FDA Introductory Remarks

Pharmacy Compounding Advisory Committee Meeting

July 24, 2026

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Compounding Basics

- Compounded Drug Products
  - Are not FDA-approved, meaning they are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing
  - Can serve an important role for patients whose medical needs cannot be met by an FDA-approved drug product but at times have been associated with adverse events specific to the quality of the compounded drug product
  - Under 503A are primarily overseen by state regulators

503A Evaluation Process

- FDA evaluates:
  - Information provided by the nominator: proposed use(s), including any relevant peer-reviewed medical literature submitted in support of the proposed use(s)
  - Additional use(s) that are widespread, for serious conditions, or that pose serious risks to patients, as needed
  - Publicly available information from published medical literature, clinical guidelines, various databases/websites, etc.
- FDA assesses each substance according to four criteria:
  1. Physical and chemical characterization
  2. Safety issues raised by use in compounded products
  3. Available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance
  4. Historical use in compounded products

503A Evaluation Process

- Multidisciplinary evaluation team:
  - Office of Compounding Quality and Compliance
  - Office of New Drugs
  - Office of Pharmaceutical Quality

When a BDS is placed on the 503A Bulks List:

1. The compounded drug product is not FDA approved
2. A drug product compounded under Section 503A is not required to have a label to inform patients and providers how to use it
3. The compounded drug product is not required to comply with current good manufacturing practice however, the prohibition on insanitary conditions still applies
4. Compounders operating under section 503A are not required to report adverse events associated with compounded drug products to the FDA
5. Unless specific limitations are included on the entry, the bulk drug substance (BDS) can be compounded for any use or via any route of administration (dosage form)

Real World Evidence

- Real-world evidence:
  - The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data
  - Sources of real-world data can be analyzed in non-interventional studies, including registries, electronic health records (EHRs), and medical claims
  - Information on dispensing or patient use is not the same thing as real-world data or clinical evidence about the usage and potential benefits or risks of a medical product

Other Pathways for Study and Use

- Expanded Access Investigational New Drug Application
    - Presents opportunity to access an investigational medical product for patients with a serious or immediately life-threatening disease or condition who have no comparable or satisfactory alternative therapies
    - Goal is access for treatment use
- Clinical Trial under an Investigational New Drug Application
    - Provide necessary data to determine safety and effectiveness
    - Most efficient path to market and broad availability
    - Goal is research about the drug potentially leading to approval
- Not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List

Orphan Drug Designation

- Orphan Drug Designation
  - Designation as an orphan drug is a separate process from seeking FDA approval or licensure
  - A request for orphan drug designation must include a discussion of the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition
  - Drugs for rare diseases must still go through the same rigorous scientific review process as any other drug for approval or licensing
  - The process for evaluating bulk drug substances for inclusion on the 503A Bulks List is also a separate process from seeking FDA approval or licensure, but the considerations differ from those for orphan drug designation

July 24, 2026 PCAC Bulk Drug Substances

- July 24, 2026
  - Emideltide-related BDSs (Emideltide (free base) and Emideltide acetate)
  - Epitalon-related BDSs (Epitalon (free base) and Epitalon acetate)
  - Semax-related BDSs (Semax (free base) and Semax acetate)

FDA's Human Drug Compounding Website

Human Drug Compounding

Drug Compounding

Compounding is generally a practice in which a licensed pharmacist, a licensed physician or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.

Compounded drugs are not FDA approved, which means the agency does not review their safety, effectiveness or quality before they are marketed. Although compounded drugs can serve an important medical need for certain patients, they also may pose risks to patients.

FDA's compounding program aims to protect patients from poor-quality compounded drugs, while preserving access to lawfully-marketed compounded drugs for patients who have a medical need for them.

Email us: compounding@fda.hhs.gov

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Find information on FDA's compounding oversight and compliance actions

Get the latest information on policies and rules related to drug compounding


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Pharmacy Compounding Advisory Committee: Bulk Drug Substance (BDS) Discussion of Conflated Bulks and Common Name Challenges July 23 and 24, 2026

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Disclosure

- **This speaker has no conflicts of interest to disclose**

Rationale and Objectives

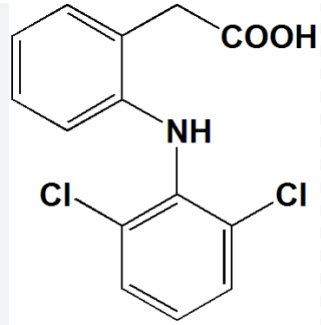
- In an evaluation(s) presented today, FDA will discuss multiple “related” but distinct bulk drug substances (BDSs) conflated in compounding nomination submissions
- We are also encountering significant challenges associated with the use of common or company names
- This is concerning because its not clear what is being nominated, compounded, or what substance patients are being dosed with
- Goals of this presentation
  - Discuss regulatory definitions for BDS, active pharmaceutical ingredient (API) and active moiety (AM) and how BDS differences have implications for the drug products made with them
  - Discuss challenges with company and common name BDS lacking United States Adopted Names Council (USAN)

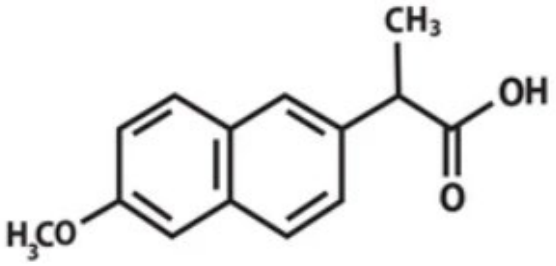
There Are Often Different BDS Forms…

- **Different salt and ester forms, as well as different active moiety**

- Diclofenac	- Naproxen
- Diclofenac Epolamine	- Naproxen Sodium
- Diclofenac Sodium	
- Diclofenac Potassium	

How many distinct BDSs and Active Moieties?





BDS/API Forms – Why Do They Exist?

- **The specific form of API used in a formulated product is typically chosen for its physical, chemical, or pharmacokinetic-pharmacodynamic (PK/PD) characteristics which renders it more suitable for drug product processing**
- **The selection can be dosage form-specific due to unique critical quality attributes (CQAs) associated with a dosage form**
- **Each of those forms is a distinct BDS under the FD&C Act**

Statute and Regulations

- **Per 21 CFR 207.3, a BDS is the same as an Active Pharmaceutical Ingredient (API):**

  "*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."

- **API is defined in FDA regulations at 21 CFR 207.1:**

  "*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."

What is an Active Moiety?

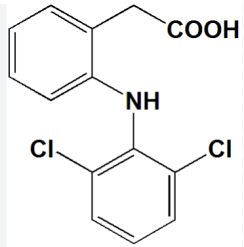
- **An active moiety is defined at 21 CFR 314.3:**

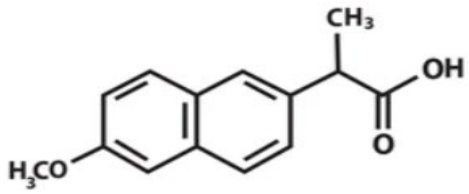
  "*Active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the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

Two Active Moieties and Six BDS

- Diclofenac	- Naproxen
- Diclofenac Epolamine	- Naproxen Sodium
- Diclofenac Sodium	
- Diclofenac Potassium	

All NSAIDs
6 Distinct BDSs
2 Active Moieties





Each of those 6 forms above is a distinct BDS and API under the FD&C Act

Why Does This Matter From Regulatory Perspective?

When FDA places a BDS on the 503A Bulks List through rulemaking, and a salt or ester of an active moiety is listed, only that particular salt or ester may be used.

The base compound and other salts or esters of the same active moiety must be evaluated for eligibility.

See, for example, 81 FR 91071.

Why Does This Matter From Patient's Perspective?

- Different salts, esters and the free base can have very different properties and toxicities
  - Physicochemical properties
    - Chemical formula/Molecular weight
    - Solid state stability
    - Solution stability
    - Solubility
    - Polymorphism
  - Pharmacology/Toxicology profile
  - PK/PD profile

- These definitions and distinctions are as important in compounding as they are in drug product manufacturing. This is not just a matter of regulations or definitions; this is a critical matter scientifically as these different forms have different chemical structures as well as different physical, chemical, PK/PD characteristics. This can impact patient safety and product efficacy.

