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.

Emideltide-Related Bulk Drug Substances (Emideltide (free base) and Emideltide acetate)

Table of Contents

1. FDA Evaluation of Emideltide-related bulk drug substances...…..….....4
   - I. Introduction…..……..…….....9
   - II. Evaluation Criteria…….…….……..…….....10
     - A. Is the substance well characterized, physically and chemically?.....10
     - B. Has the substance been used historically in compounding?.....20
     - C. Available evidence of effectiveness or lack of effectiveness of drug products compounded with the substance …….……...…23
     - D. Are there concerns about the safety of the substance for use in compounding?.....41
   - III. Conclusion and Recommendation…..……..……..……..53
   - IV. References……..…….……...……...……..57
   - V. Appendices…….……...64
2. Emideltide-related bulk drug substance Nominations…...……..……...…….....71
   - I. LDT Health Solutions Inc……...……..……...72
   - II. Wells Pharmacy Network…….....78

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

DATE: 5/11/2026

FROM: Hong Ding, Ph.D. (Primary)
Chemist, Office of Product Quality Assessment II (OPQAII),
Office of Pharmaceutical Quality (OPQ)

Jamiele Mattocks, Pharm.D., B.C.A.C.P.
Consumer Safety Officer (CSO),
Office of Compounding Quality and Compliance (OCQC),
Office of Compliance (OC)

Tracy Rupp, Pharm.D., M.P.H., B.C.P.S.
Lead Consumer Safety Officer, OCQC, OC

Edna Albuquerque, Ph.D.
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, Ph.D.
Nonclinical Team Leader, DPT-RPURM/SM, OND

Katie Park, Pharm.D., M.P.H.
Clinical Analyst, Pharmacy Compounding Review Team (PCRT),
Office of Specialty Medicine (OSM), OND

Suhail Kasim, M.D. M.P.H.
Lead Physician, PCRT, OSM, OND

THROUGH: Russell Wesdyk, B.S., MBA
Associate Director for Regulatory Affairs, OPQA2, OPQ

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

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

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

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Emideltide-related bulk drug substances: Emideltide (free base) and Emideltide acetate for Inclusion on the 503A Bulk Drug Substances List. Emideltide is also referred to as Delta Sleeping Inducing Peptide (DSIP).

List of Abbreviations

Abbreviation	Term
AASM	American Academy of Sleep Medicine
ACP	American College of Physicians
AE	adverse event
API	active pharmaceutical ingredient
ASAM	American Society of Addiction Medicine
BDS	bulk drug substance
BET	bacterial endotoxins test
BSA	body surface area
CAS	Chemical Abstract Service
CBT-I	cognitive behavioral therapy for insomnia
CDC	Centers for Disease Control and Prevention
CINA	Clinical Institute Narcotic Assessment
CO	crossover
CoA	certificate of analysis
COWS	Clinical Opioid Withdrawal Scale
CQA	critical quality attribute
CSF	cerebrospinal fluid
DB	double-blind
DNS	disturbed nocturnal sleep
DORA	dual orexin receptor antagonist
DSIP	Delta Sleeping Inducing Peptide
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision
EDS	excessive daytime sleepiness
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
EWL	Eigenschaftswörterliste
FAERS	FDA Adverse Event Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
$GABA_B$	Gamma-hydroxybutyric acid B subtype
GC	gas chromatography
GRAS	Generally Recognized as Safe
HH	hypnagogic/hypnopompic hallucination
HPLC	high-performance liquid chromatography
HSA	human serum albumin
ICV	intracebroventricular
INN	International Nonproprietary Name
IP	intraperitoneal
IPS	International Peptide Society Submission

IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
KF	Karl Fischer
LDT	Laboratory Diagnosis Testing
MRT	multiple relaxation test
MS	mass spectrometry
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NF	National Formulary
NMR	nuclear magnetic resonance
NOA	number of awakenings
NREM	non-rapid eye movement
OOWS	Objective Opioid Withdrawal Scale
OTC	over-the-counter
OUD	opioid use disorder
PBS	phosphate buffered solution
PC	placebo-controlled
POMS	profile of mood states
QOS	quality of sleep
R	randomized
REM	rapid eye movement
ROA	route of administration
SAMHSA	Substance Abuse and Mental Health Services Administration
SC	subcutaneous
SE	sleep efficiency
SOL	sleep onset latency
SOREM	sleep-onset REM
SOWS	Subjective Opioid Withdrawal Scale
SP	sleep paralysis
SPPS	solid phase peptide synthesis
SSS	Stanford Sleepiness Scale
SWS	slow-wave sleep
TST	total sleep time
USAN	United States Adopted Name
USP	United States Pharmacopeia
WASO	wake after sleep onset
WHO	World Health Organization

I. INTRODUCTION

The Food and Drug Administration (FDA, the Agency, or we) received nominations for emideltide-related bulk drug substances (BDSs) 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).[1] Emideltide is also referred to as Delta Sleeping Inducing Peptide (DSIP).[2] The nominators of emideltide-related BDSs provided inconsistent information in the nomination packages regarding the specific BDS proposed. Specifically, it is unclear whether the nominations were for emideltide (free base) or emideltide acetate. Emideltide (free base) and emideltide acetate are different BDSs. Please see additional information in section II.A. The nominations were withdrawn,[3] and FDA is evaluating the substances at its discretion.

Emideltide is reported to be a nonapeptide. FDA has decided to evaluate both emideltide (free base) and emideltide acetate because it is unclear which substance the nominators intended to nominate and the available information often did not clearly identify the specific bulk drug substance at issue or whether drug products containing such substance were compounded.

Emideltide acetate and emideltide (free base) were evaluated for the following use(s): opioid withdrawal and two sleep disorders that included chronic insomnia[4] and narcolepsy.[5,6] FDA evaluated emideltide-related BDSs to compound drug products for subcutaneous (SC) injection administration in a 1000 mcg/mL (1 mg/mL) concentration.

---

[1] The nomination of "emideltide" from Wells Pharmacy Network (Document ID:FDA-2015-N-3534-0287) can be accessed at https://www.regulations.gov/document/FDA-2015-N-3534-0287. The nomination of "emideltide" from LDT Health Solutions, Inc. (Document ID: FDA-2018-N-2973-0002) can be accessed at https://www.regulations.gov/document/FDA-2018-N-2973-0002. These nominations were withdrawn, but because FDA is evaluating emideltide (free base) and emideltide acetate on its own initiative, FDA considered information submitted in these nominations as part of this evaluation.

[2] DSIP promotes a particular type of sleep which is characterized by an increase in the delta rhythm of the EEG (Pollard and Pomfrett 2001).

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

[4] Emideltide was nominated for "insomnia", but we focused on "chronic insomnia" as this is the condition that was discussed in the references submitted by the nominators.

[5] 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.

[6] Emideltide was also nominated for "paradoxical sleep disorder." However, FDA did not evaluate this proposed use because the nominations did not include sufficient information for the Agency to evaluate whether the substance is appropriate for this use in compounded products.

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

We have evaluated publicly available data on the physicochemical characteristics, historical use, safety, and effectiveness in compounding of these substances. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing both emideltide (free base) and emideltide 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?[7]

Emideltide is a common name and not United States Adopted Name (USAN).[8] FDA has encountered multiple salts, and derivatives, including different active moieties, sold commercially under the same common name. Inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC)[9,10] represent a safety risk for patients as they may be dosed with a different bulk drug substance than the physician ordered. From a chemical analysis standpoint, inconsistent naming conventions for emideltide-related BDSs also introduce risks because of the inability to determine which bulk drug substance a particular reference standard is referencing.

As discussed above, this evaluation pertains to emideltide (free base) and emideltide acetate.

---

[7] 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 CoA. 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).

[8] 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. This program and naming convention are intended to help physicians, pharmaceutical manufacturers of active ingredients and finished dosage forms, and pharmacists ensure that the patient is provided with the drug the physician intended.

[9] INN: International Nonproprietary Name from World Health Organization (WHO).

[10] IUPAC: International Union of Pure and Applied Chemistry.

A BDS or API[11] 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.[12] Different active moieties are not interchangeable because they can have different safety and efficacy profiles. Similarly, a free base or the various salts or esters of an active moiety are distinct chemical entities, 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.

Emideltide, originally found in rabbit cerebral venous blood (Monnier M, 1963), is reported to be a nine amino acid peptide composed of Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu, and was synthesized later (Monnier M, 1976).

There is no applicable USP or NF drug substance monograph for emideltide (free base) or its acetate form. Common names for the BDSs listed in public databases include DSIP moiety.[13]

Table 1 below summarizes the identifying information available in the public domain for each BDS.

[11] 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 FD&C 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."

[12] "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.

[13] Information available at https://www.lifetein.com/peptide-product/emideltide-delta-sleep-inducing-peptide-p-10003.html?srsltid=AfmBOoo9sXOnen9N8ltrLR-oUN8s_o_qd0el0IE51Mj-Syz4jQ3gij8d. Accessed 05/22/25.

Table 1. Summary of Basic Information on Emideltide Related BDSs

Characteristic	Emideltide (Free Base)	Emideltide Acetate
UNII Code	YN28Z5YZ73	N/A
CAS No.*	62568-57-4	N/A
MF/MW (g/mol)	$C_{35}H_{48}N_{10}O_{15}$/848.814	$C_{35}H_{48}N_{10}O_{15}$. Acetate/908.8
Chemical Structure	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu. CH_3COOH
Supplier	Yes	Yes
Active moiety	Emideltide (free base)	Emideltide (free base)

Information available at https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6478191.htm.
Abbreviations: CAS, Chemical Abstract Service; MF, molecular formula; MW, molecular weight; UNII, Unique Ingredient Identifier

Two nominations were submitted which, as discussed above, were later withdrawn. The nominators provided inconsistent information about the different emideltide-related BDSs in their nominations. Due to the inconsistencies in the nominations as well as inconsistencies in the public domain and literature, there was lack of clarity about emideltide-related BDSs including the nominated BDS. 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	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))*

Italics in the table above represents the information identified by FDA.
Abbreviations: BDS, bulk drug substance; CAS, Chemical Abstract Service; CoA, Certificate of Analysis; DSIP, Delta Sleeping Inducing Peptide; MF, molecular formula; MW, molecular weight; UNII, Unique Ingredient Identifier

One nomination named "emideltide" as nominated BDS. The nomination included a certificate of analysis (CoA) for the nominated BDS. The chemical name provided in CoA by the nominator does not correspond to the emideltide. The chemical name, Chemical Abstract Service (CAS) number, molecular formula, molecular weight, and amino acid sequence information provided by the nominator refers to emideltide (free base), but the chemical name and acetic acid

content testing in CoA refers to emideltide acetate. Clinical references provided in the nomination refer to emideltide (free base). It is unclear whether emideltide or emideltide acetate was intended to be the nominated BDS based on the information provided.

The second nomination identified the nominated BDS as "DSIP" which is consistent with the CoA for the nominated BDS. The chemical name, molecular formula, and molecular weight provided by the nominator refers to emideltide (free base).

FDA is choosing to concurrently evaluate both BDSs under different sub-sections of this evaluation: (II.A.1) emideltide (free base) and (II.A.2) emideltide acetate.

The nominators have proposed to compound this BDS into the following dosage form:

- Injection/SC Injection

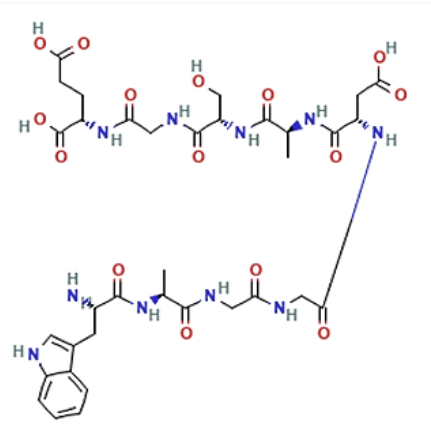
For an injection product, in general, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET), and foreign particulates are critical safety factors. For this reason, bioburden load (i.e., microbial enumeration test) and BET are critical for the BDSs to be used in compounding injectable solutions. Evaluation of the solubility of the BDS is also critical to ensure that no BDS precipitates are formed in the compounded drug product.

There is no USP drug substance monograph for any of the emideltide-related BDSs. We reviewed physical and chemical characterization-related information provided by the nominators and performed a literature search for additional information on each of the emideltide-related BDSs. Databases searched for information on emideltide-related BDSs in preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. Emideltide (Free Base)

Emideltide (free base) is reported to be a naturally occurring nonapeptide (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu) that is commercially available as a synthetic peptide as showed in Figure 1. The molecular formula of emideltide (free base) is $C_{35}H_{48}N_{10}O_{15}$, and its molecular weight is 848.8 g/mol.

Figure 1. The Structure of Emideltide (Free Base)



a. Stability of the Bulk Drug Substance and Likely Dosage Forms

Emideltide (free base) as a white crystalline or powder is stored at -20°C,[14] and the BDS remains stable for three years. Under 4°C, the BDS remains stable for two years. It is reported that lyophilized emideltide (free base) is stable at room temperature for 3 weeks. For long-term storage it is recommended to add a carrier protein (0.1% human serum albumin [HSA] or body surface area [BSA]) and prevent freeze-thaw cycles.[15]

FDA notes that peptides such as emideltide (free base) can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients etc.), 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, involving equipment compounders may not be typically available in a compounding facility. Hence, peptides may require more and/or specific analytical in-process and final 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. 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. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions.

b. Probable Routes of Bulk Drug Substance Synthesis

The emideltide (free base), originally found in rabbit cerebral venous blood, is reported to be a naturally occurring nonapeptide (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu) that is commercially

[14] Information available at https://www.novoprolabs.com/p/emideltide-318939.html. Accessed 05/22/25.
[15] Information available at https://www.invivochem.com/emideltide.html. Accessed 05/22/25.

available as a synthetic peptide. There is a lack of information on the route of synthesis of the BDS.

c. Likely Impurities[16]

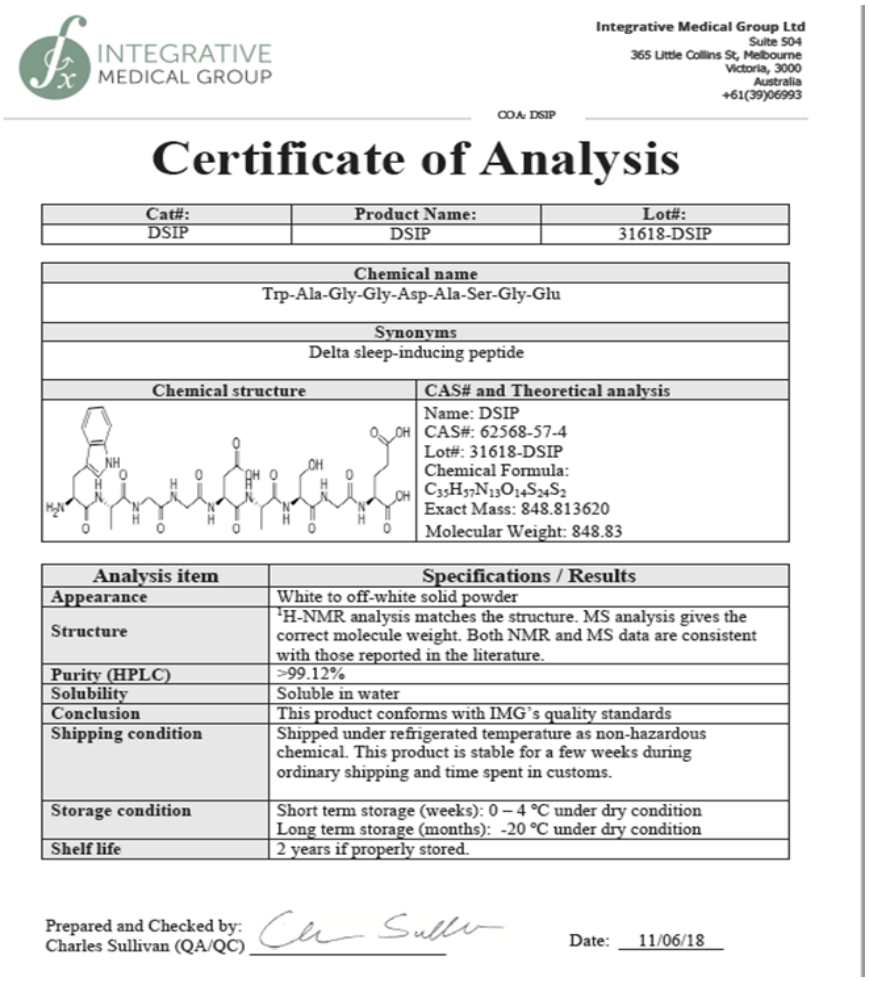
Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including emideltide (free base). For most synthetic peptides, the solid-phase peptide synthesis method has been widely 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 (SPPS) process related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

The CoA for emideltide (free base) was provided in the withdrawn nomination packages (Figure 2). The following analytical methods were applied in CoA: visual test for appearance, solubility determination, nuclear magnetic resonance (NMR) and mass spectrometry (MS) for chemical structure confirmation, and high-performance liquid chromatography (HPLC) method for purity. However, there is no information on the impurity limits/testing results as attribute control in the withdrawn nominator's CoA to demonstrate quality control of impurity profile of emideltide (free base).

Because there is lack of information regarding potential impurities that can be present in emideltide (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.

[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 CoA 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 (ROA), 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.

Figure 2. Nominator-Submitted Example of a CoA for Emideltide (Free Base)



INTEGRATIVE MEDICAL GROUP

Integrative Medical Group Ltd
Suite 504
365 Little Collins St, Melbourne
Victoria, 3000
Australia
+61(39)06993

COA: DSIP

Certificate of Analysis

Cat#:	Product Name:	Lot#:
DSIP	DSIP	31618-DSIP

Chemical name
Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu
Synonyms
Delta sleep-inducing peptide

Chemical structure	CAS# and Theoretical analysis
	Name: DSIP CAS#: 62568-57-4 Lot#: 31618-DSIP Chemical Formula: $C_{35}H_{57}N_{13}O_{14}S_{24}S_2$ Exact Mass: 848.813620 Molecular Weight: 848.83

Analysis item	Specifications / Results
Appearance	White to off-white solid powder
Structure	^{1}H-NMR analysis matches the structure. MS analysis gives the correct molecule weight. Both NMR and MS data are consistent with those reported in the literature.
Purity (HPLC)	>99.12%
Solubility	Soluble in water
Conclusion	This product conforms with IMG's quality standards
Shipping condition	Shipped under refrigerated temperature as non-hazardous chemical. This product is stable for a few weeks during ordinary shipping and time spent in customs.
Storage condition	Short term storage (weeks): 0 – 4 °C under dry condition Long term storage (months): -20 °C under dry condition
Shelf life	2 years if properly stored.

