semax under Conditions of Acute and Chronic Immobilization Stress. Bulletin of Experimental Biology and Medicine, 149(1), pp.44–46. Available at: http://dx.doi.org/10.1007/s10517-010-0871-x.
	Bakhmet, A.A. & Koplik, E.V., 2012. Antistress Effect of Semax in the Course of Recovery of Spleen Lymphoid Structures after the Stress in Rats with Different Behavioral Activity. Bulletin of Experimental Biology and Medicine, 153(5), pp.661–663. Available at: http://dx.doi.org/10.1007/s10517-012-1792-7.

	Boyarshinova, O.S. et al., 2008. Audiogenic epilepsy in young mice of different strains after neonatal semax treatment. Bulletin of Experimental Biology and Medicine, 146(1), pp.86–88. Available at: http://dx.doi.org/10.1007/s10517-008-0212-5.
	Ivanova, D.M. et al., 2007. Comparative study of analgesic potency of ACTH4–10 fragment and its analog semax. Bulletin of Experimental Biology and Medicine, 143(1), pp.5–8. Available at: http://dx.doi.org/10.1007/s10517-007-0002-5.
	Cherkasova, K.A., et al., 2001. Comparative Study of Modulatory Effects of Semax and Primary Proline-Containing Peptides on Hemostatic Reactions. Bulletin of Experimental Biology and Physiology, 132(1), 625-626. https://www.ncbi.nlm.nih.gov/pubmed/11687836.
	Lyapina, L.A. et al., 2006. Comparison of anticoagulant effects of regulatory proline-containing oligopeptides. Specificity of glyprolines, semax, and selank and potential for their practical application. Biology Bulletin, 33(2), pp.153–161. Available at: http://dx.doi.org/10.1134/s1062359006020099.
	Orlov, A.V. et al., 1999. Effect of semax and semax-heparin mixture on isolated heart activity after total ischemia in rats. Bulletin of Experimental Biology and Medicine, 128(5), pp.1084–1086. Available at: http://dx.doi.org/10.1007/bf02433405.
	Eremin, K.O. et al., 2004. Effects of Semax on Dopaminergic and Serotoninergic Systems of the Brain. Doklady Biological Sciences, 394(1-6), pp.1–3. Available at: http://dx.doi.org/10.1023/b:dobs.0000017114.24474.40.
	Kolik, L.G., Nadorova, A.V. & Kozlovskaya, M.M., 2014. Efficacy of Peptide Anxiolytic Selank during Modeling of Withdrawal Syndrome in Rats with Stable Alcoholic Motivation. Bulletin of Experimental Biology and Medicine, 157(1), pp.52–55. Available at: http://dx.doi.org/10.1007/s10517-014-2490-4.
	Eremin, K.O. et al., 2005. Semax, An ACTH(4-10) Analogue with Nootropic Properties, Activates Dopaminergic and Serotoninergic Brain Systems in Rodents. Neurochemical Research, 30(12), pp.1493–1500. Available at: http://dx.doi.org/10.1007/s11064-005-8826-8.
	Agapova, T.Y. et al., 2007. Expression changes caused by the peptide semax in the intracellular signal pathway genes in rat hippocamp. Doklady Biochemistry and Biophysics, 417(1), pp.334–336. Available at: http://dx.doi.org/10.1134/s1607672907060129.