Challenges with Unique Identifiers and Databases

- Global Substance Registration System (GSRS)
  - Used by multiple worldwide regulatory agencies
  - Home of the Unique Ingredient Identifier (UNII)

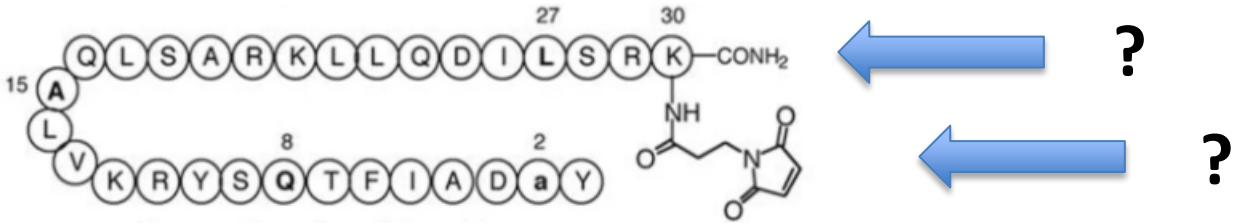
- Chemical Abstracts Services (CAS)
  - Home of unique identifier known as CAS Registry Number (CAS RN)

- Manufacturers/suppliers populate these databases
  - They provide structure and related information
  - Regulators do not own or police the data contained therein

Company and Common Name Challenges, and USAN

- Common or company names often used for experimental substances have no meaning
  - New forms are frequently synthesized as part of drug discovery process to mitigate toxicities or improve efficacy or other properties

- Multiple forms and derivatives of experimental substances do exist and might be sold under the same name
  - CJC-1295 for example



- This naming/identity problem is unique to the intersection of experimental substances and compounding
  - While not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List, the Investigational New Drug (IND) pathway helps to address this problem and provides patient access
    - Compounders can avail themselves to this pathway
  - USAN (or similar naming conventions) also addresses this issue

Physical and Chemical Characterization

- **[For] physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this *criterion weigh against its inclusion […] because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency*." *Emphasis added*.**
  - **2016 Proposed Rule, Docket No. FDA-2016-N-3464.**
  - **See 81 FR 91071**

Conclusion

- BDS is defined as the same as an API in the regulations and each distinct form is a distinct BDS each with unique physical, chemical and PK/PD characteristics which can impact patient safety and product efficacy
  - Our physical chemical characterization assessment and conclusion is specific to each unique BDS
- Nominators, BDS Manufacturers, and Compounders need to be aware of which single BDS is nominated, manufactured, and used to formulate a compounded product
- UNII and CAS# databases are not controlled by FDA
- Common and company names are highly problematic for experimental substances
  - USAN are useful to clearly identify for compounders, providers, and patients a specific substance
  - While not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List, establishing an IND to evaluate a substance of interest can provide patient access to a specified, well-characterized substance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Emideltide-related Bulk Drug Substances: Emideltide (Free Base) and Emideltide Acetate

Pharmacy Compounding Advisory Committee Meeting

July 24, 2026

Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration (FDA)

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Introduction

- Emideltide-related (also know as Delta Sleep Inducing Peptide, DSIP) bulk drug substances (BDSs) were nominated for inclusion on the list of BDSs that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)(503A Bulks List)
  - Emideltide (free base)
  - Emideltide acetate

- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for emideltide (free base) or its acetate form

- Neither is a component of an FDA-approved drug

Evaluation

- Emideltide-related BDSs were evaluated for:
  - Sleep disorders (chronic insomnia, narcolepsy)
  - Opioid withdrawal

- Proposed drug product:
  - 1000 mcg/mL (1 mg/mL) subcutaneous (SC) injection [injectable]

- The nominations were withdrawn, and FDA is evaluating these substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety concerns
- Historical use in compounding

BDS Nomenclature

- Emideltide is a common name and not a USAN, INN, or IUPAC name

- FDA has encountered multiple salts, and derivatives, including different active moieties, being marketed under the same common name
  - Inconsistent naming conventions can contribute to a potential safety risk for patients

- USAN program and other naming conventions exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

Summary of Basic Information on Emideltide (Free Base) and Emideltide Acetate

	Emideltide (free base)	Emideltide Acetate
UNII Code	YN28Z5YZ73	Not available
CAS No.	62568-57-4	Not available
MF/MW (g/mol)	$C_{35}H_{48}N_{10}O_{15}$ /848.814	$C_{35}H_{48}N_{10}O_{15}•C_2H_4O_2$/908.8
Peptide sequence	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu.CH_3CO_2H
Supplier	Yes	Yes
Active moeity	Emideltide (free base)	Emideltide (free base)

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

Summary of Information Submitted in the Withdrawn Nominations

Nominator	Nomination 1	Nomination 2
Nominated BDS	Emideltide	DSIP
BDS per UNII code	YN28Z5YZ73 (*matches emideltide free base*)	YN28Z5YZ73 (*matches emideltide free base*)
CoA	CoA provided for DSIP Acetate	CoA provided for DSIP free base
CAS No.	62568-57-4 (*matches emideltide free base*)	62568-57-4 (*matches emideltide free base*)
MF	$C_{35}H_{48}N_{10}O_{15}$ (*provided in the CoA, matches emideltide free base*)	$C_{35}H_{57}N_{13}O_{14}S_{24}S_2$ (*provided in the CoA, Does not correspond to any emideltide structure*)
MW	848.814 (*provided in the CoA, matches emideltide free base*)	848.814 (*provided in the CoA, matches emideltide free base*)
Chemical Name	H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-OH (*matches emideltide free base*)	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu (*matches emideltide free base*)
Proposed Products	Subcutaneous Injection, 1000 mcg/mL	Subcutaneous Injection, 1000 mcg/mL

Italics in the table above represents the information identified by the FDA.
CoA: Certificate of Analysis

Critical Quality Attributes (CQAs) for Nominated Dosage Form

Injection/subcutaneous injection:

- Bioburden load (i.e., microbial enumeration test)
- Bacterial endotoxins test (BET)
- Solubility

Physical and Chemical Characterization (1)

Emideltide Acetate:

- Acetate salt form of emideltide (free base), which is a synthetic nonapeptide
- Solid powder
- According to publicly available scientific literature, emideltide acetate is soluble in water at 10 mg/mL in phosphate buffered solution (PBS, pH7.2)
- No USP drug substance monograph
- BDS Storage and Stability:
  - Manufacturer recommends storing in sealed container at 2°C to 8°C in a fridge or freezer under dry conditions
  - Sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- The CoA provided:
  - No information regarding the nature of individual impurities. Such information also was not found from publicly available scientific literature.
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form

Physical and Chemical Characterization (3)

Conclusion: Emideltide acetate is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form due to potential for aggregation as well as peptide-related impurities

Physical and Chemical Characterization (4)

Emideltide (Free Base)

- A synthetic nonapeptide (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu)
- White crystalline or powder. Soluble in water at 0.5 mg/mL.
- Has no USP drug substance monograph
- BDS storage and stability:
  - Manufacturer recommends storing in sealed container at 0°C to 4°C for two years, or -20°C for three years under dry conditions.
  - Sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers

- In the CoA provided:
  - No information on impurity limits/testing results
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests

- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form

Physical and Chemical Characterization (6)

Conclusion: Emideltide (free base) is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Concern of limited water solubility (0.5 mg/mL)
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form due to potential for aggregation as well as peptide-related impurities

Emideltide (Free Base) or Emideltide Acetate

- The nonclinical and clinical references reviewed do not clearly identify whether the substance discussed is emideltide (free base) or emideltide acetate

- In the next sections, the substances will be generally referred to as emideltide or DSIP

General Pharmacology (1)