Prepared and Checked by:
Charles Sullivan (QA/QC) _____ Date: 11/06/18

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

Emideltide (free base) is a white to off-white lyophilized powder. It is soluble in water at 0.5 mg/mL for free base.[17] Because the emideltide (free base) has limited solubility in water, formulation of the proposed SC injectable dosage form at the concentration of 1,000 mcg/mL may have solubility issue upon reconstitution.

[17] Information available at https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6478191.htm. Accessed 05/22/25.

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the Bulk Drug Substance is Poorly Characterized or Difficult To Characterize.

No bioburden/endotoxin test is mentioned in the CoA provided by the nominator. Endotoxin testing is considered a CQA to control microbiological quality of a BDS intended for an injection product. No such relevant information for emideltide (free base) was identified in the public domain. In addition, there is no residual solvent testing in the nomination.

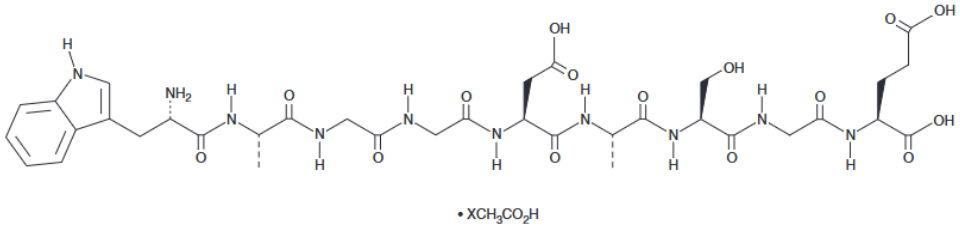
Conclusions: Emideltide (free base) is reported to be a peptide consisting of nine amino acids. As reported in the literature, emideltide (free base) is expected to be stable under reported storage conditions below -20°C. Also, since emideltide (free base) peptide has limited water solubility, the particle size distribution (PSD) control for emideltide (free base) powder may be needed.

Emideltide (free base) is considered not well-characterized from the physical and chemical characterization perspectives based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) certain critical characterization data specific to emideltide (free base), including specific tests for impurities, aggregates, and endotoxins, were not found in the publicly available scientific literature, and the nominations did not provide scientific literature or other information such as CoAs as evidence to establish identity, purity, and impurity profiles of the substance. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of emideltide (free base) when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide-related impurities, as discussed in the impurity section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as emideltide (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. In addition, due to reportedly limited water solubility of emideltide (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with the concentration of 1 mg/mL.

2. Emideltide Acetate

Emideltide acetate is the acetate salt of emideltide. It is a synthetic nonapeptide (Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu) as showed in Figure 3. The molecular formula of emideltide acetate is $C_{35}H_{48}N_{10}O_{15}$, $x(C_2H_4O_2)$ and its molecular weight is 848.8 plus x60 g/mol.

Figure 3. The Structure of Emideltide Acetate



a. Stability of the Bulk Drug Substance and Likely Dosage Forms

Emideltide acetate as a solid powder is stored at -20°C, and the BDS remains stable for four years. Emideltide acetate BDS solution can maintain efficacy for more than one month if the solution is stored at -20°C. Repeated freeze and thaw cycles should be avoided.[18]

FDA notes that peptides such as emideltide acetate can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients, etc.), 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, involving equipment compounders may not be typically available in a compounding facility. Hence, peptides may require more and/or specific analytical in-process and final 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. 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. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions.

b. Probable Routes of Bulk Drug Substance

Emideltide acetate is a synthetic nonapeptide. There is a lack of information on the route of synthesis of the BDS.

c. Likely Impurities[19]

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 emideltide 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

[18] Information available at https://www.caymanchem.com/product/34426/helping-make-research-possible. Accessed 05/22/25.

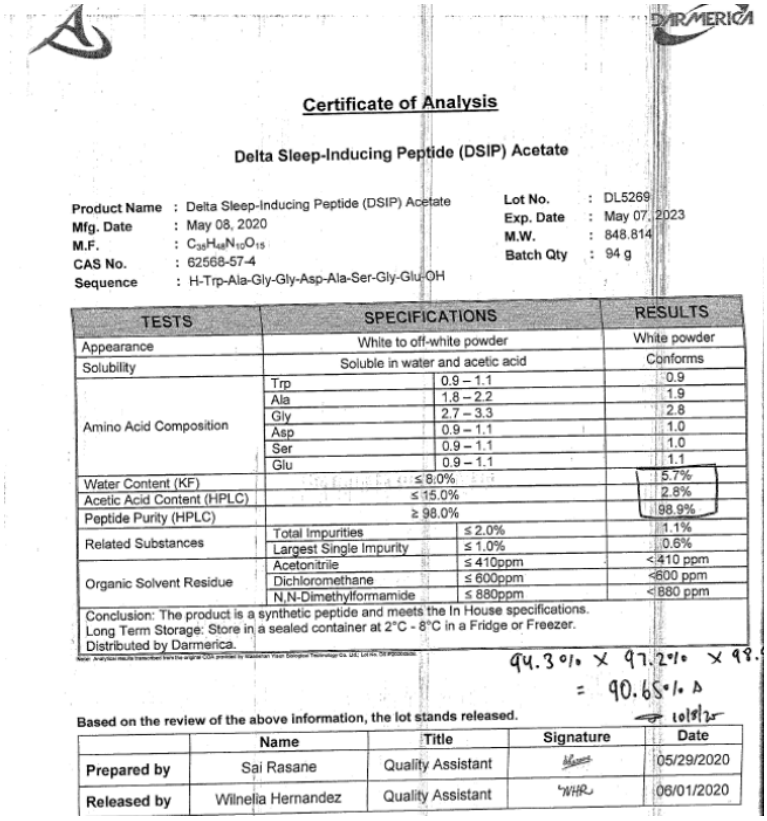
[19] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the CoA accompanying the bulk 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, ROA, 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.

carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as SPPS process related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

The CoA for emideltide acetate was provided in the withdrawn nomination package (Figure 4). The following analytical methods were applied in CoA: visual test for appearance, solubility determination, amino acid composition confirmation, Karl Fischer (KF) method for water content testing, HPLC method for purity, acetic acid and related substances content, gas chromatography (GC) method for organic solvent residue, and MS spectrum for identification. However, there is no information on the specified impurity limits/testing results as attribute control in the withdrawn nomination CoA to demonstrate quality control of impurity profile of emideltide acetate.

Because there is a lack of information regarding potential impurities that can be present in emideltide 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.

Figure 4. Nominator-Submitted Example of a CoA for Emideltide Acetate



DARMERICA

Certificate of Analysis

Delta Sleep-Inducing Peptide (DSIP) Acetate

Product Name	: Delta Sleep-Inducing Peptide (DSIP) Acetate	**Lot No.**	: DL5269
Mfg. Date	: May 08, 2020	**Exp. Date**	: May 07, 2023
M.F.	: $C_{35}H_{48}N_{10}O_{15}$	**M.W.**	: 848.814
CAS No.	: 62568-57-4	**Batch Qty**	: 94 g
Sequence	: H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-OH		

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water and acetic acid		Conforms
Amino Acid Composition	Trp	0.9 – 1.1	0.9
	Ala	1.8 – 2.2	1.9
	Gly	2.7 – 3.3	2.8
	Asp	0.9 – 1.1	1.0
	Ser	0.9 – 1.1	1.0
	Glu	0.9 – 1.1	1.1
Water Content (KF)	≤ 8.0%		5.7%
Acetic Acid Content (HPLC)	≤ 15.0%		2.8%
Peptide Purity (HPLC)	≥ 98.0%		98.9%
Related Substances	Total Impurities	≤ 2.0%	1.1%
	Largest Single Impurity	≤ 1.0%	0.6%
Organic Solvent Residue	Acetonitrile	≤ 410ppm	< 410 ppm
	Dichloromethane	≤ 600ppm	< 600 ppm
	N,N-Dimethylformamide	≤ 880ppm	< 880 ppm

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

94.3% × 97.2% × 98.
= 90.65% ∆

Based on the review of the above information, the lot stands released. 10/8/25

	Name	Title	Signature	Date
Prepared by	Sai Rasane	Quality Assistant		05/29/2020
Released by	Wilnelia Hernandez	Quality Assistant	WHR	06/01/2020

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

Emideltide acetate is a solid powder. It is soluble in water at 10 mg/mL in phosphate buffered solution (PBS, pH7.2) base.[20] Because the emideltide acetate has high solubility in water, formulating the proposed SC injectable dosage form at the concentration of 1,000 mcg/mL should not be an issue.

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the Bulk Drug Substance is Poorly Characterized or Difficult To Characterize

No bioburden/endotoxin test is mentioned in the CoA provided by the withdrawn nominator. Endotoxin testing is considered a CQA to control microbiological quality of a BDS intended for an injection product. No such relevant information for emideltide acetate was identified in the public domain.

Conclusions: Emideltide acetate is a salt form of peptide consisting of nine amino acids. As reported in the literature, emideltide acetate is expected to be stable under reported storage conditions below -20°C.

Emideltide acetate is considered not well-characterized from the physical and chemical characterization perspectives based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC) , and (2) certain critical characterization data specific to emideltide acetate were not found in the publicly available scientific literature, and the provided CoA, which was offered to establish identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, and endotoxins). As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of emideltide acetate when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as emideltide acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

B. Has the Substance Been Used Historically in Compounding?

This evaluation focuses on emideltide (free base) and emideltide acetate for SC administration and its use in opioid withdrawal and two sleep disorders that included chronic insomnia and narcolepsy; however, FDA searched generally for information on the historical use of emideltide-related BDSs in compounding. Information about use may not specify specific attributes of the product, such as ROA. Databases searched for information on for this evaluation included PubMed, EMBASE, European Pharmacopoeia (11.8 Edition)[21], Japanese

[20] Information available at https://cdn.caymanchem.com/cdn/insert/34426.pdf. Accessed 05/22/25.
[21] Information available at https://pheur.edqm.eu/home (subscription required). Accessed 03/31/25.

Pharmacopoeia (18th Edition),[22] International Pharmacopoeia (12th Edition),[23] NatMed Pro Database,[24] GlobalEdge,[25] USP/NF,[26] FDA Adverse Event Reporting System (FAERS) public dashboard,[27] Compounding Today,[28] Google/Google Scholar and the Outsourcing Facility Product Reporting Database.[29] It is often unclear which form of emideltide is being discussed in information from these sources and whether it was compounded or not. Therefore, FDA will consider the information discussed in this section in its evaluation of all forms of emideltide, as appropriate.

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

The nominators submitted 33 articles but none of the articles explicitly discussed the use of a compounded formulation of emideltide-related products in humans.[30] A literature search revealed a human study involving emideltide published as early as 1981 (Schneider-Helmert et al. 1981). However, it is unclear whether this study used a compounded emideltide-related drug product. Based on a press release from the office of the U.S. Attorney for the Eastern District of Kentucky, a pharmacy compounded and distributed products containing emideltide from 10/25/18 to 4/1/20, but it is unclear which form of emideltide was being used to compound the products.[31]

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

A literature search revealed that emideltide-related BDS have been studied in various medical conditions. Several articles discuss the use of emideltide for sleep disorders (Schneider-Helmert and Schoenenberger 1981; Bes et al. 1992; Monti et al. 1987). It is unclear whether these studies used compounded emideltide-related drug products.

Emideltide has also been studied for alcohol and opioid withdrawal (Dick et al. 1984; Backmund et al. 1998). One study discussed the use of intravenous (IV) emideltide 35 nmol/kg body weight diluted in 4 mL of 0.9% saline for opioid detoxification. This study noted that emideltide was provided by Strathmann AG & Co., Hamburg, Germany and is "not yet available for clinical

---

[22] Information available at https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0029.html. Accessed 03/31/25.
[23] Information available at https://digicollections.net/phint/2025/index.html#d/b.1. Accessed 04/13/26.
[24] Information available at https://naturalmedicines.therapeuticresearch.com/ (subscription required). Accessed 04/02/25.
[25] Information available at https://globaledge.msu.edu/industries/healthcare/regulatory-agencies. Accessed 04/02/25.
[26] Information available at https://www.uspnf.com/ (subscription required). Accessed 04/02/25.
[27] Information available at https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. Accessed 04/02/25.
[28] Information available at https://compoundingtoday.com (subscription required). Accessed 04/02/25.
[29] Information available at https://dps.fda.gov/outsourcingfacility. Accessed 04/02/25.
[30] Nomination of "emideltide" from Wells Pharmacy Network (Document ID:FDA-2015-N-3534-0287) can be accessed at https://www.regulations.gov/document/FDA-2015-N-3534-0287; Nomination of "DSIP" from LDT Health Solution Inc (Document ID: FDA-2018-N-2973-0002) can be accessed at https://www.regulations.gov/document/FDA-2018-N-2973-0002. Accessed 04/02/25.
[31] Information available at https://www.justice.gov/usao-edky/pr/nicholasville-compounding-pharmacy-and-its-owner-sentenced-unlawful-distribution. Accessed 03/01/24.

use" (Backmund et al. 1998, 258). Another article discusses the use of intravenous emideltide for alcohol or opiate withdrawal. The study authors note that emideltide was administered once "withdrawal symptoms had become obvious" at a dose of 25 nmol/kg body weight diluted in 10 mL of "physiological serum" (Dick et al. 1984, 365). The study authors noted that the emideltide used in the study was provided by Hoffman-La Roche & Cie S.A., Basel. It is unclear whether the emideltide used in either of these studies was compounded.

An online search revealed integrative neurology clinics, medical concierge services, medical spas, wellness clinics, and online retailers in the US marketing emideltide-related drug products for various uses including sleep disorders, stress reduction, pain management, cancer, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease), alcohol and drug detoxification. It is unclear whether compounded products are being used in these instances.[32]

3. How Widespread Its Use Has Been

No outsourcing facilities have reported compounding drug products containing emideltide-related BDS to FDA.[33] An online search identified websites of integrative neurology clinics, medical concierge services, medical spas, wellness clinics, and online retailers in the US that are marketing emideltide injection and nasal spray products.[34] Many of the websites do not describe or clearly state whether the emideltide-related products marketed are compounded.

One website offers emideltide 2 mg/mL in a 4 mL vial and provides "sterile injection syringes" and "detailed instructions" in a "ready to use" kit. This website claims that their emideltide product is "pharmaceutical grade" and is "made in the USA." The website also offers a "complementary telemed consult" for "training purposes at the request of the patient."[35] An online neurology clinic offers prescriptions for emideltide 5 mg and states that it is available as a "lyophilized powder form that can be reconstituted using sterile water." The website claims that emideltide is available for SC injection or as a nasal spray and recommends purchasing emideltide from "reputable compounding pharmacies" but does not specifically name any compounding pharmacies offering emideltide-related products.[36] An online retail website offers emideltide 5 mg vials in 3 mL vacuum-sealed vials and states that the product is "American-

[32] Information available at https://drjennpb.com/product/dsip-kit/, https://lifexmd.com/peptide-therapy-for-sleep-all-about-dsip/, https://mindbodyneurology.com/product/dsip/, https://www.limitlesslifenootropics.com/product/dsip-delta-sleep-inducing-peptide-5mg/. Accessed 08/21/24.

[33] Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the FD&C 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 six-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.

[34] Information available at https://drjennpb.com/product/dsip-kit/, https://lifexmd.com/peptide-therapy-for-sleep-all-about-dsip/, https://mindbodyneurology.com/product/dsip/, https://www.limitlesslifenootropics.com/product/dsip-delta-sleep-inducing-peptide-5mg/. Accessed 03/18/24.

[35] Information available at https://drjennpb.com/product/dsip-kit/. Accessed 04/04/24.

[36] Information available at https://mindbodyneurology.com/product/dsip/. Accessed 04/04/24.

made" and is of the "highest standard possible."[37] None of the websites searched indicate whether their marketed products contain the base or a salt or ester of emideltide. An online search did not identify any compounding pharmacies marketing emideltide-related compounded preparations.

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

No form of emideltide is recognized in the European Pharmacopoeia (11th Edition, 11.8), the Japanese Pharmacopoeia (18th Edition), or the International Pharmacopoeia (11th Edition). Emideltide (free base) and emideltide acetate are not registered drugs in any country searched via GlobalEdge.

Conclusions: It is often unclear whether the emideltide discussed in the sources considered for this section is a salt formulation or the free base. Emideltide-related BDS have been studied for use in humans since at least 1981. There is evidence that emideltide-related BDS have been used in compounding since at least 2018. Emideltide-related injection and intranasal products are available in the US through integrative neurology clinics, medical concierge services, medical spas, wellness clinics, and online retailers for various uses. However, it is unclear whether these products are compounded or if pharmacies are currently compounding products containing emideltide-related BDS. At the time of this evaluation, currently available data and published literature is too limited to inform the historical use of any form of emideltide compounded drug products.

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

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 review of pertinent information from these databases, this section provides a brief overview and a discussion of the uses evaluated, chronic insomnia, narcolepsy, and opioid withdrawal.

The clinical articles submitted by the nominators and those identified by FDA do not always clearly identify whether the emideltide form administered in the clinical studies was a salt formulation or the free base. Therefore, the substance will be generally referred to as emideltide, unless the article under discussion clearly specifies the use of the free base or the acetate salt.

1. Chronic Insomnia

American Academy of Sleep Medicine (AASM) clinical practice guideline defined insomnia 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 (Sateia et al. 2017). Appendix 1 includes diagnostic criteria on insomnia disorder as

[37] Information available at https://www.limitlesslifenootropics.com/product/dsip-delta-sleep-inducing-peptide-5mg/. Accessed 04/04/24.

published in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision (DSM-5-TR).

Prevalence of chronic insomnia is estimated to be at least 6% to 10% and is more common in women, older adults, persons who work irregular shifts, and in persons with disabilities (Medalie and Cifu 2017; Winkelman 2015). Chronic insomnia is associated with numerous adverse effects on function, health, and quality of life (Sateia et al. 2017). Direct and indirect costs of insomnia in the United States estimates $100 billion, primarily due to lost productivity, health care resource use and accidents (Shaha 2023).

Goals of treating insomnia are to improve sleep quality or satisfaction and to resolve daytime consequences (Edinger et al. 2015). AASM clinical practice guideline developed a list of patient-oriented clinically relevant outcome measures to guide clinical decision making and defined clinical significance thresholds for each outcome to determine if a change in an outcome was clinically significant (Appendix 2). These include sleep onset latency (SOL),[38] total sleep time (TST),[39] wake after sleep onset (WASO),[40] quality of sleep (QOS),[41] sleep efficiency (SE),[42] and number of awakenings (NOA).[43] The sleep variables can be objectively assessed in a sleep laboratory with polysomnography or actigraphy, or subjectively with patient-reported sleep diaries, questionnaires, and sleep logs (Sateia et al. 2017).