	Kopylova, G.N. et al., 2003. Glyprolines and Semax Prevent Stress-Induced Microcirculatory Disturbances in the Mesentery. Bulletin of Experimental Biology and Medicine, 136(5), pp.441–443. Available at: http://dx.doi.org/10.1023/b:bebm.0000017087.90585.a9.
	Shevchenko, K.V. et al., 2006. Kinetics of semax penetration into the brain and blood of rats after its intranasal administration. Russian Journal of Bioorganic Chemistry, 32(1), pp.57–62. Available at: http://dx.doi.org/10.1134/s1068162006010055.
	Levitskaya, N.G. et al., 2010. Influence of semax on the emotional state of white rats in the norm and against the background of cholecystokinin-tetrapeptide action. Biology Bulletin, 37(2), pp.186–192. Available at: http://dx.doi.org/10.1134/s1062359010020147.
	Meshavkin, V.K. et al., 2006. Naloxone-blocked depriming effect of anxiolytic selank on apomorphine-induced behavioral manifestations of hyperfunction of dopamine system. Bulletin of Experimental Biology and Medicine, 142(5), pp.598–600. Available at: http://dx.doi.org/10.1007/s10517-006-0428-1.
	Cherkasova, K. et al., 2002. Neuropeptide semax — Effective antithrombotic drug. European Neuropsychopharmacology, 12, pp.406–407. Available at: http://dx.doi.org/10.1016/s0924-977x(02)80695-2.
	Romanova, G.A. et al., 2006. Neuroprotective and antiamnesic effects of Semax during experimental ischemic infarction of the cerebral cortex. Bulletin of Experimental Biology and Medicine, 142(6), pp.663–666. Available at: http://dx.doi.org/10.1007/s10517-006-0445-0.
	Agapova, T.Y. et al., 2007. Neurotrophin gene expression in rat brain under the action of Semax, an analogue of ACTH4–10. Neuroscience Letters, 417(2), pp.201–205. Available at: http://dx.doi.org/10.1016/j.neulet.2007.02.042
	Ivanova, D.M. et al., 2004. P.2.16 ACTH(4–10) analogue SEMAX attenuates opioid-induced analgesia. European Neuropsychopharmacology, 14, pp.S32–S33. Available at: http://dx.doi.org/10.1016/s0924-977x(04)90039-9.
	Glazova, N.Y., Levitskaya, N.G. & Andreeva, L.A., 2005. P.5.013 Study of neurotropic effects ofSemax analogues depending on their structure. European Neuropsychopharmacology, 15, p.S207. Available at: http://dx.doi.org/10.1016/s0924-977x(05)80415-8.

	Ivanova, D.M. et al., 2005. P.4.037 Study of mechanisms of the ACTH(4–10) analogue SEMAX analgesic activity. European Neuropsychopharmacology, 15, pp.S192–S193. Available at: http://dx.doi.org/10.1016/s0924-977x(05)80390-6.
	Slominsky, P.A. et al., 2017. Peptides semax and selank affect the behavior of rats with 6-OHDA induced PD-like parkinsonism. Doklady Biological Sciences, 474(1), pp.106–109. Available at: http://dx.doi.org/10.1134/s0012496617030048.
	Malyshev, A.V. et al., 2013. Semax corrects brain dysfunction caused by prenatal introduction of valproic acid. Doklady Biological Sciences, 450(1), pp.126–129. Available at: http://dx.doi.org/10.1134/s0012496613030046.
	Inozemtsev, A.N. et al., 2013. Semax prevents functional impairments of avoidance response in rats. Doklady Biological Sciences, 448(1), pp.1–3. Available at: http://dx.doi.org/10.1134/s0012496613010018.
	Inozemtsev, A.N. et al., 2016. Semax prevents learning and memory inhibition by heavy metals. Doklady Biological Sciences, 468(1), pp.112–114. Available at: http://dx.doi.org/10.1134/s0012496616030066.
	Tsai, S.-J., 2007. Semax, an analogue of adrenocorticotropin (4–10), is a potential agent for the treatment of attention-deficit hyperactivity disorder and Rett syndrome. Medical Hypotheses, 68(5), pp.1144–1146. Available at: http://dx.doi.org/10.1016/j.mehy.2006.07.017.
	Lebedeva, I.S. et al., 2018. Effects of Semax on the Default Mode Network of the Brain. Bulletin of Experimental Biology and Medicine, 165(5), pp.653–656. Available at: http://dx.doi.org/10.1007/s10517-018-4234-3.
	Shevchenko, K.V. et al., 2013. Stability of Semax acetyl to proteolysis in various biological media. Doklady Biological Sciences, 449(1), pp.110–112. Available at: http://dx.doi.org/10.1134/s0012496613020166.
	Solov'ev, V.B. et al., 2016. The activities of basic carboxypeptidases in the nervous system of rats during exercise stress and in response to semax and selank. Neurochemical Journal, 10(1), pp.59–63. Available at: http://dx.doi.org/10.1134/s1819712416010141.