- Pharmacological effects of emideltide administered to animals include:
  - Increases in the power of electroencephalogram (EEG) delta waves and in EEG spindle activity, which are characteristic features of non-rapid eye movement (non-REM) sleep, in rabbits, cats, and rats (Kafi et al. 1979; Monnier et al. 1977a; Monnier et al. 1977b; Schoenenberger and Monnier 1977; Šušić et al. 1987; Ursin and Larsen 1983)
  - Prolongation of sleep duration in rabbits, cats, and rats, with differential effects on the duration of REM and non-REM sleep depending on route of administration and animal species (Polc et al. 1978; Šušić et al. 1987; Tobler and Borbély 1980; Ursin and Larsen 1983; Young and Key 1984)
  - Anticonvulsant and analgesic effects in rats and mice (Khvatova et al. 1995; Khvatova et al. 2003; Kovalzon and Strekalova 2006)

General Pharmacology (2)

- Mechanism of Action
  - The opioid antagonist naloxone inhibits emideltide-induced analgesia and prolongation of sleep duration in animals, suggesting that the pharmacological effects of emideltide involve activation of the opioid system (Young and Key 1984; Nakamura et al. 1988)
    - Emideltide does not appear to bind to or directly interact with opioid receptors (Nakamura et al. 1989)
    - Instead, via a calcium-dependent mechanism, emideltide facilitates the release of enkephalins from neurons in different brain regions (Nakamura et al. 1991)

Nonclinical Pharmacokinetics

- According to in-vivo and in-vitro studies:
  - Emideltide can cross the blood brain barrier and the blood-cerebral spinal fluid (CSF) barrier (Banks et al. 1982; Kastin et al. 1981; Zlokovic et al. 1988)
  - The half-life of emideltide is <10 min (Kato et al., 1984; Graf et al. 1987)
  - Emideltide is metabolized by reactions catalyzed by peptidases in blood and tissues (Graf et al. 1987; Huang and Lajtha 1978; Marks et al. 1977)

Chronic Insomnia

- Insomnia is defined as a complaint of trouble initiating or maintaining sleep, which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep (American Academy of Sleep Medicine (AASM))
- Chronic insomnia (disorder lasting > 3 months) is associated with numerous adverse effects on function, health, and quality of life
- Treatment strategies - cognitive behavioral therapy and pharmacologic treatment:
  - Benzodiazepines, nonbenzodiazepine sedative-hypnotics, ramelteon, doxepin, dual orexin receptor antagonists (DORAs)
  - FDA evaluated endpoints such as sleep latency (SL), sleep duration, sleep efficiency (SE), number of awakening (NOA) and patient reports
- AASM practice guidelines or American College of Physicians (ACP) practice guidelines do not mention emideltide for the treatment of chronic insomnia

Clinical Effectiveness: Chronic Insomnia (1)

Authors	Study design/dose/ treatment duration	Subjects (n)	Author Reported Outcomes
Schneider-Helmert and Schoenenberger 1981	R, DB, PC, CO 25 nmol/kg x 3 nights	6	• Sleep-promoting effects persisted up to 6 hours • Lower NOA, higher SE • No influence on SOL or final waking times compared to placebo
*Schneider-Helmert and Schoenenberger 1983	DB, PC 25 nmol/kg III (single dose), IV (4 nights), V (6 mornings)	III (n=6), IV (n=4), V (n=2)	• Sleep-promoting effects persisted for at least 6 hours • Higher SE Compared to externally controlled healthy subjects (study IV)
*Schneider-Helmert 1986	DB 30 nmol/kg x 5 nights	18 Middle-aged (n=9) Older adults (n=9)	• Improvement on TST, SE, SOL, WASO
*Schneider-Helmert 1987	DB, “placebo-controlled” 30 nmol/kg x 7 nights	14	• Improvement on TST, SOL, WASO • Normalized SE, SOL, WASO

R = Random; DB = Double blind; PC = Placebo controlled; CO = Crossover; NOA = Number of awakening; SE = Sleep efficiency; SOL = Sleep onset latency; TST = Total sleep time; WASO = Wake after sleep onset

* Compared to externally controlled healthy subjects

Clinical Effectiveness: Chronic Insomnia (2)

Authors	Study design/ dose/treatment duration	Subjects (n)	Author Reported Outcomes
Monti et al. 1987	R, DB, PC, CO 25 nmol/kg x 4 nights (repeated twice with 4 days washout period)	6	• No significant differences compared to baseline measures or placebo phase in intra-subject study
Bes et al. 1992	DB, PC 25 nmol/kg x 3 nights	16	• Short SOL • No significant difference in other sleep measures

R = Random; DB = Double blind; PC = Placebo controlled; CO = Crossover; SOL = Sleep onset latency
* Compared to externally controlled healthy subjects

Graf and Kastin 1986

- The review article considered data from most of the clinical studies discussed.
- The authors stated that although emideltide appeared to exert an effect on disturbed sleep, the results were preliminary and that there was insufficient evidence to show that emideltide reliably induced or maintained sleep

Clinical Effectiveness: Chronic Insomnia (3)

- **Limitations**
  - Lack of or poor selection of control group
  - Small sample sizes with few test subjects
  - Different baseline characteristics in subjects across these studies
  - Imbalanced outcomes in sleep measures
  - Different treatment regimen
  - No information on benefit from long-term administration with intravenous (IV) emideltide

Clinical Effectiveness: Chronic Insomnia (4)

Conclusion

- No data to support use of emideltide via the nominated SC route of administration (ROA) for chronic insomnia
- Insufficient evidence to make a conclusion on the effectiveness of IV emideltide for chronic insomnia
  - Although some studies suggested that short-term IV emideltide may have an effect on disturbed sleep, the results appear inconclusive and at best preliminary
  - Clinical studies authored by Schneider-Helmert reported improved sleep outcomes following short-term IV emideltide in subjects with chronic insomnia, whereas the two DB PC studies by Bes et al. 1992 and Monti et al. 1987 with similarly designed investigations did not reach the same conclusions. Interpretation of studies that reported positive treatment response is limited, and it is unclear whether observed effects on sleep parameters were clinically meaningful
  - Similar observations were noted in another article by Graf and Kastin (1986)
- Professional society guidelines do not discuss the use of emideltide for insomnia
- Insomnia is a serious condition, and there are FDA approved therapies with established efficacy

Narcolepsy

- Characterized by sleep-wake instability manifested as excessive daytime sleepiness (EDS), cataplexy, sleep paralysis (SP), hypnagogic/hypnopompic hallucinations (HH) and disturbed nocturnal sleep (DNS)
  - Often associated with REM sleep parasomnia (i.e., vivid dreams) and non-REM sleep parasomnia (i.e., sleepwalking)
- Pharmacological interventions are the mainstay
  - Stimulants, Selective H3 receptor antagonist/inverse agonist, Gamma-hydroxybutyric acid B subtype (GABA B) receptor agonist
- American Academy of Sleep Medicine (AASM) practice guidelines and European Narcolepsy guideline do not mention emideltide for the treatment of narcolepsy

Clinical Effectiveness: Narcolepsy (1)

- Nominator did not provide any clinical references to support use of emideltide in narcolepsy

- FDA identified 1 case report (**Schneider-Helmert 1984**):
  - 35-year-old male with 10-year history of narcolepsy treated with IV emideltide for a week of evening dose and a week of morning dose

- Authors reported that emideltide:
  - Reduced frequency of sleep attacks and frequency of naps
  - Subject reported increased activity, alertness and performance
  - Did not provoke cataplectic symptoms, SP or HH

- Limitations:
  - Single subject case report limits interpretation of effectiveness due to insufficient methodological rigor, potential recall bias, researcher subjectivity and issues of reliability and external validity

SP = sleep paralysis; HH = halucinations

Clinical Effectiveness: Narcolepsy (2)

Conclusion

- There is no study evaluating effectiveness to support use of emideltide via the nominated SC ROA for narcolepsy
- There is insufficient evidence to make a conclusion on the effectiveness of IV emideltide for narcolepsy
- Single-subject case report limits interpretation of effectiveness of emideltide
- Professional society guidelines do not discuss the use of emideltide for narcolepsy
- Narcolepsy is a serious condition, and there are FDA approved therapies with established efficacy for the treatment of cataplexy or EDS in pediatric patients and adults with narcolepsy