Treatment of insomnia often involves psychological therapy, pharmacologic therapy, or multimodal approaches. The American College of Physicians (ACP) clinical practice guideline recommends that all adult patients receive cognitive behavioral therapy (CBT-I)[44] as the initial treatment for chronic insomnia disorder (Qaseem et al. 2016). Pharmacologic therapies (see Section II.C.1.c) include benzodiazepines, nonbenzodiazepine sedative-hypnotics, ramelteon, doxepin, and dual orexin receptor antagonists (DORAs). The AASM or ACP practice guidelines on the treatment of chronic insomnia in adults do not discuss the use of emideltide.

[38] SOL refers to the amount of time from lights turned off until the onset of any sleep stage. Normal SOL in adults is less than 20 minutes. In children, sleep latency is estimated at 10–26 min, depending on study methods. Sleep latency does not change between childhood and adolescence (Zolovska and Shatkin 2013). Prolonged sleep latency would be characterized as difficulty falling asleep.

[39] TST refers to sleep duration during a given sleep period time (usually at night). Reduced TST relates to prolonged SOL, night awakenings, and early-morning waking.

[40] Wake after sleep onset is defined as the sum of wake time individuals spend awake after sleep onset and before awakening (or sleep offset). Night awakenings reference the number of complete awakenings occurring after sleep initiation.

[41] QOS is a patient-reported measure, the definition of which varies by measurement tools and patient perceptions.

[42] SE is defined as the percentage of time spent in bed during which sleep occurs; it is calculated as (TST / time in bed) × 100.

[43] NOA is defined as the number of awakenings after sleep onset, excluding the final awakening.

[44] CBT-I is multimodal cognitive behavioral therapy targeted specifically to insomnia. It consists of a combination of cognitive therapy, behavioral interventions (such as sleep restriction and stimulus control), and educational interventions (such as sleep hygiene).

Clinical trials to support efficacy of FDA-approved drugs indicated for insomnia evaluated endpoints such as sleep latency, sleep duration, SE, and NOA as recorded on polysomnogram and by patient reports to establish efficacy in confirmatory clinical trials.

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

The nominator cited four articles that discussed emideltide for the treatment of chronic insomnia. However, we limited our discussion in this section to three articles (Schneider-Helmert and Schoenenberger 1981; Schneider-Helmert 1987; Bes et al. 1992). The fourth article (Schneider-Helmert et al. 1981) discussed use of emideltide in healthy volunteers (See Section II.D.2.a).

We also searched published medical literature on emideltide for the treatment of chronic insomnia and retrieved additional publications (Graf and Kastin 1986; Monti et al. 1987; Schneider-Helmert and Schoenenberger 1983; Schneider-Helmert 1986). The key findings of publications identified in the FDA search and those included in the nomination are summarized below.

Schneider-Helmert and Schoenenberger 1981:

This randomized (R), double-blind (DB), intra-subject placebo-controlled (PC) crossover (CO) study in six middle-aged subjects with chronic insomnia investigated the effects of IV emideltide on disturbed sleep.[45] During three nights of test periods, subjects were randomly assigned to either the sequence placebo-emideltide-placebo or emideltide-placebo-emideltide and received placebo or emideltide 25 nmol/kg IV over 4 minutes immediately before bedtime. Study analyzed polysomnographic recordings as well as subjective ratings of sleepiness and daytime activities self-reported in a diary and questionnaire using Stanford Sleepiness Scale (SSS).[46]

Compared to the nights that each subject was on placebo, an analysis of 60-min intervals of sleep recording showed slight arousing effect in the first hour after emideltide injection, however, sleep-promoting effects began in the second hour after emideltide injection and persisted up to 6 hours during the night, with fewer interruptions during sleep. Emideltide did not influence SOL or final waking times compared to placebo treatment, whereas the authors reported "tendencies toward a lower NOA and a higher total SE (ratio time asleep/recording time)". The SSS ratings showed no significant difference in day-time activity or sleepiness although mean sleepiness scale indicated higher alertness in the morning after emideltide than placebo.

There were several study limitations. The study had small sample size that evaluated six subjects where there was intra-(within) subject comparison of effects of drug versus placebo on sequential nights. It was unclear based on the sequence for the treatment period: either placebo-emideltide-placebo or emideltide-placebo-emideltide, whether there may have been delayed

[45] Subjects complaining primarily of unstable sleep with too many awakenings and difficulties in staying asleep; this was objectively confirmed by the sleep recording data of the initial nights on placebo.
[46] The SSS represents a scale for the subjective evaluation of sleepiness based upon self-rating (Schneider-Helmert et al.1981). A 7-point scale with '1' for the highest possible level of alertness (Schneider-Helmert 1987).

effects of emideltide when subsequent night polysomnography recording was obtained when subjects were on placebo. Schneider-Helmert et al. (1981) reported that 13-22 hours after emideltide administration delayed effects of emideltide on subsequent sleep were observed (see Section II.D.2.a). Furthermore, there was insufficient information to interpret effectiveness for the following reasons: results were reported in p values and the differences in some of the outcomes reported mean change in percentages without numerical data for sleep outcomes following emideltide treatment only without reporting results for placebo. It is unclear whether the observed "tendencies toward a lower NOA and a higher total sleep efficiency" in small numbers of subjects were clinically meaningful changes.

Schneider-Helmert 1987:

This DB, "placebo-controlled"[47] study investigated the effects of IV emideltide on sleep and daytime performance in 14 middle-aged subjects with chronic insomnia. Subjects received seven successive emideltide IV injections 30 nmol/kg on nights 3 (treatment 1) through 9 (treatment 7). Placebo (IV glucose) was administered during the first night of adaptation period (also considered baseline) and on the posttreatment night. After the first night, the subjects spent a full day in the psychophysiological laboratory for testing of daytime performance and evaluating subjective sleepiness and relaxation using SSS and multiple relaxation test (MRT). These tests were repeated after six emideltide injections. Data on subjective evaluation of sleep, daytime behavior and psychological state were also collected on self-rating post-sleep inventories, mood scale, SSS, and diaries.

Study results for sleep and daytime performance were compared with baseline values within study subjects as well as with an age and sex-matched external control groups of healthy subjects who were administered placebo IV injections to establish normative values for night sleep variables, performance tests[48] and spontaneous sleep tendency as measured by the MRT.

The study reported that initial dose of IV emideltide improved sleep induction and maintenance when compared to the baseline values and were further augmented with continuation of treatment over one week. Mean SOL of 58.4 minutes at baseline was reduced to 38.9 minutes after first emideltide injection and 27.6 minutes after final injection, indicating that subjects went to sleep earlier. Wake after sleep onset was also reduced from mean 120.8 minutes at baseline to 78 minutes and 65.6 minutes after first and last injection, respectively. Total sleep time increased from mean 313 minutes at baseline to 363.1 and 385 minutes, after first and last injections, respectively. Sleep efficiency, which takes TST into consideration, also increased by 27% of the baseline value. Compared to baseline measures, these effects were maintained for the first post-

[47] Because study subjects were compared with externally matched control group who received placebo, FDA interpreted the study design as "externally matched controlled" study rather than the authors interpretation as "placebo-controlled" study. Although author used the term "placebo control" on study subjects who received placebo during baseline and posttreatment night, the analyses were based on subjects who were compared with externally matched control group.

[48] Prior to the study, for assessments of daytime performance, authors conducted independent experiment in 13 subjects with normal sleep and 13 study subjects with chronic insomnia (matched for age and sex) to establish reference values of performance tests that included the MRT. There was insufficient information regarding the reliability and validity of the outcomes for daytime performance that were considered by the authors.

treatment night and were reported statistically significant during study period. Mean values of subjective estimates on mood scales and postsleep inventories, when compared to baseline, also showed higher activation, concentration and wellbeing, less anxiety and lower sleepiness. Daytime performance showed that "there was no significant performance decrement after emideltide in any of the measures extending over a period from 1.5 through 10 hours after morning awakening" suggesting "absence of hang-over effects."

When sleep and daytime performance before and after emideltide were compared with externally matched control group with normal sleep, study reported that emideltide treatment normalized SE, induction (SOL) and maintenance of sleep (WASO) after only one week of treatment. Daytime performance also increased after emideltide to an average of 29% above that of controls, even though daytime performance in subjects with chronic insomnia (prior to any treatment at baseline) was initially not different from that of the controls.

Although the author concluded that emideltide was effective in treatment of impaired sleep and improved daytime functioning in subjects with chronic insomnia there were several study limitations. Particularly, the small sample size and poor study methodology limit interpretations to conclude whether the observed changes in small number of subjects (n=14) were clinically meaningful changes. AASM clinical practice guideline defined clinical significance thresholds and that an adequate control group needs to be appropriately defined to compare the magnitude of these outcomes. Even though the authors described the study as "placebo-controlled", there was no placebo arm in the study, therefore, no results for placebo arm were reported. Comparing clinical benefit of emideltide to matched external control group of healthy subjects is challenging to interpret due to inherent limitations of the externally controlled design (e.g., imbalances in measured and unmeasured confounders).

Bes et al. 1992:

This DB, PC study investigated sleep-inducing, sleep-maintaining or sleep modulating effects of emideltide in 16 subjects with chronic insomnia in the sleep laboratory over five consecutive nights; first two nights were baseline (B1, B2) and three following nights were treatment nights (T1, T2, T3). Half of the subjects received IV emideltide 25 nmol/kg and half of the subjects received placebo (glucose solution) between 5 pm and 7 pm. Independent raters measured objective polysomnographic recordings every night and study subjects filled out profile of mood states (POMS)[49] and sleep quality scale every morning to evaluate subjective tiredness and sleep quality.

Emideltide treated subjects had (numerically) shorter SOL compared to placebo. None of the other variables for objective sleep measures showed any differences neither between nor within the groups. There was no significant difference in objective sleep measures or subjective sleep quality between emideltide group and placebo group.

The authors reported that short-term treatment of chronic insomnia with IV emideltide had little therapeutic benefit as indices of sleep quality, sleep latency and tiredness showed weak effect

[49] POMS was used to measure fatigue and vigor, as expression of subjective tiredness.

compared to placebo, and that difference in sleep latency should be interpreted with caution because the sleep latency for placebo group on second treatment night was considerably higher than any of other nights while there were no changes in sleep latency within emideltide group. The results of the present study indicated that three doses of emideltide showed at best some weak effects. Also, there was a significant difference in POMS dimension of fatigue within emideltide group but not between the groups. Additionally, author addressed several factors to consider when interpreting the results; improvement of baseline night (B2) might have been due to possible rebound sleep from the first night of slight sleep-deprived state.

Schneider-Helmert and Schoenenberger 1983:

This study that discussed the pharmacodynamic response of different regimens of emideltide injections included series of five different investigational studies conducted in small numbers of subjects with chronic insomnia in addition to healthy volunteers. Investigational studies that were series I and II were conducted in healthy subjects who received a single emideltide injection (see Section II.D.2.a. for discussions of data in healthy volunteers for investigational studies). Series III, IV and V in the publication referred to three DB, PC investigational studies in small numbers of subjects with chronic insomnia when IV emideltide 25 nmol/kg (21.3 µg/kg) infusion was administered either over 4 minutes 1 hour prior to bedtime as a single dose (series III) or repeated on four consecutive evenings (series IV) or repeatedly administered on six consecutive mornings (series V).[50]

In series III and IV of investigational studies in subjects with chronic insomnia the authors observed that emideltide infusion over 4 minutes when administered 1 hour prior to bedtime either as single dose or on four consecutive evenings, sleep-promoting effects started to appear in the second hour after emideltide injection and persisted for at least 6 hours during the night with fewer interruptions during sleep. In series IV, when data were compared with normative values, means of sleep variables including SE, percent time of awake and drowsiness, and proportion of rapid eye movement (REM) sleep improved with consecutive treatments. The author stated that these variables after the fourth emideltide injections were closer to the normal values compared to placebo. Of note, the author did not indicate nor describe the methods of obtaining normal values of each sleep variables.

In series V, two sleep-disturbed neurotic subjects with insomnia received repeated emideltide injections in the morning (9:00 AM) for 6 days, which was preceded and followed by days on placebo injections. Improvements in the amount and stability of sleep (i.e., higher SE and reduced indices of arousals or full awakenings from sleep) were reported following emideltide

[50] "In series III, emideltide was administered prior to sleep to six severe chronic insomniacs in a placebo controlled, double-blind, randomized crossover design. In series IV, treatment of 4 severe insomniacs was for the first time repeated daily; emideltide was injected 1 h prior to sleep on 4 consecutive evenings after a baseline placebo period, again with extensive polygraphy under double-blind conditions. Series V was carried out in order to evaluate primarily other psychotropic effects than sleep; emideltide repeated daily injections under double-blind conditions in the morning to 2 sleep-disturbed neurotic inpatients on 6 days, which was preceded and followed by placebo periods, providing wide psychological testing, evaluating psychotherapeutic work and recording night sleep throughout the 2-week experimental period."

when compared with data for days on placebo in the intra-subject assessment. Authors observed that when these two subjects with "disturbed nocturnal sleep" would remain fully active during the day and sleeping was allowed 13 h after emideltide, sleep only occurred when the sleep phase of the circadian rhythm came about, and/or if the environmental conditions were appropriate (i.e., going to bed, no stimulation). Subjective assessment by two psychotherapists indicated that aside from being alert and showing performance improvement, emideltide also improved stress tolerance and coping ability. There are limitations to interpret study results in the series of investigational studies conducted in small numbers of subjects with chronic insomnia where there were insufficient details on study design.

Schneider-Helmert 1986:

This DB study evaluated sleep outcomes in middle-aged (29-59 years, n=9) and elderly (60-83 years, n=9) subjects with chronic insomnia over eight successive nights. After first two nights of placebo (baseline periods), each group stratified by age received IV emideltide 30 nmol/kg each evening over five nights and followed up after one week. Sleep outcomes were recorded during placebo baseline period, emideltide treatment day 5 and 6, and post-treatment nights.

The study reported that the objective sleep outcomes for mean SOL, WASO, TST and SE improved in both groups. In the middle-aged insomnia group, the authors reported improved sleep that reached normal levels by the end of emideltide treatment (compared to externally controlled middle-aged healthy subjects) and was maintained during the follow-up week. In elderly insomnia group who took between 1-2 hours to go to sleep at baseline, sleep latency reduced to within 22-30 minutes after IV emideltide. Although the elderly insomnia group slept fewer hours at baseline (mean TST 241.6 vs. 329.1 middle-aged group) larger immediate treatment effect for TST were observed on IV emideltide compared to middle-aged group (+ 97 minutes in elderly group vs + 57 minutes in middle-aged group).

The author concluded that emideltide corrected pathophysiological mechanisms underlying chronic insomnia. However, small sample sizes, lack of adequate control group and comparing clinical benefits of emideltide to matched external control group limit the interpretation of effectiveness of emideltide for insomnia.

Monti et al. 1987:

This R, DB, PC, CO study evaluated the effects of IV emideltide in six subjects with severe chronic insomnia over nine nights. First three nights were adaptation periods to the laboratory and baseline measurements when subjects were given placebo. During the four nights, subjects randomly received IV emideltide 25 nmol/kg over 4 minutes or placebo. The last two nights were used for assessing withdrawal effects when placebo was again administered. This same procedure was completed twice with a four-day washout period where subjects did not receive any medications.

Although IV emideltide showed slightly decreased sleep latency, almost no change in mean number of nocturnal awakenings and mean increase 20 minutes TST, there were no significant differences compared to baseline measures or placebo phase in this intra-subject study. Subjective ratings of QOS were also not significantly different compared to placebo. The authors

concluded that emideltide effects observed on sleep improvement were of little clinical significance.

Graf and Kastin 1986:

The review article considered data from most of the above-mentioned clinical studies. 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.

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

Insomnia is a commonly encountered disorder; however, it is underdiagnosed and undertreated, leading to a significant health burden characterized by decreased quality of life and increased morbidity and mortality (Shaha 2023). Insomnia is associated with increased motor vehicle accidents and falls, increased healthcare utilization, and decreased survival rates. Insomnia also interacts with various medical conditions and predisposes to development of number of psychiatric disorders (Asnis et al. 2015).

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

There are FDA-approved drug products indicated for the same medical condition as that proposed for the emideltide compounded drug product(s).[51] FDA approved therapies for insomnia in adults are listed in Table 3.

Table 3. FDA-Approved Therapies for Insomnia in Adults[52,53]

FDA Approved Therapy
Ambien, Elduar (zolpidem)
Belsomra (suvorexant)
Dayvigo (lemborexant)
Doral (quazepam)

[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 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.

[52] Information about the drugs listed in this table can be found at the following website: https://fdalabel.fda.gov/fdalabel/ui/search. Accessed 03/26/24.

[53] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information. Accessed 03/26/24.

FDA Approved Therapy
Estazolam
Flurazepam
Halcion (triazolam)
Lunesta (eszopiclone)
Quviviq (daridorexant)
Restoril (temazepam)
Rozerem (ramelteon)
Seconal (secobarbital)
Silenor (doxepin)
Sonata (zaleplon)

There are no FDA-approved treatments for insomnia in the pediatric population. FDA-approved drugs are sometimes prescribed off-label for the management of some sleep disorders in children and adolescents (e.g., antihistamines, a-adrenergic agonists like clonidine, antidepressants, antipsychotics) for their sedative side effects without sufficient information on their efficacy, safety, or the dosing regimen in these populations (Gringras et al. 2017). The dietary supplement melatonin is also sometimes used for sleep in pediatric populations (Ivanenko et al. 2021, Gringras et al. 2017).

Conclusion: There was no study evaluating effectiveness to support use of emideltide (free base) or emideltide acetate via the nominated SC route of administration (ROA) for chronic insomnia. We were only able to find data regarding administration of emideltide via IV ROA.

There is insufficient evidence to make a conclusion on the effectiveness of IV emideltide for chronic insomnia. Although some studies showed that short-term IV emideltide appeared to exert 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 in the two DB PC studies by Bes et al. 1992 and Monti et al. 1987 who conducted similarly designed investigations did not reach the same conclusions. Even when studies yielded positive treatment response, it seems unclear whether observed effects on sleep outcomes provided clinically significant improvement and that the changes were clinically meaningful. Similar observation was noted in another article by Graf and Kastin (1986). This is particularly due to lack of or poor selection of control groups (i.e., externally matched control group); many of the studies included intra-(within) subject comparison of effects of drug versus placebo treatment at baseline, rather than comparing treatments in subjects with chronic insomnia who were in a separate study arm treated with placebo. AASM clinical practice guideline defined clinical significance thresholds and that an

adequate control group needs to be appropriately defined to compare the magnitude of these outcomes. Additionally, small sample sizes in the clinical studies, different baseline characteristics in subjects across these studies and imbalanced outcomes in sleep measures, heterogeneity of subjects with insomnia, different treatment regimens and environmental conditions limit the interpretation of effectiveness of emideltide for insomnia. There was also no information regarding benefit with long-term administration of IV emideltide for chronic insomnia.