	Bakaeva, Z.V. et al., 2009. The comparison of gastroprotective properties of Semax and its metabolites. Moscow University Biological Sciences Bulletin, 64(4), pp.137–140. Available at: http://dx.doi.org/10.3103/s0096392509040014.
	Stavchansky, V.V. et al., 2010. The Effect of Semax and Its C-End Peptide PGP on the Morphology and Proliferative Activity of Rat Brain Cells During Experimental Ischemia: A Pilot Study. Journal of Molecular Neuroscience, 45(2), pp.177–185. Available at: http://dx.doi.org/10.1007/s12031-010-9421-2.
	Ivanova, D.M. et al., 2003. The Effect of Semax on Animal Pain Sensitivity in Various Experimental Models. Doklady Biological Sciences, 388, 5-8. https://www.ncbi.nlm.nih.gov/pubmed/12712960.
	Tsai, S.-J., 2007. Semax, an analogue of adrenocorticotropin (4–10), is a potential agent for the treatment of attention-deficit hyperactivity disorder and Rett syndrome. Medical Hypotheses, 68(5), pp.1144–1146. Available at: http://dx.doi.org/10.1016/j.mehy.2006.07.017.
	Manchenko, D.M. et al., 2012. The Nootropic and Analgesic Effects of Semax Given via Different Routes. Neuroscience and Behavioral Physiology, 42(3), pp.264–270. Available at: http://dx.doi.org/10.1007/s11055-012-9562-6.
	Safarova, E.R. et al., 2002. Trophic Effects of Nootropic Peptide Preparations Cerebrolysin and Semax on Cultured Rat Pheochromocytoma. Bulletin of Experimental Biology and Medicine, 133(4), 401-3. https://www.ncbi.nlm.nih.gov/pubmed/12124658.
	Vlasova, I.M., Buravtcov, D.E. & Saletsky, A.M., 2009. Luminescence analysis of blood components in studies of the neuroprotective properties of the drug “Semax” in cerebral ischemia. Journal of Applied Spectroscopy, 76(1), pp.121–126. Available at: http://dx.doi.org/10.1007/s10812-009-9141-y.
Used Previously to compound drug products	Yes
Proposed use	ADHD
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Added as an attachment

AX Pharmaceutical Corp

CERTIFICATE OF ANALYSIS

Semax Acetate

Lot Number	D325-18I12SH	**MFG Date**	Sept 12, 2018
Molecular Formula	$C_{37}H_{51}N_9O_{10}S$	**Retest Date**	Sept 12, 2020
CAS Number	80714-61-0	**Batch QTY**	10G
Storage: Keep the product frozen at temperature -20°C.			

Tests	**Specifications**	**Results**
Appearance	White powder	Conforms
Identification	MS: As per standard	Conforms
Single impurity (HPLC)	≤ 2.0%	< 2.0%
Acetate content (HPLC)	5.0% ~ 12.0%	6.37%
Peptide content	≥ 80.0%	88.78%
Water content	≤ 10.0%	2.00%
Amino acid composition	15% of theoretical	Conforms
Purity (HPLC)	≥ 98%	99.42%
MS (ESI)	Conforms	Conforms

Conclusion: The product complies with specifications.
Original Reference#: P180306-E013

Transcription:	**Issued by:**	**Approved by:**
Date:	**Date:**	**Date:**

Note: Non-finished form for pharmacy compounding only. The above information is based on our manufacturer's product Certificate of Analysis.

100 West Beaver Creek Road, Unit 12; Richmond Hill, ON L4B 1H4, Canada
Email: sales@axpharmacetuical.com; Tel: (289)842-3088/(905)886-4994; Fax: (416) 352-1618

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
Contact Phone	**352-622-2913**
Contact Email	**ACampbell@wellsrx.com**

503A Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	Semax
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.	YES
Is the ingredient listed in any of the three sections of the Orange Book?	NO
Were any drug monographs for the ingredient found in the USP or NF monographs?	NO
What is the chemical name of the substance?	**IUPAC Name:** L-methionyl-L-alpha-glutamyl-DL-histidyl-L-phenylalanyl-L-prolyl-glycyl-L-proline $C_{37}H_{51}N_9O_{10}S$
What is the common name of the substance?	Semax 80714-61-0 Pro-gly-pro-acth (4-7) ACTH (4-7), Pro-Gly-Pro- ACTH (4-7), prolyl-glycyl-proline-
Does the substance have a UNII code?	I5FAL2585H
What is the chemical grade of the substance?	Provided by FDA Registered Supplier/COA