Opioid Withdrawal

- Abrupt cessation of chronic opioid use results in acute withdrawal symptoms that are both physiological and psychological (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR))
- Clinician-rated and patient-reported scales for assessing opioid withdrawal
  - Objective Opioid Withdrawal Scale (OOWS), Clinical Opioid Withdrawal Scale (COWS), Subjective Opioid Withdrawal Scale (SOWS) and Clinical Institute Narcotic Assessment (CINA)
- Treatments
  - Opioid agonist (methadone) or partial opioid agonist (buprenorphine)
  - Alpha-2-adrenergic agonist (lofexidine)
- American Society of Addiction Medicine (ASAM), Substance Abuse and Mental Health Services Administration (SAMHSA) do not mention emideltide for the treatment of opioid withdrawal

Clinical Effectiveness: Opioid Withdrawal (1)

Dick et al. 1984:

- Open-label study, subjects with alcohol (n=47) or opioid (n=60) use
  - Emideltide, IV, 25 nmol/kg, max 6 injections per day up to 6 days
  - Injection on request during recurrence of withdrawal symptoms or injections at fixed intervals every 6-8 hours during 3 consecutive days
- Authors conclusion:
  - Improved both objective and subjective signs and symptoms of opioid withdrawal; recurrent anxiety and insomnia more often when injections given on request
- Limitations:
  - Small sample size, lack of blinding, absence of comparison group, use of subjective assessments which were not evaluated using standard clinical scales, not adequately described the methods used to confirm the outcomes of improved or unimproved

Clinical Effectiveness: Opioid Withdrawal (2)

Backmund et al. 1998:

- Open-label study, subjects diagnosed with opioid dependence (n=7) and SOWS 1 score > 25
  - Emideltide, IV, 35 nmol/kg for 7 days using fixed schedule
- Authors conclusion:
  - Reduced opioid withdrawal symptoms after the first injection
    - Mean SOWS1 scores decreased from 34.4 before the first injection to 17.8 after the first injection (timepoint of post-injection comparison measurement not provided by the authors)
    - Only 2 subjects received all scheduled emideltide injections and successfully detoxified
  - "It remains an open question whether DSIP could be an effective alternative detoxification approach"
  - Further placebo-controlled studies should be performed to verify effectiveness of emideltide in the treatment of acute opioid withdrawal symptoms
- Limitations:
  - Small sample size, lack of blinding, absence of a comparison group

Clinical Effectiveness: Opioid Withdrawal (3)

Conclusion

- There is no study evaluating effectiveness to support use of emideltide via the nominated SC ROA for treatment of opioid withdrawal
- There is insufficient evidence to make a conclusion on the effectiveness of emideltide via the IV ROA for the treatment of opioid withdrawal
- Results should be interpreted cautiously due to small number of published studies, small sample size, different treatment regimen, nonrandomized and uncontrolled study design
- Professional society guidelines do not discuss the use of emideltide for opioid withdrawal
- There are FDA approved therapies with established efficacy for opioid withdrawal

Nonclinical Safety

- Although stimulation of the opioid system by emideltide could lead to development of addiction, FDA did not identify in the literature nonclinical studies to inform the potential addictive liability of emideltide-related BDSs

- In addition, the nominators did not submit, and FDA did not identify, in the literature nonclinical toxicity studies to inform safety considerations for potential clinical uses of emideltide-related BDSs

Clinical Safety – FAERS

- FDA Adverse Event Reporting System (FAERS):
  - Search retrieved no adverse event (AE) reports for emideltide[1]

[1] Note the lack of reports for emideltide does not imply that the substance is safe or lacks toxicities. FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products.

Clinical Safety: Clinical Studies

- There was no safety information for emideltide for the proposed SC ROA
- IV emideltide for chronic insomnia- well tolerated and no significant AEs

Dick et al. 1984:

- No significant AEs in 95 of the 107 subjects with withdrawal symptoms
  - 9 subjects with minor side effects (e.g., perspiration, headache, nausea, vertigo)
  - 3 subjects with serious AEs: hypotension at the first injection (n=2), repetitive episodes of general discomfort with perspiration and nausea (n=1)
    - No additional information for one of these subjects who received a second injection and experienced "progressive hypotension"
- Some experienced relapse of anxiety with marked insomnia after treatment cessation
- Author reported that some AEs were attributed to the "solubility difficulties" of some of the vials
- Limitations:
  - "Solubility difficulties" were not reported in other publications
  - AEs confounded to interpretation due to underlying nature of symptoms experienced during opiate and alcohol withdrawal

Additional Safety Information – Immunogenicity Concerns

- Emideltide-related substances are reported to be 9 amino acid peptides
- Peptides may elicit an immune response; this response may be enhanced when peptides are given via the proposed SC ROA
- Emideltide poses a risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
- The nominations did not include, and FDA did not identify, information about emideltide-related impurities to suggest that the substances do not present these risks

Clinical Safety: Conclusion

- There was no safety data for emideltide via proposed SC ROA
- Safety for IV emideltide is insufficiently characterized
- SC ROA may present a particular risk for immunogenicity due to potential for aggregation as well as potential peptide-related impurities
- There are currently available FDA-approved therapies for the treatment of insomnia, narcolepsy and opioid withdrawal

Historical Use in Compounding (1)

- The nominators did not provide information regarding the historical use of emideltide in compounding
  - Submitted 33 articles but none of the articles explicitly discussed the use of a compounded formulation of emideltide-related products in humans
- Compounding with forms of emideltide can be traced back to at least 2018
  - A compounding pharmacy and its owner pled guilty and were sentenced for unlawful distribution of compounded prescription drugs, including emideltide
- Outsourcing facilities did not report compounding any drug products containing emideltide-related BDSs to FDA
- No studies were found in the literature in which a compounded drug product containing an emideltide-related BDS was administered

Historical Use in Compounding (2)

- An online search did not identify any compounding pharmacies offering emideltide-related compounded preparations
- Integrative neurology clinics, medical concierge services, medical spas, wellness clinics, and online retailers appear to offer emideltide-related BDSs online:
  - Injection and intranasal products
  - For sleep disorders, stress reduction, pain management, cancer, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease), alcohol and drug detoxification
  - None of the websites searched indicate whether the products they appear to offer contain the base or a salt or ester of emideltide
    - Many of the websites do not describe or clearly state whether the emideltide-related products are compounded

Historical Use in Compounding (3)

- Not recognized in the European, Japanese, or International Pharmacopeias
- Emideltide (free base) and emideltide acetate are not registered drugs in any country searched

Historical Use in Compounding (4)

Conclusion

Currently available data and published literature is too limited to inform the historical use of any form of emideltide compounded drug products. Internet search results show that integrative neurology clinics, medical concierge services, medical spas, wellness clinics, and online retailers appear to offer emideltide-related BDSs as injectable and intranasal formulations for various uses.