Professional society guidelines do not discuss the use of emideltide (free base) or emideltide acetate for insomnia. Insomnia is a serious condition, and there are FDA approved therapies with established efficacy for insomnia.

2. Narcolepsy

Narcolepsy is characterized by sleep-wake instability that manifests as excessive daytime sleepiness (EDS),[54] cataplexy,[55] sleep paralysis (SP),[56] hypnagogic/hypnopompic hallucinations (HH),[57] and disturbed nocturnal sleep (DNS)[58] (Abad 2023). Appendix 3 includes diagnostic criteria on narcolepsy and its subtypes as published in DSM-5-TR.

Narcolepsy is also often associated with REM sleep parasomnias such as vivid dreams and nightmares and non-REM sleep parasomnias such as sleepwalking and enuresis (Barateau et al. 2023). There is a high burden of illness associated with comorbid conditions such as hypertension, stroke, heart failure, myocardial infarction, hyperlipidemia, insulin resistance, thyroid disease, obesity, neuropsychiatric conditions, and other sleep disorders (Abad 2023, Anderson 2021). Mortality rate is 1.5 times higher compared to non-narcoleptics. It is important to diagnose the condition early and manage effectively.

Objective confirmation of narcolepsy diagnosis is required because many narcolepsy patients require life-long therapy with potentially addictive drugs (Abad 2023). The gold standard tests are an overnight polysomnogram followed by a Multiple Sleep Latency Test (MSLT)[59] and a

---

[54] EDS is the most prominent symptom associated with narcolepsy and consists of daily episodes of overwhelming need for sleep or lapse into sleep (sleep attacks) which usually last less than 10 minutes but can last up to an hour.
[55] Cataplexy is an emotionally triggered sudden and transient involuntary loss of skeletal muscle tone with preserved consciousness ranging from partial muscle weakness to complete paralysis, which last from several seconds to several minutes (Abad 2023). Frequency of attacks varies from dozens per day to a few per year (Bassetti et al. 2019).
[56] SP is described as a terrifying and temporary inability to move the limbs, speak, breathe deeply, or open the eyes.
[57] Rapid transitions between wake and REM sleep can result in SP or hallucinations during sleep onset (hypnagogic) or sleep offset (hypnopompic) in 33-80% of narcolepsy patients. Hallucinations can be visual, auditory, kinetic, and tactile.
[58] About 30-95% of patients with narcolepsy experience disrupted night sleep with inability to stay asleep, frequent awakening and reduced TST.
[59] MSLT is an objective measure of a patient's ability or tendency to fall asleep. MSLT checks for EDS by measuring how quickly you fall asleep in a quiet environment during the day. Patient is given five opportunities to

cerebrospinal fluid (CSF) hypocretin-1 test. Evaluation should include a thorough workup of other possible contributing factors of EDS. FDA-approved products for narcolepsy evaluated endpoints such as polysomnogram findings, the MSLT, the Maintenance of Wakefulness Test (MWT)[60] and the Epworth Sleepiness Scale (ESS).[61]

Narcolepsy currently has no known cure, and patients may need long-term treatment. Pharmacological interventions are the mainstay of treatment and are primarily symptom-based. Treatment goals are geared toward reducing EDS, cataplexy, other REM-related symptoms, and nocturnal sleep disruptions to improve patient quality of life. Currently, there are several FDA approved drugs for treatment of EDS and/or cataplexy (see Section II.C.2.c.). AASM[62] recommends that off-label treatments for cataplexy may be considered. Non-pharmacological approaches, including behavioral and psychosocial strategies, are important adjunct interventions to consider alongside pharmacological treatments.

The AASM and the European Narcolepsy guideline[63] published practice guidelines on the treatment of narcolepsy in adults. These guidelines do not discuss the use of emideltide.

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

The nominator did not provide any clinical references to support use of emideltide in narcolepsy. We identified one case report that is described below.

Schneider-Helmert 1984:

35-year-old male with 10 years history of narcolepsy was administered emideltide to evaluate its potential effects on narcolepsy. Three investigational periods included: a week of baseline (B) measurements, a week of evening dose (E) of IV emideltide 25 nmol/kg, and a week of morning dose (M) of IV emideltide 25 nmol/kg. Effects on wakefulness and sleep were evaluated using

---

nap during the day under standardized conditions (usually at a medical sleep facility). Each scheduled nap is 20 minutes in length, with anywhere from 1.5 to 3 hours between naps. A mean sleep-onset latency of 8 minutes of less, and two or more sleep-onset REM episodes (SOREMs) during the naps is consistent with narcolepsy (Anderson 2021). Also known as a daytime nap study, the MSLT is used to diagnose narcolepsy and idiopathic hypersomnia. Available at https://sleepeducation.org/patients/multiple-sleep-latency-test/. Accessed 04/15/24.

[60] The MWT is used to measure how alert you are during the day. It shows whether you can stay awake for a defined period of time. The test is based on the idea that, in some cases, your ability to stay awake may be more important than how fast you fall asleep. This is an indicator of how well you can function and remain alert in quiet times of inactivity. Available at https://sleepeducation.org/patients/maintenance-of-wakefulness-test/. Accessed 10/23/23.

[61] The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP), or their 'daytime sleepiness'. Available at https://epworthsleepinessscale.com/about-the-ess/. Accessed 04/15/24.

[62] Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine Clinical Practice Guideline (Maski et al. 2021).

[63] European guideline and expert statements on the management of narcolepsy in adults and children (Bassetti et al. 2021).

the self-reported SSS, performance test, MSLT, and all-night polysomnography. The study showed that emideltide reduced frequency of sleep attacks (from 6 sleep attacks at B to 3 sleep attacks during weeks of E or M dosing), frequency of naps (from napping daily at B to every second day on E dosing and every third day on week of M dosing). The subject reportedly experienced increased activity, alertness, and performance during daytime. These effects, however, were more pronounced with morning injections than evening injections since the performance dropped in the late afternoon with evening injections whereas steady level of performance maintained throughout the day with morning injections. The TST following M injections was 287 minutes whereas at B and E dosing TST was up to 349 minutes. In addition, the study reported that emideltide treatment did not provoke cataplectic symptoms, SP or HH.

The author concluded that these effects were due to an accentuation of circadian wake-sleep rhythm similar to emideltide effects on insomnia found in several studies. However, single-subject case report limits interpretation of effectiveness of emideltide due to insufficient methodological rigor, potential recall bias, researcher subjectivity and issues of reliability and external validity.

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

Narcolepsy is a rare, disabling, and chronic sleep disorder characterized by EDS that is associated with psychiatric co-morbidities and medical comorbidities affecting the endocrinological and cardiovascular domains. There is increased risk of mortality associated with narcolepsy. A constellation of altered neuropsychological process as well as other psychological aspects contributes to a detrimental impact on the patient's quality of life and economic burden (Franceschini et al. 2020).

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

There are FDA-approved drug products indicated for the same medical condition as that proposed for the emideltide compounded drug product(s).[64] FDA approved therapies for narcolepsy in adults are listed in Table 4.

[64] 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.

Table 4. FDA-Approved Therapies for Narcolepsy in Adults[65]

FDA Approved Therapy
Stimulants
Modafinil
Armodafinil
Solriamfetol
Methylphenidate
Amphetamine and Dextroamphetamine
Selective H3 receptor antagonist/inverse agonist
Pitolisant
Gamma-hydroxybutyric acid B subtype (GABA B) receptor agonist
Sodium oxybate
Sodium oxybate extended release
Low sodium oxybate

Pharmacological treatments for reducing EDS in adults include stimulants/wake-promoting agents, selective H3 receptor antagonist/inverse agonist and gamma-hydroxybutyric acid B subtype ($GABA_B$) receptor agonist. First-line medications include modafinil and armodafinil, solriamfetol, pitolisant, sodium oxybate, sodium oxybate extended release and low sodium oxybate (Barateau et al. 2023). Second-line medication includes methylphenidate. Third-line medications include amphetamine and dextroamphetamine (Franceschini et al. 2020).

Pharmacological treatments for cataplexy include sodium oxybate and pitolisant. Anti-depressants such as selective serotonin reuptake inhibitors (e.g., fluoxetine), selective serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) and tricyclic antidepressants (e.g., clomipramine) are used off label. However, abrupt withdrawal from antidepressant medications can trigger rebound status cataplecticus.

Conclusion: There was no study evaluating effectiveness to support use of emideltide (free base) or emideltide acetate via the nominated SC ROA for narcolepsy. We were only able to find one case report regarding administration of emideltide via IV ROA for narcolepsy.

[65] Information about the drugs listed in this table can be found at the following website: https://fdalabel.fda.gov/fdalabel/ui/search. Accessed 03/26/24.

There is insufficient evidence to make a conclusion on the effectiveness of IV emideltide (free base) or emideltide acetate for narcolepsy. The single-subject case report limits interpretation of effectiveness of emideltide due to insufficient methodological rigor, potential recall bias, researcher subjectivity, issues of reliability and external validity that limits its generalizability. Narcolepsy is a chronic condition and there is lack of long-term data on effectiveness. Professional society guidelines do not discuss the use of emideltide (free base) or emideltide acetate 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.

3. Opioid Withdrawal

Physical dependence to opioids is an expected physiological response to chronic opioid exposure, associated with a down-regulation of endogenous endorphins and dynorphins. Abrupt cessation of opioids in physically dependent patients results in acute withdrawal symptoms. Opioid withdrawal symptoms occur both in patients who have been using prescribed opioids appropriately and in patients with opioid use disorder (OUD). Precipitated opioid withdrawal occurs when substances with opioid antagonist properties, such as naltrexone, naloxone, or buprenorphine, are taken concurrently with full opioid agonists.

OUD is a chronic, relapsing neurobiological disease influenced by genetic, psychosocial, and environmental factors included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Pergolizzi et al. 2020; Appendix 4). Among people aged 12 or older in the United States in 2023, 2.0 percent (or 5.7 million people) met diagnostic criteria for OUD in the past year.[66] With an increase in fentanyl in the illicit drug supply, the age-adjusted rate of opioid overdose deaths increased over the past two decades, from 4.1 deaths per 100,000 standard population in 2002 to 25.0 in 2022.[67] In patients with OUD, the occurrence of withdrawal symptoms and the relief of withdrawal when opioids are used are important drivers of continuing use. Concern about withdrawal prevents some patients with OUD from seeking treatment, and symptoms of withdrawal contribute to relapse in patients attempting to recover from OUD.

Opioid withdrawal syndrome consists of a wide range of symptoms that are both physiological and psychological as outlined in DSM-5-TR (Appendix 5). These symptoms are related to noradrenergic hyperactivity. Opioid withdrawal symptoms can be very uncomfortable but are usually not life-threatening. The onset of opioid withdrawal symptoms depends on the half-life of the specific opioid used. For instance, discontinuation of short-acting opioids (e.g., heroin) may result in symptoms starting within 12 hours, reaching maximum intensity in 36-72 hours and lasting 7-10 days. In contrast, discontinuation of long-acting opioids (e.g., methadone) may

[66] See Substance Abuse and Mental Health Services Administration (SAMHSA). Key Substance Use and Mental Health Indicators in the United States: Results from the 2023 National Survey on Drug Use and Health. Available at https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf. Accessed 06/25/25.

[67] See CDC. NCHS Data Brief: Drug Overdose Deaths in the United States, 2002–2022. March 2024. Available at https://www.cdc.gov/nchs/data/databriefs/db491.pdf. Accessed 06/25/25.

result in withdrawal symptoms within 30 hours, peak at 72-96 hours and last for ≥ 14 days (Pergolizzi et al. 2020).

Several clinician-rated and patient-reported scales for assessing opioid withdrawal have been developed, including: Objective Opioid Withdrawal Scale (OOWS),[68] Clinical Opioid Withdrawal Scale (COWS)[69], Subjective Opioid Withdrawal Scale (SOWS)[70] and the Clinical Institute Narcotic Assessment (CINA).[71] These scales have been used to measure opioid withdrawal symptoms during the initial assessment to make the diagnosis or to assess effectiveness of withdrawal management in clinical practice.[72]

Effective opioid withdrawal management is important for treatment engagement and mitigation of risks of opioid relapse and overdose (Torres-Lockhart et al. 2022). The primary goals of opioid withdrawal management are to relieve acute suffering of opioid withdrawal and engage patients in initiating treatment for OUD (Torres-Lockhart et al. 2022). For most patients with OUD, the maintenance use of either mu agonist, partial agonist, or antagonist medications (combined with psychosocial treatment) is considered superior to withdrawal management (combined with psycho-social treatment), followed finally by psychosocial treatment on its own. Withdrawal management is generally believed to be associated with higher rates of relapse to illicit opioid use and overdose compared to maintenance treatment options.[73]

Opioid withdrawal is usually medically managed in either inpatient or outpatient settings using one of two approaches. In the first approach, the opioid of abuse is replaced with the opioid agonist methadone or partial opioid agonist buprenorphine to relieve symptoms. The dose of methadone or buprenorphine is then gradually reduced to allow the patient to adjust to the absence of an opioid ("detoxification") (Schuckit 2016). In the second approach, alpha-2-adrenergic agonists, such as clonidine or lofexidine, are used to reduce withdrawal symptoms after opioid cessation. Of these medications, only lofexidine is approved for the treatment of opioid withdrawal. In addition, a variety of "comfort medications" to treat specific withdrawal symptoms (e.g., over-the-counter OTC analgesics, anti-diarrheals, anti-emetics, etc.) are often used, either by health care providers or by patients themselves. These medications may also be used as adjunctive treatment with buprenorphine or methadone for withdrawal management.

---

[68] OOWS is an objective measure in which the clinician checks for 13 signs of opioid withdrawal (e.g., yawning, perspiration).
[69] COWS is a clinical assessment for 11 medical signs and symptoms of opioid withdrawal (e.g., gastrointestinal distress).
[70] SOWS is a measure of 16 subjective symptoms of withdrawal, in which the patient rates their experience on a 5-point scale (e.g., I feel restless).
[71] CINA is a mix of subjective and objective measures assessing 11 common signs and symptoms of opioid withdrawal.
[72] The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update, page 25/91.
[73] The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update, page 27/91.

Professional Society and Other Guidelines:

The American Society of Addiction Medicine (ASAM) published clinical practice guideline[74] on the treatment of opioid withdrawal. The Substance Abuse and Mental Health Services Administration (SAMHSA) has also published best practices for detoxification, including opioid detoxification.[75] Neither of these guidelines discuss the use of emideltide in adults or children.

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

The nominators cited two references for opioid withdrawal (Dick et al. 1984; Backmund et al. 1998)

Dick et al. 1984:

The uncontrolled, open-label study evaluated emideltide in the treatment of withdrawal in individuals who use alcohol (n=47) or opioid (n=60; 40 males and 20 females) and were admitted to the inpatient facility at the University Hospital of Psychiatry in Geneva, Switzerland. However, we limit our discussions to effectiveness of emideltide in the sub-group of individuals who used opioids. These subjects reported taking heroin, methadone, both methadone and heroin, or pentazocine with varying doses and duration. Emideltide IV 25 nmol/kg (0.0214 mg/kg) was administered for withdrawal symptoms with maximal daily number of 6 injections for up to six days. Two different regimens were utilized; (1) Injection on request during recurrence of withdrawal symptoms and discontinuation after definitive clearance, and (2) Injections at fixed intervals scheduled every 6-8 hours during 3 consecutive days. For both regimens, additional injection was administered within 1 hour if it was ineffective. If still unsuccessful, the subject was considered a treatment failure and switched to other therapeutics. Treatment effects were assessed based on the clinical evaluation of objective signs of withdrawal by staff members and subjective report by the study subjects.

Of the 60 subjects enrolled who used opioids, 40 subjects who were assessed, were reported to show "good decrease or complete disappearance of the following objective signs": tachycardia, hypertension, tremor, perspiration, gooseflesh, yawning, lacrimation, diarrhea, rhinorrhea as well as subjective somatic symptoms: abdominal cramps, aching bones and muscles, hot and cold fleshes, nausea and anorexia. Anxiety decreased slowly within hours following several injections. However, certain number of subjects who were considered to have been successfully treated experienced a relapse of anxiety with marked insomnia within 24-72 hours after treatment discontinuation; only 13 subjects did not experience insomnia. When comparing the influences of the two different treatment regimens stated above, recurrent anxiety and insomnia occurred more often when injections were given on request.

[74] The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update, pages 1-91.

[75] See SAMHSA. Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) 63. Available at https://library.samhsa.gov/sites/default/files/pep21-02-01-002.pdf. Accessed 06/25/25.

The authors concluded that emideltide improved both objective and subjective clinical signs and symptoms of opioid withdrawal. However, the authors noted that "nothing allows [sic] to draw any conclusion as to a potential usefulness of a maintenance treatment with DSIP." The study design also limits interpretation of effectiveness of emideltide due to small study sample size, ill-defined study population, lack of blinding, absence of a comparison group, and use of subjective assessments which were not evaluated using standard clinical scales (refer to Section II.C.3). Most importantly, the study protocol did not adequately describe the methods used to confirm the outcomes of improved or unimproved.

Backmund et al. 1998:

This open label study evaluated effectiveness of short-term emideltide for treatment of acute opioid withdrawal syndrome in seven subjects meeting the DSM-4 diagnosis of opioid dependence. The presence and severity of withdrawal symptoms were measured before and during detoxification using the SOWS 1. Subjects with a score more than 25 on the SOWS 1 were administered emideltide IV 35 nmol/kg using a fixed schedule: on day 1, four and up to six injections; on days 2, 3, and 4, four injections; on days 5, 6, and 7, two injections. The study reported mean SOWS 1 scores decreased from 34.4 one hour before the first injection to 17.8 after the first injection (timepoint of post-injection comparison measurement not provided by the authors). The study also reported improvements in both physical and withdrawal symptoms. However, only two subjects received all scheduled emideltide injections and successfully detoxified after the scheduled regimen. These two subjects on day 3 required doxepin to treat insomnia. The recurrence of withdrawal symptoms was not suppressed after the second and following injections except in one subject.

The authors concluded that emideltide reduced opioid withdrawal symptoms after the first injection, however "it remains an open question whether DSIP could be an effective alternative detoxification approach" and stated that further placebo-controlled studies should be performed to verify effectiveness of emideltide in the treatment of acute opioid withdrawal symptoms. Similar to previous experimental studies, the study design also limits interpretation of effectiveness of emideltide due to small sample size, lack of blinding, and absence of a comparison group.