What is the strength, quality, stability, and purity of the ingredient?	Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Russian Pharmacopoeia
Has information been submitted about the substance to the USP for consideration of drug monograph development?	YES
What dosage form(s) will be compounded using the bulk drug substance?	Intranasal Spray Subcutaneous Injection
What strength(s) will be compounded from the nominated substance?	7,500 mcg/mL 1,000 mcg/ml
What is the anticipated route(s) of administration of the compounded drug product(s)?	Intranasal Spray Subcutaneous Injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Eremin KO, Kudrin VS, Saransaari P, et al. Semax, an ACTH(4-10) analogue with nootropic properties, activates dopaminergic and serotoninergic brain systems in rodents. *Neurochem Res*. 2005;30(12):1493-1500. doi:10.1007/s11064-005-8826-8 Eremin KO, Kudrin VS, Grivennikov IA, Miasoedov NF, Rayevsky KS. Effects of Semax on dopaminergic and serotoninergic systems of the brain. *Dokl Biol Sci*. 2004;394:1-3. doi:10.1023/b:dobs.0000017114.24474.40 Koroleva, M.V., Meizerov, E.E., Nezavibat'ko, V.N. *et al.* Analgesic action of the new drug Semax. *Bull Exp Biol Med* 122, 1107–1109 (1996). doi:10.1007/BF02447659 Shevchenko KV, Nagaev IIu, Alfeeva LIu, et al. [Kinetics of Semax penetration into the brain and blood of rats after its intranasal administration] *Bioorg Khim*. Jan/Feb 2006;32(1):64-70. doi:10.1134/s1068162006010055 Romanova GA, Silachev DN, Shakova FM, et al. Neuroprotective and antiamnesic effects of Semax during experimental ischemic infarction of the cerebral cortex. *Bull Exp Biol Med*. 2006;142(6):663-666. doi:10.1007/s10517-006-0445-0

Tsai SJ. Semax, an analogue of adrenocorticotropin (4-10), is a potential agent for the treatment of attention-deficit hyperactivity disorder and Rett syndrome. *Med Hypotheses*. 2007;68(5):1144-1146. doi:10.1016/j.mehy.2006.07.017

Lebedeva IS, Panikratova YR, Sokolov OY, et al. Effects of Semax on the Default Mode Network of the Brain. *Bull Exp Biol Med*. 2018;165(5):653-656. doi:10.1007/s10517-018-4234-3

Manchenko, D.M., Glazova, N.Y., Levitskaya, N.G. *et al.* The Nootropic and Analgesic Effects of Semax Given via Different Routes. *Neurosci Behav Physi* 42, 264–270 (2012). Doi: 10.1007/s11055-012-9562-6

Medvedeva EV, Dmitrieva VG, Povarova OV, et al. The peptide semax affects the expression of genes related to the immune and vascular systems in rat brain focal ischemia: genome-wide transcriptional analysis. *BMC Genomics*. 2014;15:228. Published 2014 Mar 24. doi:10.1186/1471-2164-15-228

Gusev EI, Martynov MY, Kostenko EV, Petrova LV, Bobyreva SN. Éffektivnost' semaksa pri lechenii bol'nykh na raznykh stadiiakh ishemicheskogo insul'ta [The efficacy of semax in the tretament of patients at different stages of ischemic stroke]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2018;118(3. Vyp. 2):61-68. doi:10.17116/jnevro20181183261-68

Vlasova, I.M., Buravtcov, D.E. & Saletsky, A.M. Luminescence analysis of blood components in studies of the neuroprotective properties of the drug “Semax” in cerebral ischemia. *J Appl Spectrosc* **76,** 121–126 (2009). doi: 10.1007/s10812-009-9141-y

Grigorjeva, M, Lyapina L. 2010. Anticoagulation and Antiplatelet Effects of Semax under Conditions of Acute and Chronic Immobilization Stress. *Bulletin of Experimental Biology and Medicine*, 149(1), pp.44–46. Available at: http://dx.doi.org/10.1007/s10517-010-0871-x.

Bakhmet, A.A. & Koplik, E.V., 2012. Antistress Effect of Semax in the Course of Recovery of Spleen Lymphoid Structures after the Stress in Rats with Different Behavioral Activity. Bulletin of Experimental Biology and Medicine, 153(5), pp.661–663. Available at: http://dx.doi.org/10.1007/s10517-012-1792-7.

Boyarshinova, O.S. et al., 2008. Audiogenic epilepsy in young mice of different strains after neonatal semax treatment. Bulletin of Experimental Biology and Medicine, 146(1), pp.86–88. Available at: http://dx.doi.org/10.1007/s10517-008-0212-5.

Ivanova, D.M. et al., 2007. Comparative study of analgesic potency of ACTH4–10 fragment and its analog semax. Bulletin of Experimental Biology and Medicine, 143(1), pp.5–8. Available at: http://dx.doi.org/10.1007/s10517-007-0002-5.