Evaluation Conclusion

- A balancing of the criteria weighs against emideltide (free base) and emideltide acetate being placed on the 503A Bulks List
- FDA's conclusion is based on the facts that these substances:
  - Are not well characterized from a physical and chemical perspective
  - Insufficiently characterized data to support the safety of these substances when used in humans
    - Additional concerns related to potential immunogenicity risk
  - Lack of evidence to support effectiveness for use in chronic insomnia, narcolepsy, and opioid withdrawal which are associated with multiple serious adverse health outcomes
- There are currently FDA-approved therapies for the management of chronic insomnia, narcolepsy, and opioid withdrawal

Recommendation

FDA is proposing that emideltide (free base) and emideltide acetate NOT be included on the 503A Bulks List.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Epitalon-related Bulk Drug Substances: Epitalon (Free Base) and Epitalon Acetate

Pharmacy Compounding Advisory Committee Meeting

July 24, 2026

Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration (FDA)

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Introduction

- Epitalon-related bulk drug substances (BDSs) were nominated for inclusion on the list of BDSs that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - Epitalon (free base)
  - Epitalon acetate
- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for epitalon (free base) or its acetate form
- Neither is a component of an FDA-approved drug

Evaluation

- Epitalon-related BDSs were evaluated for treatment of:
  - Insomnia
- Proposed product:
  - 10 mg/mL and 3000 mcg/mL subcutaneous (SC) injections [injectables]
- The nominations were withdrawn, and FDA is evaluating the substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety concerns
- Historical use in compounding

BDS Nomenclature

- Epitalon is a common name and not a USAN, INN, or IUPAC name

- FDA has encountered multiple salts, and derivatives, including different active moieties, being marketed under the same common name
  - Inconsistent naming conventions can contribute to a potential safety risk for patients

- USAN program and other naming conventions exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

Summary of Basic Information on Epitalon Free Base and Epitalon Acetate

	Epitalon (Free Base)	Epitalon Acetate
UNII Code	O65P17785G	Not available
CAS No	307297-39-8	307297-40-1
MF/MW (g/mol)	$C_{14}H_{22}N_4O_9$/ 390.35	$C_{14}H_{22}N_4O_9 \cdot C_2H_4O_2$/ 450.40
Chemical Structure	H-Ala-Glu-Asp-Gly-OH	H-Ala-Glu-Asp-Gly-OH·CH_3CO_2H
Supplier	Yes	Yes
Active Moiety	Epitalon (free base)	Epitalon (free base)

CAS = Chemical Abstracts Service; MF = molecular formula; MW = molecular weight

Summary of Information Submitted in Two Withdrawn Nominations

Nominator	Nomination 1	Nomination 2
Nominated BDS	Epitalon	Epitalon
BDS per UNII code	O65P17785G *(matches Epitalon (free base))*	Not Provided
CoA	CoA provided for Epitalon acetate	CoA provided for Epitalon acetate
CAS No.	307297-39-8 *(provided in CoA) (matches Epitalon (free base))*	307297-40-1 *(provided in CoA) (matches Epitalon acetate)*
MF	$C_{14}H_{22}N_4O_9$ *(provided in CoA) (matches Epitalon (free base))*	$C_{14}H_{22}N_4O_9$ *(provided in the nomination) (matches Epitalon (free base))* $C_{16}H_{26}N_4O_{11}$ *(provided in CoA) (matches Epitalon acetate)*
MW	390.35 *(provided in CoA) (matches Epitalon (free base))*	390.35 *(provided in CoA and in the nomination) (matches Epitalon (free base))*
Chemical Name	H-Ala-Glu-Asp-Gly-OH *(matches Epitalon (free base))*	H-Ala-Glu-Asp-Gly-OH *(matches Epitalon (free base))*
Proposed Products	Subcutaneous Injection 10 mg/mL	Subcutaneous Injectable 3,000 mcg/mL

Italics in the table above represents the information identified by FDA.
CoA: Certificate of Analysis

Critical Quality Attributes (CQA) for Nominated Dosage Form

- Injection/SC injectable:
  - Bioburden load (i.e., microbial enumeration test)
  - Bacterial endotoxins test (BET)
  - Solubility

Physical and Chemical Characterization (1)

Epitalon Acetate

- Acetate salt of the tetrapeptide epitalon (free base), a synthetic tetrapeptide (L-Alanine-L-Glutamate-L-Aspartate-L-Glycine)
- White to almost white fluffy powder, soluble in water and acetic acid
- Has no USP drug substance monograph
- BDS storage and stability:
  - Manufacturer recommends storing in sealed container at 2°C to 8°C or -20°C under dry conditions
  - Can be sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential Impurities:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- In the CoA provided:
  - No information regarding the nature of individual impurities. Such information also was not found in publicly available scientific literature.
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity:
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form for SC administration

Physical and Chemical Characterization (3)

Conclusion: Epitalon acetate is not well-characterized

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data (impurities, aggregates, bioburden, and bacterial endotoxins)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities

Physical and Chemical Characterization (4)

Epitalon (Free Base)

- Synthetic tetrapeptide (L-Alanine-L-Glutamate-L-Aspartate-L-Glycine)
- White to off-white lyophilized (freeze-dried) powder
- Has no USP drug substance monograph
- BDS storage and stability:
  - Manufacturer recommends storing desiccated below -18°C
  - Upon reconstitution, epitalon (free base) in solution should be stable for 2-7 days at 4°C
  - Can be sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential Impurities:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities (e.g., isomeric impurities, free amino acids, starting materials, residual solvents, coupling reagents, activators, catalysts, and scavengers)
- No CoA for epitalon (free base) in the nominations
- The CoA for epitalon (free base) from public domain lacks the following CQAs control:
  - No information on impurity limits/testing results
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or BET
- Potential for immunogenicity:
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form for SC administration

Physical and Chemical Characterization (6)

Conclusion: Epitalon (free base) is not well-characterized

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Concern of limited water solubility data
- Lack of certain critical characterization data (impurities, aggregates, bioburden, and bacterial endotoxins)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities

Epitalon (Free Base) or Epitalon Acetate

- The nonclinical and clinical references reviewed do not clearly identify whether the substance discussed is epitalon (free base) or epitalon acetate
- In the next sections, the substances will be generally referred to as epitalon

General Pharmacology (1)

- In old female Rhesus monkeys, epitalon (2 mcg/kg/day, intramuscular, 10 days) increased evening serum melatonin levels and reduced evening serum cortisol levels (Goncharova et al. 2001)
  - Although the increase of evening serum melatonin levels could affect the sleep-awake cycle, the effects of epitalon on sleep behavior are unknown
- The mechanisms by which epitalon regulates melatonin levels in vivo are unlikely to involve direct stimulation of the pineal gland because epitalon (up to 100 microM) failed to induce melatonin release from the pineal gland in vitro (Djeridane et al. 2003)

General Pharmacology (2)

Mechanism of Action:

- In primary cultures of human fetal lung fibroblasts, epitalon: (i) increased expression of telomerase, and (ii) extended telomere length (Khavinson et al. 2003; Malinin and Khavinson 2005)
  - Telomeres are DNA-protein structures at both ends of each chromosome that decrease genomic instability
  - Epitalon-induced extension of telomeres could suppress cellular senescence (Anisimov and Khavinson 2010; Khavinson et al. 2003; Malinin and Khavinson 2005). However, the relationship between epitalon-induced upregulation of telomerase and sleep was not evaluated in the studies and is currently unknown

Overview of Insomnia

- Insomnia is a common sleep disorder associated with trouble falling asleep, staying asleep, or getting good quality sleep, despite adequate time and the right environment to sleep well
- Insomnia can result in daytime sleepiness and impact daily activities, memory, and concentration
- Chronic insomnia (disorder lasting > 3 months) increases risk of high blood pressure, heart disease, diabetes, cancer, psychiatric disorders, suicide, etc.
- Treatment strategies - healthy sleep habits, cognitive behavioral therapy, and pharmacologic treatment:
  - Benzodiazepine receptor agonists, melatonin receptor agonists, orexin receptor antagonists, and benzodiazepines
- American Academy of Sleep Medicine (AASM) practice guidelines do not mention epitalon for the treatment of insomnia

Clinical Effectiveness - Insomnia (1)

- There are no publications that discussed efficacy of epitalon administered in patients with insomnia.
- There are no studies reporting use via the proposed SC route of administration (ROA).
- A literature review article (Khavinson and Linkova 2012) cited in the nominations described the morphology, molecular, and functional aspects of pineal gland aging, states:
  - "[t]he effect of a course of epithalamine or epithalon administration on the melatonin-forming function of the PG [pineal gland] depends on the initial degree of preservation of this function in elderly subjects… The MT [melatonin] concentration increased by a factor of two under the effect of epithalamine and epithalon in elderly subjects with involution changes in the PG…"

Clinical Effectiveness - Insomnia (2)

FDA identified a clinical study in healthy subjects (**Ivko et al. 2021**):