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

Opioid use disorder is a public health crisis. Between 1999 and 2017, there were more than 702,000 deaths from drug overdose in the United States, of which 57% involved opioids. There has been an increase in hospitalization due to illicit opioid use and their comorbid conditions (Herscher et al. 2020). Opioid withdrawal symptoms, however, can be very uncomfortable but are usually not life-threatening (Pergolizzi et al. 2020).

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

There are FDA-approved and/or OTC monograph drug products indicated for the same medical condition as that proposed for the emideltide compounded drug product(s).[76] Approved therapies for opioid withdrawal are listed in Table 5 below.

Table 5. FDA-Approved Therapies for Opioid Withdrawal in Adults[77]

Clinical Indication	FDA-Approved Therapy
Opioid withdrawal	**Full mu-opioid receptor agonist** Methadone Hydrochloride **Alpha-2 adrenergic agonists** Lofexidine

Methadone is the only FDA-approved opioid for detoxification (Pergolizzi et al. 2020).

FDA has approved numerous buprenorphine and buprenorphine/naloxone formulations for the treatment of OUD. However, none of the available forms of buprenorphine are FDA-approved for withdrawal management, specifically, but they may be used for this indication. Due to risk of precipitated opioid withdrawal (see section II.C.3. for definition) with buprenorphine, it is recommended that opioid-dependent patients wait until they experience mild to moderate opioid withdrawal before starting the medication.[78]

Alpha$_2$-adrenergic receptor agonists such as FDA-approved lofexidine and off-label clonidine can be used for symptomatic management of opioid withdrawal. They are used to mitigate opioid withdrawal symptoms by reducing noradrenergic hyperactivity and do not confer abuse liability (Pergolizzi et al. 2020). They are also used when patients taper off buprenorphine or methadone and in preparation for initiating naltrexone.[79] Other non-opioid adjunctive medications including

[76] 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.

[77] Information about the drugs listed in this table can be found at the following website: https://fdalabel.fda.gov/fdalabel/ui/search. Accessed 03/26/24.

[78] The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update, page 42/91.

[79] The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update, page 35/91.

analgesics, antiemetics, antidiarrheals, and antihistamines are used for specific symptoms associated with opioid withdrawal and are available over the counter (Hersher et al. 2020).

Conclusion: There was no study evaluating effectiveness to support use of emideltide (free base) or emideltide acetate via the nominated SC ROA for treatment of opioid withdrawal. We were only able to find data regarding administration of emideltide via IV ROA.

There is insufficient evidence to make a conclusion on the effectiveness of emideltide (free base) or emideltide acetate via the IV ROA for the treatment of opioid withdrawal. Although available clinical studies reported positive outcomes of emideltide on improvement of both objective and subjective opioid withdrawal symptoms, results should be interpreted cautiously due to small number of published studies, small sample sizes, different treatment regimen and several limitations owing to nonrandomized and uncontrolled study design. Professional society guidelines do not discuss the use of emideltide (free base) or emideltide acetate for opioid withdrawal. There are FDA approved therapies with established efficacy for opioid withdrawal.

Overall Conclusion

Based on available clinical data, there is insufficient evidence concerning effectiveness to support the use of emideltide (free base) or emideltide acetate via the IV ROA for the treatment of chronic insomnia, narcolepsy, and opioid withdrawal. Clinical studies for chronic insomnia appear to be inconclusive and at best preliminary. Publications included in this evaluation by several authors did not reach same conclusion and for those studies that showed positive treatment response had poor study methodologies (i.e., lack of or poor selection of control groups) to assess whether any changes in outcomes were clinically meaningful. Studies were also limited by small sample sizes, different baseline characteristics in subjects across studies, different treatment regimen and unknown long-term benefit. Clinical studies for narcolepsy and opioid withdrawal were limited by clinical study design (case report, study without blinding or randomization), small sample size, large variabilities of subjective assessments, and wide range of doses and treatment durations.

FDA did not identify any data to support the effectiveness of emideltide (free base) or emideltide acetate for the treatment of chronic insomnia, narcolepsy, and opioid withdrawal via the nominated SC ROA.

Clinical practice guidelines do not discuss the use of emideltide (free base) or emideltide acetate for the management of chronic insomnia, narcolepsy, and opioid withdrawal. Sleep disorders encompassing chronic insomnia and narcolepsy as well as opioid withdrawal are serious conditions and there are FDA-approved treatments with established efficacy for these medical conditions.

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

1. Nonclinical Assessment

The nominators submitted nonclinical information. Specifically, Wells Pharmacy Network submitted a list of four articles reporting nonclinical studies of emideltide-related BDSs. Three

articles report pharmacological properties of emideltide,[80] and one reports the effects of repeat-dose exposures to an emideltide-containing product on the incidence of spontaneous cancers in mice.[81] LDT Health Solutions submitted a list of 16 additional nonclinical studies published in the literature. Of the 16 studies, 15 describe pharmacological properties of emideltide-related BDSs[82] and one describes the blood brain barrier permeability of a derivative of emideltide.[83]

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

The nonclinical articles submitted by the nominators and those identified by FDA do not always clearly identify emideltide as free base or acetate salt. Therefore, in this section, the substance used in in-vitro and in-vivo experiments discussed in the articles will be generally referred to as emideltide-related BDS, unless the article under discussion clearly specifies the use of the free base or the acetate salt.

a. General Pharmacology of the Drug Substance

Emideltide[84] is the nonproprietary name assigned to a nonapeptide that was first isolated from the blood of rabbits in response to electrical stimulation of the thalamus and shown to have sleep-inducing properties (Schoenenberger et al. 1977). Figure 5 illustrates the amino acid sequence of emideltide, which is the active moiety of emideltide (free base) and emideltide acetate.

Figure 5. Amino Acid Sequence of Emideltide (Adapted From Bjartell et al. 1988)

Sequence is from the N- to the C-terminal domain. All are natural L amino acids.
Ala: alanine; Asp: aspartic acid; Glu: glutamic acid; Gly: glycine; Ser: serine; Trp: tryptophan.

Since its discovery in the 1970's, emideltide has been commonly referred to as delta sleep-inducing peptide (or DSIP) in the literature (Iyer et al. 1988; Kafi et al. 1979; Monnier et al. 1977a; Polc et al. 1978; Schoenenberger et al. 1977; Šušić 1987; Ursin and Larsen 1983; Young and Key 1984). The name DSIP was originally coined because treatment of animals with the

[80] Khvatova et al. 1995; Khvatova et al. 2003; Nakamura et al. 1988.
[81] Popovich et al. 2003.
[82] Gimble et al. 2009; Graf and Kastin 1984; Iyer et al. 1988; Kastin et al. 1980; Kovalzon et al. 2006; Kutilin et al. 2014; McLay et al. 2001; Mikhaleva et al. 2014; Nakamura et al. 1986; Oaknin et al. 1986; Sahu and Kalra 1987; Spath-Schwalbe et al. 1995; Stanojlovic et al. 2004; Sudakov et al. 1995; Yukhananov et al. 1992.
[83] Banks et al. 1984.
[84] World Health Organization (1993) INN Proposed List 70, available at https://www.who.int/publications/m/item/inn-pl-70. Accessed 05/28/24.

peptide consistently increased the power of electroencephalographic (EEG) delta waves and spindles, which are hallmarks of the deep sleep phase also known as non-rapid eye movement (NREM) sleep (Girardeau and Lopes-Dos-Santos 2021).[85] To be consistent with the name of the bulk drug substance the nominator submitted, the peptide is referred to as emideltide throughout this section.

The delta sleep-inducing effects of emideltide appear to be conserved across species. For instance, intracebroventricular (ICV) treatment of rabbits with an emideltide-related BDS (6 nmol/kg; 3.5-minute ICV infusion): (i) induced a significant increase in the power of EEG delta waves that was accompanied by an increase in spindle activity, and (ii) had no effect on the power of higher frequency EEG waves characteristic of REM sleep (Monnier et al. 1977a; Schoenenberger and Monnier 1977). Likewise, ICV treatment of cats or rats with an emideltide-related BDS (7 nmol/kg) significantly prolonged their NREM sleep while having no effect on the duration of their REM sleep, as assessed in EEG recordings (Šušić et al. 1987; Ursin and Larsen 1983).

The delta sleep-inducing properties of emideltide have been observed not only when it is delivered directly into the brain but also when it is delivered via peripheral parenteral routes of administration, including IV, SC, and intraperitoneal (IP). For instance, IV treatment of free-moving rabbits with an emideltide-related BDS (30 nmol/kg) significantly increased the power of EEG delta waves, with the effect being observed within 5 h after the injection of emideltide (Monnier et al. 1977b). Likewise, IV treatment of free-moving rats with an emideltide-related BDS (30, 40, or 80 nmol/kg) significantly increased the power of EEG delta waves between 1 and 4.5 h after the treatment; the effect was dose dependent and increased in magnitude with the increase in the emideltide-related BDS dose (Kafi et al. 1979).

Significant (although not always selective) increases in the power of EEG delta waves have also been observed in: (i) adult male albino rats following an IP injection of emideltide (80 µg/kg; free base dissolved in 0.9% NaCl acidified with 0.01 M acetic acid), and (ii) adult cats treated with a SC injection of an emideltide-related BDS (120 nmol/kg) (Miller et al. 1986; Šušić 1987). The findings that a systemically delivered emideltide-related BDS is pharmacologically active and induces deep sleep similarly to an emideltide-related BDS delivered directly into the brain can be accounted for by the fact that emideltide can cross the blood brain barrier (see section II.D.1.b).

There are, however, inconsistent findings in the literature regarding the effects of emideltide-related BDSs on the sleep architecture of animals. For instance, while ICV treatment of cats with an emideltide-related BDS (7 nmol/kg) selectively prolonged their NREM sleep (Šušić et al. 1987), an IV treatment of cats with a higher dose of an emideltide-related BDS (30 nmol/kg) prolonged not only their NREM sleep but also their REM sleep (Polc et al. 1978). Likewise,

[85] In humans, delta waves, which are high-amplitude EEG waves in the frequency of 0.5 to 4 Hz, prevail during the NREM sleep deepest stage (stage 3). Spindles, on the other hand, which are bursts of EEG waves in the frequency of 10 to 15 Hz, prevail during a lighter stage (stage 2) of the NREM sleep phase. Studies in humans and rodents have suggested that both slow delta waves and spindles are key for memory consolidation (Girardeau and Lopes-Dos-Santos 2021).

while the ICV treatment of rats with the emideltide-related BDS dose of 7 nmol/kg selectively prolonged their NREM sleep (Ursin and Larsen 1983), ICV treatment of rats with a slightly lower dose (6 nmol/kg) prolonged both NREM and REM sleep (Young and Key 1984). Tobler and Borbély also reported contradictory findings because they failed to detect increases in the power of EEG delta waves recorded for 2 h following treatment of rats with an emideltide-related BDS (40-160 nmol/kg, IP; 7-24 nmol/animal, ICV) (Tobler and Borbély 1980). The reasons underlying the discrepant findings have not been discussed or elucidated.

The pharmacological effects of emideltide on sleep appear to involve activation of the opioid system because treatment of rats with the opioid receptor antagonist naloxone (0.1 mg/kg, SC) prevented the ability of an emideltide-related BDS (6 nmol/kg, ICV) to prolong sleep duration (Young and Key 1984). According to data from an in-vitro study, emideltide does not interact directly with opioid receptors because it does not displace binding of the opioid receptor ligand [^{3}H]diprenorphine to rat brain membranes and human placental membranes (Nakamura et al. 1989). Instead, via a calcium-dependent mechanism, emideltide has been reported to facilitate the release of enkephalins from neurons in different brain regions, including the cerebral cortex, the hypothalamus, the hippocampus, and the thalamus (Nakamura et al. 1991).

In addition to inducing sleep, emideltide has been shown to induce hypothermia, suppress stress responses, act as an antioxidant, act as anticonvulsant, and induce analgesia in rodents (Khvatova et al. 1995; Khvatova et al. 2003; Kovalzon and Strekalova 2006). Naloxone-induced inhibition of the dose-dependent analgesic effect of centrally administered emideltide-related BDS in mice and rats indicates that emideltide-induced analgesia – like emideltide's sleep-inducing properties – is mediated at least in part by activation of the opioid system (Nakamura et al. 1988).

Researchers have hypothesized that, by virtue of stimulating the opioid system, emideltide-related BDSs could be an effective therapeutic intervention to halt the clinical signs and symptoms of opioid and alcohol withdrawal syndromes (Dick et al. 1983). However, it is important to note that the ability of psychostimulants such as cocaine and amphetamine to stimulate endorphin release in the reward brain regions has been proposed to contribute to their positive reinforcing and addictive properties (Olive et al. 2001). Thus, by stimulating endorphin release in reward brain regions, emideltide-related BDSs could have reinforcing properties that could, in turn, contribute to the development of addiction. At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical studies assessing the abuse potential of emideltide-related BDSs.

b. Pharmacokinetics/Toxicokinetics

In-vivo and in-vitro nonclinical studies have reported that emideltide can cross the blood brain barrier and the blood-CSF barrier (Banks et al. 1982; Kastin et al. 1981; Zlokovic et al. 1988).

Because emideltide can be metabolized by peptidyl dipeptidase A present in brain microvessel endothelial cells (Augustijns et al. 1995), clinically relevant drug-drug interactions may occur in subjects receiving concomitantly emideltide-related BDSs and drugs that can inhibit dipeptidase (e.g., captopril). Dipeptidase inhibitors are likely to prevent the metabolic degradation of emideltide, and, thereby, increase its pharmacologically active concentrations (Augustijns et al. 1995).

In one in-vivo study, Mongrel dogs (10 to 25 kg) received a bolus IV injection of an emideltide-related BDS (0.1 mg/kg) and had their CSF drawn at various times after the injection (Banks et al. 1982). The authors reported that CSF emideltide concentrations, measured by means of HPLC, increased significantly with time following the IV injection, peaked at 30 minutes after the injection, and declined thereafter to baseline (Banks et al. 1982).

In another in-vivo study, male Sprague Dawley rats (100 to 275 g) received a bolus IV injection of an emideltide-related BDS (low doses ranged from 0.7 to 2 mg/kg; high dose: 10 mg/kg) or vehicle (saline) and had their brains harvested 5 seconds after the injection (Kastin et al. 1981). The authors reported that concentrations of emideltide, measured by means of an immunohistochemical assay, were significantly higher in brain tissue from rats treated with the high dose of the emideltide-related BDS compared to vehicle-treated rats (Kastin et al. 1981).

In an in-vitro study, the blood-to-CSF flux of radiolabeled emideltide (^{125}I-emideltide) was assessed during in-situ perfusion of isolated choroid plexuses of the lateral ventricles of adult sheep with ^{125}I-emideltide-containing blood perfusate (Zlokovic et al. 1988). The following findings indicated that ^{125}I-emideltide crosses from the blood into the CSF: (i) radioactivity levels measured in the venous perfusate were consistently lower (by ~5%) than those measured in the arterial perfusate, and (ii) the radioactivity in the venous perfusate corresponded to ^{125}I-emideltide (rather than an emideltide metabolite or free ^{125}I). The authors provided evidence that the flux of emideltide through the choroid plexus is a saturable process and suggested that this process may contribute to the brain uptake of emideltide (Zlokovic et al. 1988).

According to findings from in-vitro and in-vivo studies, the half-life of emideltide is very short. For instance, in dogs treated with emideltide (free base; doses ranging from ~0.05 to ~0.1 mg/kg, IV), the half-life of emideltide was 3-6 min (Kato et al. 1984). In rats and in a monkey treated with emideltide (free base; rats: 2.0 mg/kg, monkey: 0.2 mg/kg, IV), the half-lives of emideltide were approximately 2-3 min (Kato et al. 1984). In an in-vitro study in which emideltide was incubated with human serum or rat serum at 37°C, the half-lives of emideltide were 5-10 min and <5 min, respectively (Graf et al. 1987).

The short half-life of emideltide appears to be due primarily to its rapid hydrolysis into shorter peptides rather than its aggregation or protein binding (Graf et al. 1987). In human and rat blood, multiple peptidases catalyze the proteolytic breakdown of emideltide starting at its N-terminal domain (Graf et al. 1987).

According to data from in-vitro studies, emideltide is a substrate for peptidases in brain tissue as well. Shorter peptides resulting from the breakdown of emideltide starting at its N-terminal domain have been detected in rat and mouse brain tissue in vitro (Huang and Lajtha 1978; Marks et al. 1977).

At the time of this evaluation, the nominator did not submit, and FDA did not identify pharmacokinetic or toxicokinetic studies of emideltide (free base) or emideltide acetate delivered via the nominated SC ROA.

c. Acute Toxicity[86]

At the time of this evaluation, the nominator did not submit acute toxicity studies of emideltide (free base) or emideltide acetate. FDA identified one published article describing the acute effects of a single dose of emideltide on colonic temperature, blood pressure, and heart frequency (Yehuda et al. 1988).

Yehuda and colleagues assigned rats to treatments at 6AM, 9AM, 12 PM, 3 PM, 6 PM, 9 PM, 12 AM, or 3 AM. At each time, rats received a single IP injection of an emideltide-related BDS (0.1 mg/kg) or saline and 30 minutes later had their mean blood pressure, colonic temperature, and heart rate measured with a tail cuff, a telethermometer, and a polygraph, respectively. Treatment with the emideltide-related BDS had no effect on mean blood pressure. However, it significantly reduced the heart rate of the rats by ~3% when treatment was delivered between 6AM and 3PM and by ~10% when treatment was delivered between 6PM and 3 AM (Yehuda et al. 1988). The treatment with the emideltide-related BDS changed the circadian rhythm of the colonic temperature of rats. Specifically, the colonic temperatures of saline-treated rats were higher in the evening than in the morning hours. The colonic temperatures of rats treated with the emideltide-related BDS between 9AM and 6PM were significantly higher than those of rats treated with saline at the same time points. They were also significantly higher than those of rats treated with the emideltide-related BDS between 9PM and 6AM (Yehuda et al. 1988).

It is unknown whether the emideltide-induced bradycardia and the emideltide-induced shift in the circadian thermoregulation toward higher diurnal temperatures are in any way related to the induction of a sleep state by emideltide.

d. Repeat-Dose Toxicity[87]

At the time of this evaluation, the nominator did not submit, and FDA did not identify repeat-dose toxicity studies of emideltide (free base) or emideltide acetate.

[86] 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.