Cherkasova, K.A., et al., 2001. Comparative Study of Modulatory Effects of Semax and Primary
Proline-Containing Peptides on Hemostatic Reactions. Bulletin of Experimental Biology and Physiology, 132(1), 625-626. https://www.ncbi.nlm.nih.gov/pubmed/11687836.

Lyapina, L.A. et al., 2006. Comparison of anticoagulant effects of regulatory proline-containing oligopeptides. Specificity of glyprolines, semax, and selank and potential for their practical application. Biology Bulletin, 33(2), pp.153–161. Available at: http://dx.doi.org/10.1134/s1062359006020099

Orlov, A.V. et al., 1999. Effect of semax and semax-heparin mixture on isolated heart activity after total ischemia in rats. Bulletin of Experimental Biology and Medicine, 128(5), pp.1084–1086. Available at: http://dx.doi.org/10.1007/bf02433405

Kolik, L.G., Nadorova, A.V. & Kozlovskaya, M.M., 2014. Efficacy of Peptide Anxiolytic Selank during Modeling of Withdrawal Syndrome in Rats with Stable Alcoholic Motivation. Bulletin of Experimental Biology and Medicine, 157(1), pp.52–55. Available at: http://dx.doi.org/10.1007/s10517-014-2490-4.

Agapova, T.Y. et al., 2007. Expression changes caused by the peptide semax in the intracellular signal pathway genes in rat hippocamp. Doklady Biochemistry and Biophysics, 417(1), pp.334–336. Available at: http://dx.doi.org/10.1134/s1607672907060129.

Kopylova, G.N. et al., 2003. Glyprolines and Semax Prevent Stress-Induced Microcirculatory Disturbances in the Mesentery. Bulletin of Experimental Biology and Medicine, 136(5), pp.441–443. Available at:
http://dx.doi.org/10.1023/b:bebm.0000017087.90585.a9

Levitskaya, N.G. et al., 2010. Influence of semax on the emotional state of white rats in the norm and against the background of cholecystokinin-tetrapeptide action. Biology Bulletin, 37(2), pp.186–192. Available at:
http://dx.doi.org/10.1134/s1062359010020147

Meshavkin, V.K. et al., 2006. Naloxone-blocked depriming effect of anxiolytic selank on apomorphine-induced behavioral manifestations of hyperfunction of dopamine system. Bulletin of Experimental Biology and Medicine, 142(5), pp.598–600. Available at: http://dx.doi.org/10.1007/s10517-006-0428-1.

Cherkasova, K. et al., 2002. Neuropeptide semax — Effective antithrombotic drug. European Neuropsychopharmacology, 12, pp.406–407. Available at: http://dx.doi.org/10.1016/s0924-977x(02)80695-2.

Agapova, T.Y. et al., 2007. Neurotrophin gene expression in rat brain under the action of Semax, an analogue of ACTH4–10. Neuroscience Letters, 417(2), pp.201–205. Available at: http://dx.doi.org/10.1016/j.neulet.2007.02.042

Ivanova, D.M. et al., 2004. P.2.16 ACTH(4–10) analogue SEMAX attenuates opioid-induced analgesia. European Neuropsychopharmacology, 14, pp.S32–S33. Available at: http://dx.doi.org/10.1016/s0924-977x(04)90039-9

Glazova, N.Y., Levitskaya, N.G. & Andreeva, L.A., 2005. P.5.013 Study of neurotropic effects of Semax analogues depending on their structure. European Neuropsychopharmacology, 15, p.S207. Available at: http://dx.doi.org/10.1016/s0924-977x(05)80415-8

Ivanova, D.M. et al., 2005. P.4.037 Study of mechanisms of the ACTH(4–10) analogue SEMAX analgesic activity. European Neuropsychopharmacology, 15, pp.S192–S193. Available at: http://dx.doi.org/10.1016/s0924-977x(05)80390-6

Slominsky, P.A. et al., 2017. Peptides semax and selank affect the behavior of rats with 6-OHDA induced PD-like parkinsonism. Doklady Biological Sciences, 474(1), pp.106–109. Available at: http://dx.doi.org/10.1134/s0012496617030048

Malyshev, A.V. et al., 2013. Semax corrects brain dysfunction caused by prenatal introduction of valproic acid. Doklady Biological Sciences, 450(1), pp.126–129. Available at: http://dx.doi.org/10.1134/s0012496613030046.