- Trial evaluated sublingual (SL) epitalon on urinary excretion of melatonin metabolite, 6-sulfatoxymelatonin (6-SMT), and expression of clock genes in blood cells in healthy women working night shifts (40-50 y/o, n=75)
- Divided into 2 groups: “normal” (n=35) or “reduced” levels urinary excretion of 6-SMT (n=40).
  - “Reduced” group given SL sprays twice a day for 20 days: Placebo (n=20) or Epitalon (n=20)
    - Urinary 6-SMT levels: placebo - no change; epitalon - increased
- Authors concluded: epitalon has a “geroprotective effect” and can stimulate melatonin synthesis and indirectly regulate expression of proteins encoded by clock genes
- Limitations:
  - Study did not evaluate sleep outcomes or discuss clinical applicability of results or therapeutic effect for insomnia or other sleep disorders
  - Epitalon was administered via SL ROA; nominated ROA is SC
  - Study has small sample size, short duration, and unclear whether blinded for bias control

Clinical Effectiveness – Conclusion

- There is a lack of evidence to support the effectiveness of epitalon for the proposed use of insomnia, a disorder which increases the risk for serious conditions
- Available clinical information discusses effects of epitalon on melatonin metabolite levels. However, we did not identify studies evaluating the use of these substances in patients with insomnia, particularly when administered via the proposed SC ROA
- Potential therapeutic effect of changes in melatonin metabolite levels induced by these substances is unclear without a corresponding evaluation of clinical outcomes
- There are currently multiple FDA-approved drug products with established efficacy indicated for insomnia

Nonclinical Safety (1)

- **Pharmacokinetics/Toxicokinetics**
  - In pregnant rabbits, following a single intravenous (IV) dose of fluorescent-labeled epitalon, fluorescence was detected in maternal and fetal organs (Lapina et al. 2005)
    - Study lacks information to confirm that fluorescence signals detected in tissue were specifically due to labeled full-length epitalon peptide and not a cleaved fluorescent label or truncated epitalon peptide
  - The nominators did not submit, and FDA did not identify, additional nonclinical pharmacokinetic, toxicokinetic, or general toxicity studies with epitalon

Nonclinical Safety (2)

- **Genotoxicity**
  - In mice, epitalon (1 mcg/mouse/day, SC, 5 days/month for 9-10 months) appeared to be non-genotoxic as it had no effect on the frequency of chromosome aberrations in bone marrow cells (Anisimov et al. 2003; Rosenfeld et al. 2002)
  - In mice, a single dose of epitalon (5 mcg/kg, SC) did not induce chromosomal breakage or damage to the mitotic apparatus (Mylniknov et al. 2012)
    - Both studies have important limitations, including testing of a single dose level with no evaluation of a dose-response relationship
- **Carcinogenicity**
  - In mice, intermittent treatment with epitalon (0.1 or 1 mcg/mouse/day, SC, 5 days/month, starting between 2 and 6 months of age) decreased incidence or size of spontaneous tumors and prolonged the lifespan of the animals (Anisimov et al. 2001, 2002, 2003)
    - The carcinogenic potential of continuous treatment with epitalon is unknown

Nonclinical Safety – Conclusion

- From the mechanistic standpoint, epitalon-induced telomere lengthening (see slide 18) raises concerns that continuous, chronic exposure to epitalon could enable cells to evade senescence and become cancerous
  - Long telomeres (generally > 0.7 x standard deviations of the mean lengths) have been associated with increased risks for malignant tumors (McNally et al. 2019)
- Nonclinical studies available at the time of this evaluation were too limited to inform safety considerations for potential clinical uses of epitalon (free base) and epitalon acetate delivered via the nominated SC ROA

Clinical Safety – FAERS and HFCS

- FDA Adverse Event Reporting System (FAERS):
  - Search retrieved no adverse event (AE) reports for epitalon[1]

- Human Foods Program (HFP) Human Foods Complaints System (HFCS):
  - Search retrieved no AE reports for epitalon

[1] Note the lack of reports for epitalon does not imply that the substance is safe or lacks toxicities; FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products.

Clinical Safety – Clinical Studies

- Nominations did not include, and our search of the published medical literature has not identified clinical studies assessing the safety of epitalon administered in humans
- A study in which 20 healthy subjects received SL epitalon for 20 days did not report safety data (Ivko et al. 2021)
- An abstract noted that preparations of the pineal gland [epitalon and epithalamin] have “no side effects” in elderly people (Korkushko et al. 2007). No details, such as ROA, dosing, duration, number of subjects, etc., were provided

Additional Safety Information – Immunogenicity Concerns

- Epitalon-related substances are reported to be 4 amino acid peptides
- Peptides may elicit an immune response; this response may be enhanced when peptides are given via the proposed SC ROA
- Epitalon poses a risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
  - The nominations did not include, and FDA did not identify, information about epitalon-related impurities to suggest that the substances do not present these risks

Clinical Safety – Conclusion

- There is no clinical data to support the safety of epitalon
- FDA has not identified safety data regarding epitalon-related BDSs when administered to humans, particularly via the proposed SC ROA
- SC ROA may present a particular risk for immunogenicity due to potential for aggregation as well as potential peptide-related impurities
- There are currently available FDA-approved therapies for the treatment of insomnia; these drug products have well-characterized safety profiles and have been shown to be safe for their labeled use

Historical Use in Compounding (1)

- The nominators stated that epitalon has been used to compound drug products but did not provide any additional information regarding the historical use of epitalon in compounding
- Studies conducted in human subjects were first published in the literature as early as 2002
  - No studies were found in the literature in which a compounded drug product containing an epitalon-related BDS was used
- Compounding with epitalon can be traced back to at least 2018
  - A compounding pharmacy and its owner were sentenced for unlawful distribution of compounded prescription drugs, including epitalon
- No outsourcing facility has reported compounding drug products containing epitalon-related BDSs to FDA

Historical Use in Compounding (2)

- Epitalon appears to be offered online by several wellness clinics and concierge medicine practices for use as an “anti-aging” agent, typically for SC or oral administration
  - Some sites state that epitalon is obtained from a compounding pharmacy
    - FDA was unable to identify any pharmacies that compound products containing epitalon
- Epitalon (free base) and epitalon acetate are not recognized in either the European or Japanese Pharmacopeias or in any of the National Medical Registries searched

Historical Use in Compounding (3)

Conclusion

The extent to which epitalon-related BDSs have been used in compounding is unclear. Currently available data and published literature are too limited for FDA to understand the historical use of epitalon-related BDSs in compounded drug products.

Evaluation Conclusion

- A balancing of the criteria weighs against epitalon (free base) or epitalon acetate being placed on the 503A Bulks List
- FDA's conclusion is based on the facts that:
  - These substances are not well characterized from a physical and chemical perspective
  - Lack of information on the historical use in compounding
  - Lack of data to support safety of these substances when used in humans as well as additional concerns related to potential immunogenicity risk
  - Lack of evidence to support effectiveness for use in insomnia which is associated with multiple serious adverse health outcomes
- There are FDA-approved drug products that are indicated to treat this condition

Recommendation

FDA is proposing that epitalon (free base) and epitalon acetate NOT be included on the 503A Bulks List


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ADMINISTRATION

Semax-related Bulk Drug Substances: Semax (Free Base) and Semax Acetate

Pharmacy Compounding Advisory Committee Meeting

July 24, 2026

Center for Drug Evaluation and Research (CDER)
U. S. Food & Drug Administration (FDA)

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Special Thanks to: **The Division of Neurology 2 (DN2) and the Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)**

Introduction

- Semax-related bulk drug substances (BDSs) were nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - Semax (free base)
  - Semax acetate

- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for semax (free base) or its acetate form

- Neither is a component of an FDA-approved drug

Evaluation

- Semax-related BDSs were evaluated for the following uses:
  - Cerebral ischemia
  - Migraine
  - Trigeminal neuralgia

- Nominated products
  - Intranasal spray or subcutaneous injection
  - 7,500 mcg/mL or 1,000 mcg/mL dosage strengths