[87] 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.

e. Genotoxicity[88]

In the nominator-submitted article published by Popovich and collaborators, the authors analyzed the frequency of chromosome aberrations in bone marrow cells harvested from female SHR mice[89] treated subcutaneously with the emideltide (free base)-containing product Deltaran[90] (to deliver the emideltide dose of 2.5 µg/mouse/day or 100 µg/kg/day) or vehicle (saline, 0.1 mL/animal/day, SC) for 5 consecutive days/month. All mice (n = 4/treatment) were treated between the ages of 3 and 12 months (Popovich et al. 2003).

The authors reported that the mean frequency of chromosome aberrations in bone marrow cells from control (saline-treated) mice increased from 2.1% at 3 months of age to 8.4% at 12 months of age. They also reported that the mean frequency of chromosome aberrations in bone marrow cells from Deltaran-treated mice at 12 months of age was approximately 23% lower than that in bone marrow cells from age-matched, vehicle-treated mice (Popovich et al. 2003).

The finding that the 9-month treatment with Deltaran reduced the frequency of chromosome aberrations in SHR mice should be interpreted with caution in part because it may be unrelated to the presence of emideltide in Deltaran. An earlier in-vitro study reported that glycine is a potent antimutagenic substance (Roy et al. 2002). Specifically, with a potency of 80nM, glycine inhibited the mutagenic effect of N-methyl-N'-nitrosoguanidine by 50% in a strain of Salmonella typhimurium (Roy et al. 2002).

At the time of this evaluation, FDA did not identify studies assessing the genotoxic potential of emideltide (free base) or emideltide acetate.

---

[88] 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.

[89] The SHR mouse strain is an outbred mouse strain derived from Swiss mice and is commonly used in experimental carcinogenicity studies (Anisimov et al. 2003).

[90] Deltaran is a product consisting of a lyophilized mixture of synthetic emideltide (free base) and glycine [1:10, weight/weight] and is reconstituted in saline (0.9% NaCl). According to Popovich et al. (2003), Deltaran is designed at the M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences and is marketed in glass ampoules containing the lyophilized powder mixture of 0.3 mg emideltide (free base) and 3.0 mg glycine (Popovich et al. 2003).

f. Developmental and Reproductive Toxicity[91]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical developmental and reproductive studies of emideltide (free base) or emideltide acetate.

g. Carcinogenicity[92]

In the nominator-submitted article published by Popovich and collaborators, the authors conducted an experiment to assess the effects of the emideltide (free base)-containing product Deltaran on the incidence of spontaneous tumors in female SHR mice. In this experiment, female SHR mice were treated with SC injections of: (i) Deltaran to deliver the emideltide dose of 2.5 µg/mouse/day or 100 µg/kg/day for 5 consecutive days/month (n = 50 mice/treatment), or (ii) vehicle (0.9% NaCl, 0.1 mL/mouse/day, SC, 5 days/month). The treatments began when mice were 3 months old and continued throughout the lifespan of each mouse (Popovich et al. 2003).

The authors reported that, starting at approximately 7 months of age, Deltaran-treated mice were approximately 10% lighter than control mice. The reduced body weight of Deltaran-treated mice was not due to reduced food consumption (Popovich et al. 2003). The mean lifespan of the last 10% of surviving Deltaran-treated mice was approximately 20% longer than that of the last 10% of surviving control mice (Popovich et al. 2003). The longer lifespan of the last surviving mice in the Deltaran group was likely due to the delayed appearance and the reduced number of tumors in this group compared to that in the control group. The Deltaran treatment significantly reduced the incidence of adenocarcinoma of the mammary gland and leukemia in female SHR mice (Popovich et al. 2003).

It is unclear whether the finding that the intermittent treatment with Deltaran reduced the incidence of malignant tumors in female SHR mice was due to emideltide because earlier studies reported that glycine, the other ingredient in Deltaran, has anti-tumorigenic properties (Rose et al. 1999). In addition, the study by Popovich and collaborators is not adequately designed to assess the potential for the emideltide-containing product to induce carcinogenicity.

---

[91] 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.

[92] 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.

In general terms, in a typical study designed to assess the carcinogenic potential of a substance or a mix of substances, male and female mice (or rats) receive daily treatments with the test article for a minimum of 2 years.[93] As discussed by Haseman and colleagues, rodent carcinogenicity studies in which treatments last 12 to 18 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). In the study by Popovich and colleagues, the intermittent treatment of SHR mice with Deltaran between the age of 3 months and end of life resulted in exposures far shorter than 12 months. Considering that the longest surviving mouse lived 2.5 years (~30 months; Popovich et al. 2003), mice received Deltaran for a maximum of 4.5 months.

At the time of this evaluation, FDA did not identify 2-year carcinogenicity studies of emideltide (free base) or emideltide (acetate). In addition, considering that the primary mechanisms of action, off-target actions, and pharmacokinetic profile of emideltide-related BDSs are unknown at this time, FDA could not conduct a weight-of-evidence analysis similar to that published the guidance entitled *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals*[94] to assess the potential for emideltide-related BDSs to induce carcinogenicity.

Conclusions: From the nonclinical pharmacological perspective, emideltide has sleep-inducing properties that are conserved across species and are mediated via opioid-dependent mechanisms. Although emideltide does not appear to interact directly with opioid receptors, it can stimulate calcium-dependent release of endorphins. Emideltide-induced stimulation of the opioid system also contributes to its analgesic properties and could potentially be beneficial to suppress signs and symptoms of alcohol and opioid withdrawal syndromes. However, stimulation of the opioid system by emideltide could lead to development of addiction and, at the time of this evaluation, FDA did not identify nonclinical studies to inform the potential addictive liability of emideltide-related BDSs. From the nonclinical toxicological perspective, the findings that Deltaran (a product containing emideltide (free base) and glycine) reduced the frequency of chromosome aberrations in bone marrow cells of female SHR mice and the incidence of spontaneous malignant tumors in those mice could not be interpreted as evidence that emideltide-related BDSs have no potential to trigger genotoxicity or carcinogenicity in part because glycine has been reported to have antimutagenic and anticarcinogenic properties. At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical toxicity studies to inform safety considerations for potential clinical uses of emideltide (free base) or emideltide acetate.

2. Human Safety

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.

---

[93] See footnote 91.

[94] *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.

The clinical articles submitted by the nominator and those identified by FDA do not always clearly identify whether the emideltide form administered in the clinical studies was a salt formulation or the free base. Therefore, the substance will be generally referred to as emideltide, unless the article under discussion clearly specifies the use of the free base or the acetate salt.

a. Pharmacokinetic Data

Although we identified limited PK information via IV ROA, there was no information for the proposed SC ROA for emideltide (free base) or emideltide acetate.

Emideltide has a short plasma half-life of 8 minutes. It is degraded in blood through reactions catalyzed by aminopeptidases (see section II.D.1.b). Plasma concentrations of emideltide correspond with the sleep-wake circadian rhythm in humans. An elevation of endogenous emideltide concentration has been shown to be associated with suppression of both slow-wave sleep (SWS) and REM sleep (Pollard and Pomfrett 2001).

We included discussions below from two articles that were studies conducted in healthy volunteers that were limited to PD data. Of note, the nominator submitted the article by Schneider-Helmert et al. 1981.

Schneider-Helmert et al. (1981):

This study was the first-in-human pilot R, DB, PC, and CO study of emideltide in six middle-aged otherwise healthy subjects to determine acute and delayed effects of emideltide on psychological, physiological as well as sleeping behavior. Objective polygraphy recordings, video monitoring, and subjective evaluations using questionnaires, EWL,[95] SSS and stress test were obtained. During two consecutive experimental days, each pair of subjects randomly received either placebo or emideltide 25 nmol/kg (21.23 mcg/kg) IV over 20 min (investigational treatments at 09:00 AM). Although five subjects reported "feeling of pressure to sleep" immediately following emideltide infusions, 2 hours after the investigational treatment subjects did not experience sleepiness, reduced vigilance, nor impaired mental functioning. Total sleep time during the 130 minutes immediately following treatments was reportedly longer (median sleep time increased by 59%) after emideltide than placebo treatment without impairing alertness. Delayed effects on subsequent night sleep after the experiment (13-22 hour after emideltide administration) were shorter sleep onset, reduced percentage of stage 1 (decrease light sleep), and prolonged deeper sleep especially SWS and REM sleep, indicating better SE. There were no differences in mood, concentration, or sleepiness.

Schneider-Helmert and Schoenenberger (1983):

This study discussed series of five different investigational studies conducted in small numbers of subjects that included healthy volunteers and subjects with insomnia. In the series of investigational studies in healthy volunteers, the dose-pharmacodynamic response of varying

[95] EWL is an adjective list developed for psychopharmacologic studies, is a sensitive measure of activity, concentration, mood, extraversion, depression, and anxiety.

infusion rates of IV emideltide 25 nmol/kg (21.3 µg/kg) administered during the day showed different effects on TST. Based on polysomnographic recordings with shorter emideltide infusion time 2.5 minutes TST increased by 30 minutes, and with emideltide infusion time 7.5 minutes the TST increased by 1 hour. Emideltide was completely ineffective if infused over 1 minute. Although the latency to sleep onset was not reported, authors reported optimal effects on TST were observed in healthy volunteers with emideltide IV infusion when given over 4 to 8 minutes range. In the series of investigational studies in subjects with insomnia the authors observed that IV emideltide infusion over 4 minutes when administered 1 hour prior to bedtime on four consecutive evenings showed latency to sleep onset of 1 hour (see Section II.C.1.a. for additional discussions of data in subjects with insomnia for investigational studies referred to as series III - V in the publication).

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 emideltide through March 3, 2024. The search retrieved zero reports.

We did not identify any relevant case reports in the medical literature.

c. Clinical Studies Assessing Safety

We identified several studies that administered IV emideltide to humans. For the list of references and details of the studies refer to Appendix 6. Based on these clinical studies, doses of emideltide between 25 – 150 nmol/kg have been administered intravenously to 209 subjects for 1 to 15 days. Clinical studies were not identified that had information for emideltide (free base) or emideltide acetate for the proposed SC ROA.

Clinical studies summarized in Appendix 6 showed that IV emideltide for chronic insomnia was found to be well tolerated and not associated with significant AEs. Dick et al. (1984) evaluated IV emideltide for the treatment of withdrawal syndrome in alcohol and opiate addicts (Appendix 6 and Section II.C.3.a).[96] Although no significant AEs were reported in 95 of the 107 subjects with withdrawal syndrome, nine subjects experienced minor transient side effects such as perspiration, headaches, nausea, and vertigo. Three subjects presented with serious adverse effects: two subjects experienced hypotension at the beginning of the first injection and the third subject experienced repetitive episodes of general discomfort with perspiration and nausea lasting 15 minutes. There was no additional information for one of these subjects who received a second injection and experienced "progressive hypotension." A certain number of successfully treated subjects who had opioid withdrawal experienced a relapse of anxiety with marked

[96] DSIP 25 nmol/kg (21.4 µg/kg) was administered intravenously for complete and abrupt withdrawal symptoms with up to 6 daily injections each day for up to six days. Two different regimens were utilized; 1. Injection on request during recurrence of withdrawal symptoms and stop after definitive clearance 2. Injections at fixed intervals scheduled every 6-8 hours during 3 consecutive days. For both regimens, new injection was administered within 1 hour if it was ineffective.

insomnia within 24-72 hours after treatment cessation. The author reported that some of the side effects were attributed to the solubility difficulties of some of the vials which were obtained from Hoffman-La Roche. It is not clear what the authors meant or how this information is applicable to the interpretations of safety. "Solubility difficulties" for emideltide was not reported in other publications. The adverse effects experienced by the subjects are confounded to interpretation because of the underlying nature of the symptoms experienced during opiate and alcohol withdrawal.

d. Other Safety Information

Immunogenicity and Aggregation Concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[97] The guidance describes immunogenicity as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins including endogenous 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 emideltide (free base) and emideltide acetate), which can similarly elicit an immune response; this immune response may be enhanced when peptides are given via injectable ROA, such as IV and SC. In general, SC ROA is associated with increased immunogenicity compared to IV 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 effectiveness or even result in the neutralization of the activity of the endogenous peptide counterpart.

Unlike 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).

As a peptide with nine amino acids that is administered through the SC ROA, emideltide may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities, as discussed above. The nominator did not provide, and FDA is not aware of, information about emideltide (free base) or emideltide acetate to suggest that these substances do not present these risks.

[97] See FDA's guidance for industry. Immunogenicity Assessment for Therapeutic Protein Products (August 2014), available at https://www.fda.gov/media/85017/download. Accessed 04/03/25.

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

There are FDA-approved drug products that treat the same medical conditions as that proposed for compounded drug products containing emideltide-related BDSs.[98] See subsections c. in Section II.C.1-3 for a list of FDA-approved drug products indicated for the medical conditions considered in this evaluation.

Conclusions: There are no safety data for emideltide (free base) and emideltide acetate administered by the nominator proposed SC ROA.

Available clinical data for emideltide-related products administered IV in small numbers of subjects with chronic insomnia reported no significant adverse effects. However, studies in subjects with withdrawal symptoms reported transient headache, nausea, and vertigo as common side effects with cases of hypotension that was "progressive" following second IV emideltide injection. Considering that the context of use may be for chronic intermittent use, safety for emideltide-related products is insufficiently characterized. In subjects treated for withdrawal symptoms any adverse effects may have been confounded to interpretation because of the underlying nature of the symptoms experienced during opiate and alcohol withdrawal.

Emideltide is a peptide containing 9 amino acids and a peptide sequence of this length has the potential to be immunogenic. Immunogenic response may be enhanced when peptides like emideltide-related BDSs are administered via injectable ROA, such as IV and SC due to potential for aggregation as well as potential peptide-related impurities. The nominator did not provide, and FDA is not aware of, information about emideltide (free base) or emideltide acetate to suggest that these substances do not present these risks.

At the time of this evaluation, there are FDA-approved drugs for treating serious conditions like insomnia, narcolepsy, and opioid withdrawal in adults.

III. CONCLUSION AND RECOMMENDATION

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

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

    1.1 Emideltide (free base) is reported to be a peptide consisting of nine amino acids. As reported in the literature, emideltide (free base) is expected to be stable under reported storage conditions below -20°C. Also, since emideltide (free base) peptide has limited

[98] 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.

water solubility, the BDS particle size distribution (PSD) control for emideltide (free base) powder may be needed.

Emideltide (free base) is considered not well-characterized from the physical and chemical characterization perspectives based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) certain critical characterization data specific to emideltide (free base), including specific tests for impurities, aggregates, and endotoxins, were not found in the publicly available scientific literature, and the nominations did not provide scientific literature or other information such as CoAs as evidence to establish identity, purity, and impurity profiles of the substance. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of emideltide (free base) when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide-related impurities, as discussed in the impurity section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as emideltide (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. In addition, due to reportedly limited water solubility of emideltide (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with the concentration of 1 mg/mL.

1.2 Emideltide acetate is a salt form of a peptide consisting of nine amino acids. As reported in the literature, emideltide acetate is expected to be stable under reported storage conditions below -20°C.

Emideltide acetate is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) certain critical characterization data specific to emideltide acetate were not found in the publicly available scientific literature, and the provided CoA, which was offered to establish identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, and endotoxins). As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of emideltide acetate when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as emideltide acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

2. Emideltide-related BDSs have been studied for use in humans since at least 1981. There is evidence that emideltide-related BDSs have been used in compounding since at least 2018. Emideltide-related injection and intranasal products are available in the US through integrative neurology clinics, medical concierge services, medical spas, wellness clinics, and online retailers for various uses. However, it is unclear whether these products are compounded or if pharmacies are currently compounding products containing emideltide-related BDSs. At the time of this evaluation, currently available data and published literature

is too limited to inform the historical use of any form of emideltide compounded drug products.

3. Based on available clinical data, there is insufficient information concerning effectiveness to support the use of emideltide (free base) and emideltide acetate via IV ROA for the treatment of chronic insomnia, narcolepsy, and opioid withdrawal. Clinical studies for chronic insomnia appear to be inconclusive and at best preliminary. Publications included in this evaluation by several authors did not reach same conclusion and for those studies that showed positive treatment response had poor study methodologies (i.e., lack of or poor selection of control groups) to assess whether any changes in outcomes were clinically meaningful. Studies were also limited by small sample sizes, different baseline characteristics in subjects across studies, different treatment regimen and unknown long-term benefit. Clinical studies for narcolepsy and opioid withdrawal were limited by clinical study design (case report, study without blinding or randomization), small sample size, large variabilities on subject report, and wide range of doses and treatment durations.

   FDA did not identify any data to support the effectiveness of emideltide (free base) or emideltide acetate for the treatment of chronic insomnia, narcolepsy, and opioid withdrawal via the nominated SC ROA.

   Clinical practice guidelines do not discuss the use of emideltide (free base) or emideltide acetate for the management of insomnia, narcolepsy, and opioid withdrawal. Sleep disorders encompassing chronic insomnia and narcolepsy as well as opioid withdrawal are serious conditions and there are FDA-approved treatments with established efficacy for these medical conditions.

4. From the nonclinical pharmacological perspective, emideltide has sleep-inducing properties that are conserved across species and are mediated via opioid-dependent mechanisms. Although emideltide does not appear to interact directly with opioid receptors, it can stimulate calcium-dependent release of endorphins. Emideltide-induced stimulation of the opioid system also contributes to its analgesic properties and could potentially be beneficial to suppress signs and symptoms of alcohol and opioid withdrawal syndromes. However, stimulation of the opioid system by emideltide-related BDSs could lead to development of addiction, and, at the time of this evaluation, FDA did not identify nonclinical studies to inform the potential addictive potential of emideltide-related BDSs. From the nonclinical toxicological perspective, the findings that Deltaran (a product containing emideltide (free base) and glycine) reduced the frequency of chromosome aberrations in bone marrow cells of female SHR mice and the incidence of spontaneous malignant tumors in those mice could not be interpreted as evidence that emideltide-related BDSs have no potential to trigger genotoxicity or carcinogenicity in part because glycine has been reported to have antimutagenic and anticarcinogenic properties. At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical toxicity studies to inform safety considerations for potential clinical uses of emideltide (free base) or emideltide acetate.

   There are no clinical safety data for emideltide (free base) and emideltide acetate administered by the nominator proposed SC ROA. Although available clinical data for emideltide-related products administered IV in small numbers of subjects with chronic

insomnia reported no significant adverse effects, studies in subjects with withdrawal symptoms reported transient headache, nausea, and vertigo as common side effects with cases of hypotension that was "progressive" following second emideltide injection administered IV. Considering that the context of use may be for chronic intermittent use, safety for emideltide-related products is insufficiently characterized. In subjects treated for withdrawal symptoms any adverse effects may have been confounded to interpretation because of the underlying nature of the symptoms experienced during opiate and alcohol withdrawal.