Inozemtsev, A.N. et al., 2013. Semax prevents functional impairments of avoidance response in rats. Doklady Biological Sciences, 448(1), pp.1–3. Available at: http://dx.doi.org/10.1134/s0012496613010018

Inozemtsev, A.N. et al., 2016. Semax prevents learning and memory inhibition by heavy metals. Doklady Biological Sciences, 468(1), pp.112–114. Available at: http://dx.doi.org/10.1134/s0012496616030066

Shevchenko, K.V. et al., 2013. Stability of Semax acetyl to proteolysis in various biological media. Doklady Biological Sciences, 449(1), pp.110–112. Available at: http://dx.doi.org/10.1134/s0012496613020166

	Solov'ev, V.B. et al., 2016. The activities of basic carboxypeptidases in the nervous system of rats during exercise stress and in response to semax and selank. Neurochemical Journal, 10(1), pp.59–63. Available at: http://dx.doi.org/10.1134/s1819712416010141 Bakaeva, Z.V. et al., 2009. The comparison of gastroprotective properties of Semax and its metabolites. Moscow University Biological Sciences Bulletin, 64(4), pp.137–140. Available at: http://dx.doi.org/10.3103/s0096392509040014 Stavchansky, V.V. et al., 2010. The Effect of Semax and Its C-End Peptide PGP on the Morphology and Proliferative Activity of Rat Brain Cells During Experimental Ischemia: A Pilot Study. Journal of Molecular Neuroscience, 45(2), pp.177–185. Available at: http://dx.doi.org/10.1007/s12031-010-9421-2 Ivanova, D.M. et al., 2003. The Effect of Semax on Animal Pain Sensitivity in Various Experimental Models. Doklady Biological Sciences, 388, 5-8. https://www.ncbi.nlm.nih.gov/pubmed/12712960 Safarova, E.R. et al., 2002. Trophic Effects of Nootropic Peptide Preparations Cerebrolysin and Semax on Cultured Rat Pheochromocytoma. Bulletin of Experimental Biology and Medicine, 133(4), 401-3. https://www.ncbi.nlm.nih.gov/pubmed/12124658
Has the bulk drug substance been used previously to compound drug product(s)?	YES
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	ADHD, Cerebral Ischemia, Analgesia, Nootropic
What is the reason for use of a compounded drug product rather than an FDA-approved product?	no FDA-approved product available
Is there any other relevant information?	Added as an Attachment

DARMERICA

Certificate of Analysis

Semax Acetate

Product Name	: Semax Acetate	**Lot No.**	: DL5373
Mfg. Date	: Jun 20, 2020	**Exp. Date**	: Jun 19, 2023
M.F.	: $C_{37}H_{51}N_{9}O_{10}S$	**M.W.**	: 813.92
CAS No.	: 80714-61-0	**Batch Qty**	: 94 g
Sequence	: H-Met-Glu-His-Phe-Pro-Gly-Pro-OH		

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to almost white fluffy powder		White fluffy powder
Solubility	Soluble in water and acetic acid		Conform
Water (KF)	≤ 8.0%		5.7%
Acetic Acid (HPLC)	≤ 15.0%		3.2%
Amino Acid Composition	Met	0.9 - 1.1	1.0
	Glu	0.9 - 1.1	1.0
	His	0.9 - 1.1	0.9
	Phe	0.9 - 1.1	0.9
	Pro	1.8 - 3.02	2.1
	Gly	0.9 - 1.1	1.0
Peptide Purity (HPLC)	≥ 98.0%		99.9%
Related Substance (HPLC)	Total Impurities	≤ 2.0%	0.1%
	Largest Single Impurity	≤ 1.0%	0.1%
Residual Solvents	Acetonitrile	≤ 0.041%	< 0.041%
	Dichloromethane	≤ 0.060%	< 0.060%
	N,N-Dimethylformamide	≤ 0.088%	< 0.088%

Conclusion: The product is a synthetic peptide and meets the specifications.
Long Term Storage: Store in a sealed container at 2°C - 8°C in a fridge or freezer.
Distributed by Darmerica.

Based on the review of above information, the lot stands released.

	Name	Title	Signature	Date
Prepared by	Seka Nadima	Quality Assistant	Seka Nadima	08/21/2020
Released by	Sai Rasane	Quality Assistant	[signature]	08/24/2020

(0.943)(0.968)(0.999) = 91.19 %

9/29/2020

Darmerica LLC, 198 Wilshire Blvd., Casselberry, Florida 32707, USA; Tel: (321) 219-9111; Fax: (321) 219-9130