- The nominations were withdrawn, and FDA is evaluating these substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety concerns
- Historical use in compounding

BDS Nomenclature

- Semax is a common name and not a USAN, INN, or IUPAC name

- FDA has encountered multiple salts, derivatives, including different active moieties, being marketed under the same common name for similarly situated products.
  - Inconsistent naming conventions can contribute to a potential safety risk for patients

- USAN program and other naming conventions exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

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

	Semax (Free Base)	Semax Acetate
UNII 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
Active Moiety	Semax (free base)	Semax (free base)
Supplier	Yes	Yes

CAS: Chemical Abstracts Service; MF: molecular formula; MW: molecular weight

Summary of Information Submitted in the Withdrawn Nominations

Nominator	Nomination 1	Nomination 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*)
Proposed Products	Intranasal Spray; Subcutaneous Injection 7,500 mcg/mL or 1,000 mcg/mL	Intranasal Spray 7,500 mcg/mL or 1,000 mcg/mL

Italics in the table above represents the information identified by the FDA.
CoA: Certificate of Analysis

Critical Quality Attributes (CQAs) for Nominated Dosage Forms

- Injection/subcutaneous injection: bioburden load (i.e., microbial enumeration test), bacterial endotoxins test (BET), and solubility

- Metered-dose nasal spray solution products:
  - The container closure system (CCS) including container, closure, 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
  - Nasal spray solution: Microbial quality, suitability/compatibility of the device components with the formulation, and solubility of the BDS

Physical and Chemical Characterization (1)

Semax (Free Base)

- A synthetic heptapeptide (H-Met-Glu-His-Phe-Pro-Gly-Pro-OH)
- White lyophilized powder. Soluble in water up to 2.0 mg/mL as reported
- Has no USP drug substance monograph
- BDS storage and stability:
  - Stable for 4 years when stored at -20 °C in a tightly closed container as reported
  - Can be sensitive to product formulation, manufacturing processes, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- No CoA for Semax (free base) in both nominations
- CoAs found from public domain:
  - No information on impurity limits/testing results
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, particularly when formulated in an injectable or nasal spray dosage form

Physical and Chemical Characterization (3)

Conclusion: Semax (free base) is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable or nasal spray dosage form due to potential for aggregation as well as peptide-related impurities
- Lack of information about the CCS, including container, closure, 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.

Physical and Chemical Characterization (4)

Semax Acetate:

- Acetate salt form of semax (free base), that is reported to be a synthetic heptapeptide
- White powder. No water solubility data available in either nominations or publicly scientific literature
- No USP drug substance monograph
- BDS Storage and Stability:
  - Long-term storage condition: in a sealed container between at 2°C to 8°C recommended in the CoA the nominator provided
  - Can be sensitive to product formulation, manufacturing processes, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- The CoAs provided:
  - No information regarding the nature of individual impurities
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
  - The FDA was unable to identify such information in the publicly available scientific literature
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, particularly when formulated in an injectable or nasal spray dosage form

Physical and Chemical Characterization (6)

Conclusion: Semax acetate is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable or nasal spray dosage form due to potential for aggregation as well as peptide-related impurities
- Lack of water solubility data, it is difficult to evaluate how the water solubility of the BDS will impact the performance of the proposed injectable and intranasal spray products
- Lack of information about the CCS, including container, closure, 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

Semax (Free Base) or Semax Acetate

- The clinical references reviewed do not clearly identify whether the substance discussed is semax (free base) or semax acetate

- In the next sections, the substances will be generally referred to as semax

Nonclinical Pharmacology (1)

- Semax is reported to be a synthetic heptapeptide analog of the adrenocorticotropic hormone 4-10 fragment ($ACTH_{4-10}$). Semax is suggested to be devoid of hormonal corticotropic and melanotropic properties while potentially retaining the neurobehavioral properties of the full-length ACTH protein (Kolomin et al. 2013)

- Potential molecular targets of semax:
  - **Enkephalinases** (enzymes that catalyze the hydrolysis of enkephalins, which are endogenous opioid peptides that modulate pain and other physiological functions) are inhibited by semax with an apparent potency of approximately 10 µM (Kost et al. 2001)

- Pharmacological effects of semax suggest its potential to:
  - Prevent ischemic brain damage in rats (Romanova et al. 2006; Stavchansky et al. 2011)
  - Prevent cortical ischemia-induced deterioration of spatial learning in rats (Silachev et al. 2009)
  - Induce antinociception in mice and rats (Ivanova et al. 2003; Manchenko et al. 2012)
    - Note: The dose-response relationships for semax to induce different effects in rodents are not defined, and the systemic exposures needed for a pharmacological effect are unknown

Nonclinical Pharmacology (2)

- Potential mechanisms of action of semax
  - *Suppression of ischemic cerebral damage:*
    - Likely related to semax's antioxidant properties and modulation of gene expression (Agapova et al. 2007a; Agapova et al. 2007b; Medvedeva et al. 2014; Vlasova et al. 2009)
  - *Antinociceptive effect:*
    - Unlikely due to inhibition of enkephalinases because semax-induced antinociception is not blocked by the opioid antagonist naloxone in rats (Ivanova et al. 2005)
    - Likely mediated by semax-induced increase in serotoninergic signaling (Ivanova et al. 2005)
  - Semax potentiates amphetamine-induced locomotor activity and striatal dopamine release in mice (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)

Overview of Cerebral Ischemia

- Cerebral ischemia (CI) 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

Treatment of Cerebral Ischemia (CI)

- Correcting the underlying cause
- Minimizing risk factors
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
- Decrease the risk of recurrence (DeSai and Shapshack 2023)
- Endpoints for acute treatment of CI
  - Neurological improvement after stroke
  - Clinical outcomes and disability at three months after stroke based on validated scales such as the modified Rankin Scale (mRS) score
- Endpoints for prevention of CI
  - Reduction in the occurrence of stroke
  - Reduction in risk of stroke
  - Time to first occurrence of new ischemic stroke
  - Reduction in blood pressure

Clinical Effectiveness - CI (1)

- Cherkasova et al. 2002 (meeting abstract)
  - Population:
    - Semax was given to both rats and humans
    - Unknown number of human subjects with chronic ischemic brain disease
  - Intervention:
    - Intranasal semax 600 mg daily for 10 days
  - Outcomes:
    - The authors report that there were changes to lab values related to blood clotting (such as plasmin, antithrombin III, and protein C)
  - Limitations:
    - The authors did not provide full results for these lab values
    - They did not discuss clinical function before and after receiving semax
    - The authors did not discuss how long the human subjects had ischemia or if they had received other medications for the prevention or treatment of this condition

Clinical Effectiveness - CI (2)

Articles published in Russian:

- Alekseeva et al. 1999
- Gusev et al. 1997
- Gusev et al. 2005
- Gusev et al. 2018
- Kaplan et al. 1992
- Miasoedova et al. 1999
- Shmyrev et al. 1998

- Limitation: Because the full references were not available in English, these references were not considered as part of this evaluation

Review articles based on data from studies completed in animals:

- Deigin et al. 2022
- Tarasov et al. 2017

- Limitation: Do not provide additional references in humans with cerebral ischemia

Review with some human references (Kolomin et al. 2013)

- Studies are written in Russian or are in healthy adults (Kaplan et al. 1996)

Clinical Effectiveness – CI (3)

Conclusion:

- There is insufficient evidence of effectiveness to support use of semax (free base) or semax acetate for cerebral ischemia

- Professional society guidelines on the treatment of cerebral ischemia do not discuss semax-related BDSs

- CI is a serious condition, and there are FDA-approved drug products for the prevention and treatment of this condition

Overview of Migraine and Trigeminal Neuralgia

Migraine

- Chronic neurologic disease
- Characterized by attacks of throbbing, often unilateral headache
- Exacerbated by physical activity
- Associated with photophobia, phonophobia, nausea, vomiting, cutaneous allodynia

Trigeminal Neuralgia (TN)