Emideltide is a peptide containing 9 amino acids and a peptide sequence of this length has the potential to be immunogenic. Immunogenic response may be enhanced when peptides like emideltide-related BDSs are administered via injectable ROA, such as IV and SC due to potential for aggregation as well as potential peptide-related impurities. The nominator did not provide, and FDA is not aware of, information about emideltide (free base) or emideltide acetate to suggest that these substances do not present these risks. At the time of this evaluation, there are FDA-approved drugs for treating serious conditions like insomnia, narcolepsy, and opioid withdrawal in adults.

On balance, physicochemical characterization, information on historical use, evidence of effectiveness, and safety information identified for both emideltide (free base) and emideltide acetate weigh against them being added to the 503A Bulks List. Although available data suggests that these substances have been used historically in compounding, FDA's proposal is based on lack of data related to physiochemical characterization, lack of evidence of effectiveness and insufficient safety information on the use of the substances. These substances are not well characterized from a physical and chemical characterization perspective, and endotoxin testing for injectable ROA is lacking. In addition, based on their limited solubility in water, it is unclear how it would be possible to formulate the proposed injectable dosage form with concentration of 1,000 mcg/ml without co-solvent used. FDA also did not identify information that addresses additional concerns related to potential aggregation and immunogenicity risks for emideltide (free base) and emideltide acetate, as described above. We do not have nonclinical and clinical safety data or effectiveness data for chronic insomnia, narcolepsy and opioid withdrawal for the proposed SC ROA. Although available clinical data for emideltide-related products administered IV in small numbers of subjects with chronic insomnia reported no significant adverse events, studies in subjects with withdrawal symptoms reported transient headache, nausea, and vertigo as common side effects with cases of hypotension that was "progressive" following second emideltide injection administered IV. The lack of data discussed above, and the existence of FDA-approved drugs to treat chronic insomnia, narcolepsy, and opioid withdrawal, particularly considering these are serious and /or life-threatening conditions, weighs against emideltide-related BDSs being added to the 503A Bulks List. Accordingly, we propose not adding emideltide (free base) or emideltide acetate to the 503A Bulks List.

IV. REFERENCES

Abad, VC, 2023, Pharmacological Options for Narcolepsy: Are They the Way Forward?, Expert Rev Neurother 23(9):819-834.

American Psychiatric Association, 2022, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision DSM-5-TR, Arlington VA, American Psychiatric Association Publishing.

Anderson, D, 2021, Narcolepsy: A Clinical Review, JAAPA, 34(6):20-25.

Anisimov, VN, VK Khavinson, IG Popovich, MA Zabezhinski, IN Alimova, SV Rosenfeld, NY Zavarzina, AV Semenchenko and AI Yashin, 2003, Effect of Epitalon on Biomarkers of Aging, Life Span and Spontaneous Tumor Incidence in Female Swiss-Derived SHR Mice, Biogerontology, 4(4):193-202.

Asnis, GM, M Thomas and MA Henderson, 2015, Pharmacotherapy Treatment Options for Insomnia: A Primer for Clinicians, Int J Mol Sci, 17(1):50.

Augustijns, PF, KY Ng, TM Williams and RT Borchardt, 1995, Peptidyl Dipeptidase A-Catalyzed Metabolism of Delta Sleep-Inducing Peptide in Bovine Brain Microvessel Endothelial Cells: A Cell Culture Model of the Blood Brain Barrier, Biochem Biophys Res Commun, 210(3):987-994.

Backmund, M, K Meyer, HB Rothenhaeusler and M Soyka, 1998, Opioid Detoxification With Delta Sleep-inducing Peptide: Results of an Open Clinical Trial, J Clin Psychopharmacol, 18(3):257-258.

Banks, WA, AJ Kastin and DH Coy, 1982, Delta Sleep-Inducing Peptide Crosses the Blood-Brain-Barrier in Dogs: Some Correlations With Protein Binding, Pharmacol Biochem Behav, 17(5):1009-1014.

Banks, WA, AJ Kastin and DH Coy, 1984, Evidence That [125I] N-Tyr-Delta Sleep-Inducing Peptide Crosses the Blood-Brain Barrier by a Non-Competitive Mechanism, Brain Res, 301(2):201-207.

Barateau, L, F Pizza, S Chenini, L Peter-Derex and Y Dauvilliers, 2023, Narcolepsies, Update in 2023, Rev Neurol (Paris), 179(7):727-740.

Bassetti, CLA, A Adamantidis, D Burdakov, F Han, S Gay, U Kallweit, R Khatami, F Koning, BR Kornum, GJ Lammers, RS Liblau, PH Luppi, G Mayer, T Pollmächer, T Sakurai, F Sallusto, TE Scammell, M Tafti and Y Dauvilliers, 2019, Narcolepsy - Clinical Spectrum, Aetiopathophysiology, Diagnosis and Treatment, Nat Rev Neurol, 15(9):519-539.

Bes, F, W Hofman, J Schuur, and C Van Boxtel, 1992, Effects of Delta Sleep-Inducing Peptide on Sleep of Chronic Insomniac Patients, A Double-blind Study, Neuropsychobiology, 26(4):193-197.

Bjartell, A, R Ekman, F Sundler and E Widerlöv, 1988, Delta Sleep-Inducing Peptide (DSIP): An Overview of Central Actions and Possible Relationship to Psychiatric Illnesses, Nordisk Psykiatrisk Tidsskrift, 42(2):111-117.

Dick, P, C Costa, K Fayolle, ME Grandjean, A Khoshbeen and R Tissot, 1984, DSIP in the Treatment of Withdrawal Syndromes From Alcohol and Opiates, Eur Neurol, 23(5):364-371.

Dick, P, M Grandjean and R Tissot, 1983, Successful Treatment of Withdrawal Symptoms with Delta Sleep-Inducing Peptide, a Neuropeptide With Potential Agonistic Activity on Opiate Receptors, Neuropsychobiol, 10(4):205-208.

Edinger, JD, DJ Buysse, L Deriy, A Germain, DS Lewin, JC Ong and TI Morgenthaler, 2015, Quality Measures for the Care of Patients With Insomnia, J Clin Sleep Med, 11(3):311-334.

Fanceschini, C, F Pizza, E Antelmi, MC Folli and G Plazzi, 2020, Narcolepsy Treatment: Pharmacological and Behavioral Strategies in Adults and Children, Sleep Breath, 24(2):615-627.

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.

Gimble, JM, AA Ptitsyn, BC Goh, T Hebert, G Yu, X Wu, S Zvonic, XM Shi and ZE Floyd, 2009, Delta Sleep-Inducing Peptide and Glucocorticoid-Induced Leucine Zipper: Potential Links Between Circadian Mechanisms and Obesity?, Obes Rev, 10(s2):46-51.

Girardeau, G and V Lopes-Dos-Santos, 2021, Brain Neural Patterns and the Memory Function of Sleep, Science, 374(6567):560-564.

Graf, MV and AJ Kastin, 1984, Delta-Sleep-Inducing Peptide (DSIP): A Review, Neurosci Biobehav Rev, 8(1):83-93.

Graf, MV and AJ Kastin, 1986, Delta-Sleep-Inducing Peptide (DSIP): An Update, Peptides, 7(6):1165-1187.

Graf, MV, B Saegesser and GA Schoenenberger, 1987, Degradation and Aggregation of Delta Sleep-Inducing Peptide (DSIP) and Two Analogs in Plasma and Serum, Peptides, 8(4):599-603.

Gringras, P, T Nir, J Breddy, A Frydman-Marom and RL Findling, 2017, Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry, 56(11):948-957 e4".

Herscher, M, M Fine, R Navalurkar, L Hirt and L Wang, 2020, Diagnosis and Management of Opioid Use Disorder in Hospitalized Patients, Med Clin North Am, 104(4):695-708.

Huang, JT and A Lajtha, 1978, The Degradation of a Nonapeptide, Sleep Inducing Peptide, in Rat Brain: Comparison With Enkephalin Breakdown, Res Commun Chem Pathol Pharmacol, 19(2):191-199.

Ivanenko, A, A Baroni, R Gruber, S Hartselle, KP Johnson, J Owens, U Ramtekkar and C Whitmore, 2021, Sleep Disorders: Parents' Medication Guide, Am Acad Child Adol Psych, 1-14.

Iyer, KS, G Marks, A Kastin and S McCann, 1988, Evidence for a Role of Delta Sleep-Inducing Peptide in Slow-Wave Sleep and Sleep-Related Growth Hormone Release in the Rat, Proc Natl Acad Sci USA, 85(10):3653-3656.

Kaeser, HE, 1984, A Clinical Trial With DSIP, Eur Neurol, 23(5):386-388.

Kafi, S, M Monnier and J-M Gallard, 1979, The Delta-Sleep Inducing Peptide (DSIP) Increases Duration of Sleep in Rats, Neurosci Lett, 13(2):169-172.

Kastin, AJ, C Nissen and DH Coy, 1981, Permeability of Blood-Brain Barrier to DSIP Peptides, Pharmacol Biochem Behav, 15(6):955-959.

Kastin, AJ, GA Olson, AV Schally and DH Coy, 1980, DSIP – More Than a Sleep Peptide?, Trends Neurosci, 3(7):163-165.

Kato, N, Y Honda, S Ebihara, H Naruse and Y Takahashi, 1984, Development of an Enzyme Immunoassay for Delta Sleep-Inducing Peptide (DSIP) and Its Use in the Determination of the Metabolic Clearance Rate of Dsip Administered to Dogs, Neuroendocr, 39(1):39-44.

Khvatova, EM, NA Rubanova, IA Prudchenko and Mikhaleva, II, 1995, Effects of Delta-Sleep Inducing Peptide (DSIP) and Some Analogues on the Activity of Monoamine Oxidase Type A in Rat Brain Under Hypoxia Stress, FEBS Lett, 368(2):367-369.

Khvatova, EM, VN Samartzev, PP Zagoskin, IA Prudchenko and Mikhaleva, II, 2003, Delta Sleep Inducing Peptide (DSIP): Effect on Respiration Activity in Rat Brain Mitochondria and Stress Protective Potency Under Experimental Hypoxia, Peptides, 24(2):307-311.

Kovalzon, VM and TV Strekalova, 2006, Delta Sleep-Inducing Peptide (DSIP): A Still Unresolved Riddle, J Neurochem, 97(2):303-309.

Kutilin, DS, TI Bondarenko, IV Kornienko and Mikhaleva, II, 2014, Effect of Delta Sleep-Inducing Peptide on the Expression of Antioxidant Enzyme Genes in the Brain and Blood of Rats During Physiological Aging, Bull Exp Biol Med, 157(5):616-619.

Laffont, F, HP Cathala, A Ernst, M Bormer, D Schneider-Helmert and GA Schoenenberger, 1984, Sleep Disturbances in a Case of Brain-Stem Lesions; Pharmacological Study, Electroencephalogr Clin Neurophysiol, 57(1):32-34.

Marks, N, F Stern, AJ Kastin and DH Coy, 1977, Degradation of Delta Sleep Inducing Peptide (DSIP) and Its Analogs by Brain Extracts, Brain Res Bull, 2(6):491-493.

Maski, K, LM Trotti, S Kotagal, RR Auger, JA Rowley, SD Hashmi and NF Watson, 2021, Treatment of Central Disorders of Hypersomnolence: An American Academy of Sleep Medicine Clinical Practice Guideline, J Clin Sleep Med, 17(9):1881-1893.

McLay, RN, W Pan and AJ Kastin, 2001, Effects of Peptides on Animal and Human Behavior: A Review of Studies Published in the First Twenty Years of the Journal Peptides, Peptides, 22(12):2181-2255.

Medalie, L and AS Cifu, 2017, Management of Chronic Insomnia Disorder in Adults, JAMA, 317(7):762-763.

Mikhaleva, II, VT Ivanov, LV Onoprienko, IA Prudchenko, LD Chikin, RI Yakubovskaya, ER Nemtsova and OA Bezborodova, 2014, [Antioxidative and Detoxifying Effects of Analogues of Delta-Sleep Inducing Peptide (DSIP)], Bioorg Khim, 40(1):3-11.

Miller, LH, BA Turnbull, AJ Kastin and DH Coy, 1986, Sleep-Wave Activity of a Delta Sleep-Inducing Peptide Analog Correlates With Its Penetrance of the Blood-Brain Barrier, Sleep, 9(1):80-84.

Monnier, M, L Dudler, R Gächter, P Maier, H Tobler and G Schönenberger, 1977a, The Delta Sleep Inducing Peptide (DSIP): Comparative Properties of the Original and Synthetic Nonapeptide, Experientia, 33(4):548-552.

Monnier, M, L Dudler, R Gächter and G Schoenenberger, 1977b, Delta Sleep-Inducing Peptide (DSIP): EEG and Motor Activity in Rabbits Following Intravenous Administration, Neurosci Lett, 6(1):9-13.

Monti, JM, J Debellis, P Alterwain, T Pellejero and D Monti, 1987, Study of Delta Sleep-Inducing Peptide Efficacy in Improving Sleep on Short-Term Administration to Chronic Insomniacs, Int J Clin Pharmacol Res, 7(2):105-110.

Nakamura, A, M Nakashima, H Kanemoto, T Sugao, Y Fukumura and H Shiomi, 1986, Delta Sleep-Inducing Peptide (DSIP) Has Potent Analgesic Activity in Mice, Eur J Pharmacol, 121(1):157-158.

Nakamura, A, M Nakashima, T Sugao, H Kanemoto, Y Fukumura and H Shiomi, 1988, Potent Antinociceptive Effect of Centrally Administered Delta-Sleep-Inducing Peptide (DSIP), Eur J Pharmacol, 155(3):247-253.

Nakamura, A, M Nakashima, K Sakai, M Niwa, M Nozaki and H Shiomi, 1989, Delta-Sleep-Inducing Peptide (DSIP) Stimulates the Release of Immunoreactive Met-Enkephalin From Rat Lower Brainstem Slices in Vitro, Brain Res, 481(1):165-168.

Nakamura, A, K Sakai, Y Takahashi and H Shiomi, 1991, Characterization of Delta-Sleep-Inducing Peptide-Evoked Release of Met-Enkephalin From Brain Synaptosomes in Rats, J Neurochem, 57(3):1013-1018.

Olive, MF, HN Koenig, MA Nannini and CW Hodge, 2001, Stimulation of Endorphin Neurotransmission in the Nucleus Accumbens by Ethanol, Cocaine, and Amphetamine, J Neurosci, 21(23):RC184.

Oaknin, S, ME Troiani, SM Webb and RJ Reiter, 1986, Influence of Delta-Sleep Inducing Peptide on Melatonin Synthesis in the Rat Pineal Gland, Neurosci Lett, 70(1):127-131.

Pergolizzi, JV, Jr., RB Raffa and MH Rosenblatt, 2020, Opioid Withdrawal Symptoms, a Consequence of Chronic Opioid Use and Opioid Use Disorder: Current Understanding and Approaches to Management, J Clin Pharm Ther, 45(5):892-903.

Polc, P, J Schneeberger and W Haefely, 1978, Effect of the Delta Sleep-Inducing Peptide (DSIP) on the Sleep-Wakefulness Cycle of Cats, Neurosci Lett, 9(1):33-36.

Pollard, BJ and CJ Pomfrett, 2001, Delta Sleep-Inducing Peptide, Eur J Anaesthesiol, 18(7):419-422.

Popovich, IG, BO Voitenkov, VN Anisimov, VT Ivanov, Mikhaleva, II, MA Zabezhinski, IN Alimova, DA Baturin, NY Zavarzina, SV Rosenfeld, AV Semenchenko and AI Yashin, 2003, Effect of Delta-Sleep Inducing Peptide-Containing Preparation Deltaran on Biomarkers of Aging, Life Span and Spontaneous Tumor Incidence in Female SHR Mice, Mech Ageing Dev, 124(6):721-731.

Qaseem, A, D Kansagara, MA Forciea, M Cooke and TD Denberg, 2016, Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians, Ann Intern Med, 165(2):125-133.

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

Rose, ML, RC Cattley, C Dunn, V Wong, X Li and RG Thurman, 1999, Dietary Glycine Prevents the Development of Liver Tumors Caused by the Peroxisome Proliferator WY-14,643, Carcinogenesis, 20(11):2075-2081.

Roy, MK, Y Kuwabara, K Hara, Y Watanabe and Y Tamai, 2002, Antimutagenic Effect of Amino Acids on the Mutagenicity of N-Methyl-N′-Nitro-N-Nitrosoguanidine (MNNG), Biosci Biotechnol Biochem, 66(6):1400-1402.

Sahu, A and SP Kalra, 1987, Delta Sleep-Inducing Peptide (DSIP) Stimulates LH Release in Steroid-Primed Ovariectomized Rats, Life Sci, 40(12):1201-1206.

Sateia, MJ, DJ Buysse, AD Krystal, DN Neubauer and JL Heald, 2017, Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline, J Clin Sleep Med, 13(2):307-349.

Schneider-Helmert, D, 1984, Effects of DSIP on Narcolepsy, Eur Neurol, 23(5):353-357.

Schneider-Helmert, D, 1986, Efficacy of DSIP to Normalize Sleep in Middle-Aged and Elderly Chronic Insomniacs, Eur Neurol, 25(6):448-453.

Schneider-Helmert, D, 1987, Effects of Delta-Sleep-Inducing Peptide on 24-Hour Sleep-Wake Behaviour in Severe Chronic Insomnia, Eur Neurol, 27(2):120-129.

Schneider-Helmert, D, F Gnirss, M Monnier, J Schenker and GA Schoenenberger, 1981, Acute and Delayed Effects of DSIP (Delta Sleep-Inducing Peptide) on Human Sleep Behavior, Int J Clin Pharmacol Ther Toxicol, 19(8):341-5.

Schneider-Helmert, D and GA Schoenenberger, 1981, The Influence of Synthetic DSIP (Delta-Sleep-Inducing-Peptide) on Disturbed Human Sleep, Experientia, 37(9):913-917.

Schneider-Helmert, D and GA Schoenenberger, 1983, Effects of DSIP in Man. Multifunctional Psychophysiological Properties Besides Induction of Natural Sleep, Neuropsychobiol, 9(4):197-206.

Schoenenberger, GA, P Maier, H Tobler and M Monnier, 1977, A Naturally Occurring Delta-EEG Enhancing Nonapeptide in Rabbits. X. Final Isolation, Characterization and Activity Test, Pflügers Archiv, 369(2):99-109.

Schoenenberger, GA and M Monnier, 1977, Characterization of a Delta-Electroencephalogram (δ-Sleep)-Inducing Peptide, Proc Natl Acad Sci USA, 74(3):1282-1286.

Schuckit, MA, 2016, Treatment of Opioid-Use Disorders, N Engl J Med, 375(4):357-368.

Shaha, DP, 2023, Insomnia Management: A Review and Update, J Fam Pract 72(s6):S31-S36.