- A condition causing severe, unilateral, episodic facial pain
- Brief, lancinating attacks triggered by eating, drinking, talking, or touching the face
- Typical trigeminal neuralgia paroxysms
  - no pain between episodic attacks
- Trigeminal neuralgia with concomitant continuous pain
  - There is background pain between attacks

Treatment of Migraine

- Endpoints for acute treatment of migraine
  - Reduction to no pain within 2 hours of receiving a treatment
  - Freedom from most bothersome symptoms such as nausea, phonophobia or photophobia following treatment

- Endpoints for prevention of migraine
  - Change from baseline in the mean monthly migraine days
  - Change from baseline in the need for acute migraine treatments

Clinical Effectiveness - Migraine and TN (1)

Koroleva et al. 1996

- Evaluated adults with migraine, trigeminal neuralgia, or dental plexalgia[1]
  - Migraine group: 12 subjects
  - Trigeminal neuralgia group: 25 adult subjects
    - Typical trigeminal neuralgia group: 16 subjects
    - Dental plexalgia group: 9 subjects
- Intervention: one dose 0.5 mg/kg intranasal semax
- Migraine Outcomes:
  - Pain severity was measured using the modified pain sensitivity test (MPST) rating scale
  - Rhoencephalogram (REG) was recorded before and 5, 15, and 30 minutes after administration of semax
- TN Outcomes:
  - Pain severity and frequency were measured using 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

1. a subtype of trigeminal neuralgia

Clinical Effectiveness – Migraine and TN (2)

Koroleva et al. 1996

- Migraine results:
  - 4 subjects out of 12 (33%) reported cessation of headache pain 90-120 minutes after semax administration
  - 8 subjects out of 12 (66%) the authors reported that “pain was not eliminated but became less severe.”
- TN results:
  - Subjects with typical trigeminal neuralgia:
    - No changes in the characteristics of pain in the MPST
    - No changes in sensation or pain thresholds and TSEP after administration of semax
  - Subjects with dental plexalgia:
    - Pain resolved in 6 subjects, 3 subjects decreased in severity
  - No reduction in frequency and duration of pain attacks, or differences in sensory characteristics of pain
  - No information on quantitative changes in TSEP after semax administration, clinical relevance is unclear

Clinical Effectiveness – Migraine and TN (3)

- **Limitations:**
  - No blinding, no control group, small sample size
  - No information about migraine headache characteristics at baseline:
    - Headache intensity or severity
    - Presence or absence of associated symptoms
    - Unilaterality or bilaterality of the headache
  - Insufficient information for the MPST rating scales or TSEP that were used to inform the study endpoints
  - Insufficient information on REG recordings and its relevance to clinical outcomes

- **Migraine Conclusion**: 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

- **TN Conclusion**: Semax was not effective in resolving pain for the majority of subjects with trigeminal neuralgia in the study

Clinical Effectiveness – Migraine and TN (4)

Conclusion:

- There is insufficient evidence of effectiveness to support use of semax (free base) or semax acetate for migraine or trigeminal neuralgia

- The results from one small, uncontrolled, open label study showed that semax was not effective in resolving headache pain for the majority of subjects with migraine, and was not effective in resolving pain for the majority of subjects with trigeminal neuralgia in the study

- Professional society guidelines on the treatment of migraine and trigeminal neuralgia do not discuss semax-related BDSs

- Migraine and TN are serious conditions, and there are FDA-approved drug products for the prevention and/or treatment of these conditions

Pharmacokinetics (PK)

Nonclinical

- Semax administered intravenously or intranasally to rats distributes to the brain
  - 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 radiolabeled semax (Potaman et al. 1991b; Shevchenko et al. 2006b)

- In-vitro, semax was quickly hydrolyzed to shorter peptides in rat blood and brain tissue
  - The tripeptide proline-glycine-proline was the main metabolite identified in the blood and brain taken from rats treated with radiolabeled semax (Shevchenko et al. 2006b)

- The nominator did not submit, and FDA did not identify, published nonclinical PK studies of semax delivered via the nominated SC ROA

Nonclinical Safety

At the time of this evaluation, the nominator did not submit, and FDA did not identify, published nonclinical studies to assess the toxicity or PK profile of semax via the nominated SC ROA to inform the abuse potential and other safety considerations for possible clinical uses of semax

Clinical Safety (1)
PK, FAERS

- Pharmacokinetics (PK)
  - No published pharmacokinetic studies in humans following exposure to semax (free base) or semax acetate via any ROA

- FDA Adverse Event Reporting System (FAERS)[1]
  - May 2025: report of eye pain and burning after using Semax 0.1% nasal drops purchased online from CosmicNootropic
  - Resulted in hospitalization and persistence of symptoms for at least a year

1. FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products.

Clinical Safety (2)

Reference	Population	Intervention	AE
Cherkasova et al. 2002[a, b]	Subjects with chronic ischemic brain disease[d]	Intranasal (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) (ROA not specified)	AEs not discussed
Aminova et al. 2016[a]	331 children with tics and Tourette Syndrome	encephabol + semax + neuroleptics (ROA not specified)	AEs not discussed
Lebedeva et al. 2018	14 healthy adults	IN semax (1.2 mg) given once	AEs not discussed
Panikratova et al. 2020[c]	14 healthy adults	IN semax (1.2 mg) given once	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

Immunogenicity

- Semax (free base) and semax acetate are reported to consist of seven amino acids
- FDA is concerned about their potential for immunogenicity when administered by an injection or nasal spray ROA as proposed due to the potential for aggregation as well as potential peptide-related impurities
- The nominators did not provide, and FDA did not identify, published clinical studies assessing immunogenicity of semax (free base) or semax acetate

Clinical Safety Conclusions

- There is insufficient clinical information to characterize the safety profile of semax via the intranasal ROA
- No safety data for semax administered by the proposed SC ROA
- No published pharmacokinetic studies in humans
- 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
- The nominators did not provide, and FDA did not identify, published clinical studies assessing immunogenicity of semax

Historical Use in Compounding (1)

- The nominators did not provide information regarding the historical use of semax in compounding
  - Submitted 38 articles but none of the articles discussed the use of a compounded formulation of semax
- Compounding with forms of semax can be traced back to at least 2018
  - A compounding pharmacy and its owner were sentenced for unlawful distribution of compounded prescription drugs, including semax
- No studies were identified that used a compounded formulation of semax
- Outsourcing facilities have not reported compounding drug products containing semax

Historical Use in Compounding (2)

- Semax-related BDSs are offered online:
  - Injection and intranasal products
  - Single ingredient and in combination with a different peptide, selank
  - For 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
  - Widely offered online through health/wellness clinics, medical concierge services, functional and regenerative medicine clinics, and online retailers
  - Some sites offer products containing semax that are listed for research use only

Historical Use in Compounding (3)

- Not recognized in the European, Japanese, or International Pharmacopeias
- Registered drug in Russia as 0.1% and 1% nasal drops

Historical Use in Compounding (4)

Conclusion: The extent to which semax-related BDSs have been used in compounding is unclear. Internet search results show that semax-related BDSs are offered as injectable and intranasal formulations for various uses. These formulations are offered by health/wellness clinics, medical concierge services, functional and regenerative medicine clinics, and online retailers.

Evaluation Conclusion

- A balancing of the criteria weighs against semax (free base) and semax acetate being placed on the 503A Bulks List
- FDA's conclusion is based on the fact that these substances:
  - Are not well characterized from a physiochemical perspective
  - There is lack of information regarding how an appropriate container and pump for an intranasal spray product would be selected and qualified
  - There is lack of information about historical use in compounding
  - Insufficiently characterized data to support the safety of these substances
    - Additional concerns related to potential immunogenicity risk
  - Insufficient evidence of effectiveness to support the use of semax-related BDSs as a treatment for cerebral ischemia, migraine and trigeminal neuralgia
- There are currently FDA-approved drugs for the management of cerebral ischemia, migraine, and trigeminal neuralgia

Recommendation

FDA is proposing that semax (free base) and semax acetate NOT be included on the 503A Bulks List.


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