Spath-Schwalbe, E, A Schafer, D Uthgenannt, J Born and HL Fehm, 1995, Delta-Sleep-Inducing Peptide Does Not Affect CRH and Meal-Induced ACTH and Cortisol Secretion, Psychoneuroendocrinology, 20(3):231-237.

Stanojlovic, O, D Zivanovic, S Mirkovic and I Mikhaleva, 2004, Delta Sleep-Inducing Peptide and Its Tetrapeptide Analogue Alleviate Severity of Metaphit Seizures, Pharmacol Biochem Behav, 77(2):227-234.

Sudakov, KV, JP Coghlan, AV Kotov, RM Salieva, V Polyntsev Yu and EV Koplik, 1995, Delta-Sleep-Inducing Peptide Sequels in the Mechanisms of Resistance to Emotional Stress, Ann N Y Acad Sci, 771:240-251.

Šušić, V, 1987, The Effect of Subcutaneous Administration of Delta Sleep-Inducing Peptide (DSIP) on Some Parameters of Sleep in the Cat, Physiol Behav, 40(5):569-572.

Šušić, V, G Maširević and S Totić, 1987, The Effects of Delta-Sleep-Inducing Peptide (DSIP) on Wakefulness and Sleep Patterns in the Cat, Brain Res, 414(2):262-270.

2020, The Asam National Practice Guideline for the Treatment of Opioid Use Disorder: Focused Update, J Addict Med, 14(2s1):1-91.

Tobler, I and AA Borbély, 1980, Effect of Delta Sleep Inducing Peptide (DSIP) and Arginine Vasotocin (AVT) on Sleep and Motor Activity in the Rat, Waking Sleeping, 4(2):139-153.

Torres-Lockhart, KE, TY Lu, MB Weimer, MR Stein and CO Cunningham, 2022, Clinical Management of Opioid Withdrawal, Addiction, 117(9):2540-2550.

Ursin, R and M Larsen, 1983, Increased Sleep Following Intracerebroventricular Injection of the Delta Sleep-Inducing Peptide in Rats, Neurosci Lett, 40(2):145-149.

Winkelman, JW, 2015, Insomnia Disorder, N Engl J Med 373(15):1437-1444.

Yehuda, S, T Caspy and RL Carasso, 1988, The Orcadian Cycle Effects of DSIP on Colonic Temperature, Blood Pressure, and Heart Rate in Control and Area Postrema-Lesioned Rats, Int J Neurosci, 42(3-4):259-265.

Young, A and B Key, 1984, Antagonism of the Effect of Delta Sleep-Inducing Peptide by Naloxone in the Rat, Neuropharmacology, 23(11):1347-1350.

Yukhananov, RY, TM Tennila, TI Miroshnicenko, VS Kudrin, AN Ushakov, EI Melnik, Michaleva, II, KS Rayevsky, MM Airaksinen and AI Maisky, 1992, Ethanol and Delta-Sleep-Inducing Peptide: Effects on Brain Monoamines, Pharmacol Biochem Behav, 43(3):683-687.

Zapadka, KL, FJ Becher, AL Gomes Dos Santos and SE Jackson, 2017, Factors Affecting the Physical Stability (Aggregation) of Peptide Therapeutics, Interface Focus, 7(6):20170030.

Zlokovic, BV, MB Segal, H Davson and RM Jankov, 1988, Passage of Delta Sleep-Inducing Peptide (DSIP) Across the Blood-Cerebrospinal Fluid Barrier, Peptides, 9(3):533-538.

Zolovska, B and J Shatkin, Key Differences in Pediatric Versus Adult Sleep, in: Kushida CA, editor, Encyclopedia of Sleep, Academic Press; 2013:573-578.

V. APPENDICES

APPENDIX 1: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, Diagnostic Criteria for Insomnia Disorder

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:

    1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention).
    2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention).
    3. Early-morning awakening with inability to return to sleep.

B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
C. The sleep difficulty occurs at least 3 nights per week.
D. The sleep difficulty is present for at least 3 months.
E. The sleep difficulty occurs despite adequate opportunity for sleep.
F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Specify if:

Episodic: Symptoms last at least 1 month but less than 3 months.

Persistent: Symptoms last 3 months or longer.

Recurrent: Two (or more) episodes within the space of 1 year.

Source: DSM-5-TR, 2022

APPENDIX 2: Clinical Significance Thresholds for Sleep Outcomes That Are "Important" for Clinical Decision Making (Sateia 2017)

	Measurement Tool [a]		
Outcome	**Polysomnography**	**Actigraphy**	**Subjective**
Sleep latency (SL), min	10	10	20
Total sleep time (TST), min	20	20	30
Wake after sleep onset (WASO), min	20	20	30
Quality of sleep (QOS), varies [b]	Varies	Varies	Varies
Sleep efficiency (SE), %	5	5	10
Number of awakenings (NOA), n	2	2	0.5

[a] Clinical significance was judged to be present when a specific agent led to a mean change in the outcome of this magnitude, compared to placebo.
[b] For standardized mean difference (SMD), an effect size of 0.5 is considered clinically significance (based on Cohen's d).

APPENDIX 3: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, Diagnostic Criteria for Narcolepsy

A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months.
B. The presence of at least one of the following:

    1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few times per month:

        a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
        b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or global hypotonia, without any obvious emotional triggers.

    2. Hypocretin deficiency, as measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of values obtained in healthy subjects tested using the same assay, or less than or equal to 110 pg/mL). Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
    3. Nocturnal sleep polysomnography showing REM sleep latency less than or equal to 15 minutes, or a MSLT showing a mean sleep latency less than or equal to 8 minutes and two or more SOREM periods.

Specify whether:

G47.411 Narcolepsy with cataplexy or hypocretin deficiency (type 1): Criterion B1 (episodes of cataplexy) or Criterion B2 (low CSF hypocretin-1levels) is met.

G47.419 Narcolepsy without cataplexy and either without hypocretin deficiency or hypocretin unmeasured (type 2): Criterion B3 (positive polysomnography/multiple sleep latency test) is met, but Criterion B1 is not met (i.e., no cataplexy is present) and Criterion B2 is not met (i.e., CSF hypocretin-1 levels are not low or have not been measured).

G47.421 Narcolepsy with cataplexy or hypocretin deficiency due to a medical condition.

G47.429 Narcolepsy without cataplexy and without hypocretin deficiency due to a medical condition.

Source: DSM-5-TR, 2022

APPENDIX 4: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Diagnostic Criteria for Opioid Use Disorder

A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12- month period.

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:

    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.

    Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

11. Witdrawal, as manifested by either of the following:

    a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

    Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Source: DSM-5-TR, 2022

APPENDIX 5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, Diagnostic Criteria for Opioid Withdrawals

A. Presence of either of the following:

   a. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer).
   b. Administration of an opioid antagonist after a period of opioid use.

B. Three (or more) of the following developing within minutes to several days after Criterion A:

   1. Dysphoric mood.
   2. Nausea or vomiting.
   3. Muscle aches.
   4. Lacrimation or rhinorrhea.
   5. Pupillary dilation, piloerection, or sweating.
   6. Diarrhea.
   7. Yawning.
   8. Fever.
   9. Insomnia.

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Source: DSM-5-TR, 2022

APPENDIX 6: Previous Human Experience With Emideltide

Study Population (Nominator-Cited Publications)	N	Described Emideltide Regimen	Adverse Events
Healthy subjects (Schneider-Helmert et al. 1981)	6	25 nmol/kg IV x one dose	Warmth, heaviness, dry mouth, deep respiration and headache (1 case of prolonged headache)
Chronic insomnia (Schneider-Helmert and Schoenenberger 1981)	6	25 nmol/kg IV x one or two doses depending on the randomized sequence	None reported
Chronic insomnia (Schneider-Helmert 1987)	14	30 nmol/kg IV x 7 doses (dosed on seven consecutive nights)	Not addressed
Chronic insomnia (Bes et al. 1992)	16	25 nmol/kg IV x 3 doses (dosed on three consecutive nights)	Not addressed
Opiate and alcohol withdrawal syndrome (Dick et al. 1984)	107 Opiate addicts (n=60) Alcohol addicts (n= 47)	25 nmol/kg IV x 1-24 doses (up to 6 daily injections each day for up to six days) Opiate addicts: 1-24 doses Alcohol addicts: 1-15 doses	Transient Perspiration, headache, nausea, vertigo Serious hypotension, repetitive episodes of perspiration and nausea
Opiate withdrawal syndrome (Backmund et al. 1998)	7	35 nmol/kg IV x 22-24 doses (fixed schedule: on day 1, four and up to six injections; on days 2, 3, and 4, four injections; on days 5, 6, and 7, two injections)	None reported

Additional Publications	N	Described Emideltide Regimen	Adverse Events
Healthy subjects and adults with chronic insomnia (Schneider-Helmert and Schoenenberger 1983)	20	25 nmol/kg IV	Headache
Case report in adult male with chronic insomnia following brain stem lesion (hemorrhage) (Laffont et al. 1984)	1	First week: 30 nmol/kg IV x 5 days Second week: 150 nmol/kg I (5x 30 nmol/kg) on day 1, then 90 nmol/kg IV (3x 30 nmol/kg) for day 2-5 Third week: 70 nmol/kg IV for 5 days (Total 27 doses)	Not addressed
Chronic insomnia (Kaeser 1984)	7	25 nmol/kg IV x 10 doses (within 14 days)	Not addressed
Chronic insomnia (Schneider-Helmert 1986)	18	30 nmol/kg IV x 6 doses (dosed on six consecutive nights)	None reported
Chronic insomnia (Monti et al. 1987)	6	25 nmol/kg IV x 4 doses (dosed on four consecutive nights)	Mild drowsiness
Narcolepsy (Schneider-Hermert 1984)	1	25 nmol/kg IV x 12 doses (dosed for six days in AM; and next six days in PM)	Not addressed

Abbreviations: AM, before midday; IV, intravenous; N, number of subjects; PM, after midday

Emideltide – Related Bulk Drug Substances (Emideltide (free base) and Emideltide 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	DSIP
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	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu
Common Name(s)	Delta Sleep Inducing Peptide, AC1MUSBD, SCHEMBL5523007
UNII Code	YN28Z5YZ73
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of Integrative Medical Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	No
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Subcutaneous Injectable
Compounded Strengths	1,000 mcg/ml
Anticipated Routes of Administration	Subcutaneous Injection
Saftey & Efficacy Data	Mikhaleva, I.I. et al., 2014. Antioxidant and detoxifying activities of analogues of the delta sleep inducing peptide. Russian Journal of Bioorganic Chemistry, 40(1), 1–8. http://dx.doi.org/10.1134/s1068162014010087.
	Sahu, A. & Kalra, S.P., 1987. Delta sleep-inducing peptide (DSIP) stimulates LH release in steroid-primed ovariectomized rats. Life Sciences, 40(12), 1201–1206. http://dx.doi.org/10.1016/0024-3205(87)90239-6.
	Nakamura, A. et al., 1986. Delta sleep-inducing peptide (DSIP) has potent analgesic activity in mice. European Journal of Pharmacology, 121(1), 157–158. http://dx.doi.org/10.1016/0014-2999(86)90407-3.

	Giusti, M. et al., 1993. DELTA SLEEP-INDUCING PEPTIDE ADMINISTRATION DOES NOT INFLUENCE GROWTH HORMONE AND PROLACTIN SECRETION IN NORMAL WOMEN. Psychoneuroendocrinology, 18(1), 79-84. doi. 0306-4530/93
	Stanojlović, O. et al., 2004. Delta sleep-inducing peptide and its tetrapeptide analogue alleviate severity of metaphit seizures. Pharmacology Biochemistry and Behavior, 77(2), 227–234. http://dx.doi.org/10.1016/j.pbb.2003.10.014.
	Regnéll, G., Widerlöv, E. & Ekman, R., 1988. Delta sleep-inducing peptide in CSF of patients with affective illness is elevated by lithium treatment. Biological Psychiatry, 24(1), 112–116. http://dx.doi.org/10.1016/0006-3223(88)90132-1.
	Graf, M.V. & Kastin, A.J., 1984. Delta-sleep-inducing peptide (DSIP): A review. Neuroscience & Biobehavioral Reviews, 8(1), 83–93.http://dx.doi.org/10.1016/0149-7634(84)90022-8.
	SPATHSCHWALBE, E., 1995. Delta-sleep-inducing peptide does not affect CRH and meal-induced ACTH and cortisol secretion. Psychoneuroendocrinology, 20(3), 231–237. http://dx.doi.org/10.1016/0306-4530(94)00050-k.
	Gray, R.A. et al., 1994. Delta-Sleep-Inducing Peptide: Solution Conformational Studies of a Membrane-Permeable Peptide. Biochemistry, 33(6), 1323–1331. http://dx.doi.org/10.1021/bi00172a006.
	Kastin, A.J. et al., 1980. DSIP — more than a sleep peptide? Trends in Neurosciences, 3(7), pp.163–165. Available at: http://dx.doi.org/10.1016/0166-2236(80)90060-0.
	Kutilin, D.S. et al., 2014. Effect of Delta Sleep-Inducing Peptide on the Expression of Antioxidant Enzyme Genes in the Brain and Blood of Rats during Physiological Aging. Bulletin of Experimental Biology and Medicine, 157(5), pp.616–619. Available at: http://dx.doi.org/10.1007/s10517-014-2628-4.
	McLay, R.N., Pan, W. & Kastin, A.J., 2001. Effects of peptides on animal and human behavior: a review of studies published in the first twenty years of the journal Peptides. Peptides, 22(12), pp.2181–2255. Available at: http://dx.doi.org/10.1016/s0196-9781(01)00550-2.
	Yukhananov, R.Y. et al., 1992. Ethanol and Δ-sleep-inducing peptide: Effects on brain monoamines. Pharmacology Biochemistry and Behavior, 43(3), pp.683–687. Available at: http://dx.doi.org/10.1016/0091-3057(92)90396-w.
	Iyer, K.S. et al., 1988. Evidence for a role of delta sleep-inducing peptide in slow-wave sleep and sleep-related growth hormone release in the rat. Proceedings of the National Academy of Sciences, 85(10), pp.3653–3656. Available at: http://dx.doi.org/10.1073/pnas.85.10.3653.

	Banks, W.A., Kastin, A.J. & Coy, D.H., 1984. Evidence that [125I]N-Tyr-delta sleep-inducing peptide crosses the blood-brain barrier by a non-competitive mechanism. Brain Research, 301(2), pp.201–207. Available at: http://dx.doi.org/10.1016/0006-8993(84)91088-6.
	Gimble, J.M. et al., 2009. Delta sleep-inducing peptide and glucocorticoid-induced leucine zipper: potential links between circadian mechanisms and obesity? Obesity Reviews, 10, pp.46–51. Available at: http://dx.doi.org/10.1111/j.1467-789x.2009.00661.x.
	Oaknin, S. et al., 1986. Influence of δ-sleep inducing peptide on melatonin synthesis in the rat pineal gland. Neuroscience Letters, 70(1), pp.127–131. Available at: http://dx.doi.org/10.1016/0304-3940(86)90450-7.
	Kovalzon, V.M. & Strekalova, T.V., 2006. Delta sleep-inducing peptide (DSIP): a still unresolved riddle. Journal of Neurochemistry, 97(2), pp.303–309. Available at: http://dx.doi.org/10.1111/j.1471-4159.2006.03693.x.
	Nakamura, A. et al., 1988. Potent antinociceptive effect of centrally administered delta-sleep-inducing peptide (DSIP). European Journal of Pharmacology, 155(3), pp.247–253. Available at: http://dx.doi.org/10.1016/0014-2999(88)90510-9.
	SUDAKOV, K.V. et al., 1995. Delta-Sleep-Inducing Peptide Sequels in the Mechanisms of Resistance to Emotional Stress. Annals of the New York Academy of Sciences, 771(1 Stress), pp.240–251. Available at: http://dx.doi.org/10.1111/j.1749-6632.1995.tb44685.x.
Used Previously to compound drug products	Yes
Proposed use	Narcolepsy, Opiod Withdrawal, paradoxical sleep disorders, insomnia
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Added as an attachment

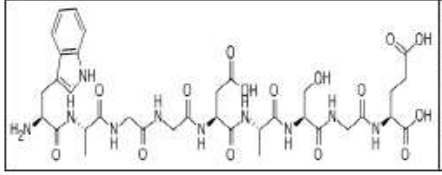
INTEGRATIVE MEDICAL GROUP

Integrative Medical Group Ltd
Suite 504
365 Little Collins St, Melbourne
Victoria, 3000
Australia
+61(39)06993

Certificate of Analysis

Cat#:	Product Name:	Lot#:
DSIP	DSIP	31618-DSIP

Chemical name
Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu
Synonyms
Delta sleep-inducing peptide

Chemical structure	CAS# and Theoretical analysis
	Name: DSIP CAS#: 62568-57-4 Lot#: 31618-DSIP Chemical Formula: $C_{35}H_{57}N_{13}O_{14}S_{24}S_2$ Exact Mass: 848.813620 Molecular Weight: 848.83

Analysis item	Specifications / Results
Appearance	White to off-white solid powder
Structure	^{1}H-NMR analysis matches the structure. MS analysis gives the correct molecule weight. Both NMR and MS data are consistent with those reported in the literature.
Purity (HPLC)	>99.12%
Solubility	Soluble in water
Conclusion	This product conforms with IMG's quality standards
Shipping condition	Shipped under refrigerated temperature as non-hazardous chemical. This product is stable for a few weeks during ordinary shipping and time spent in customs.
Storage condition	Short term storage (weeks): 0 – 4 °C under dry condition Long term storage (months): -20 °C under dry condition
Shelf life	2 years if properly stored.

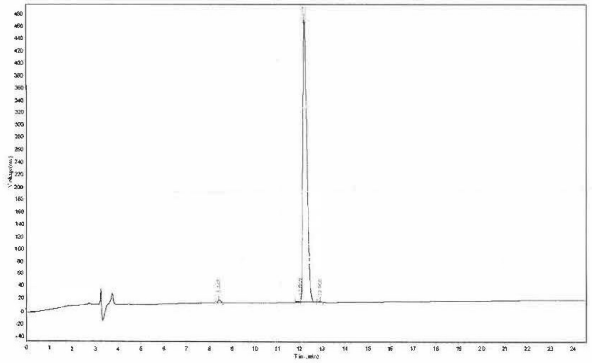
Prepared and Checked by:
Charles Sullivan (QA/QC) _____

Date: 11/06/18

Structure: DSIP
Lot NO :31618-DSIP
Number :0200049
Column :250*4.6mm,Kromasil-C18-5um
Solvent A:0.1%TFA in 100%water
Solvent B:0.1%TFA in 100%acetonitrile

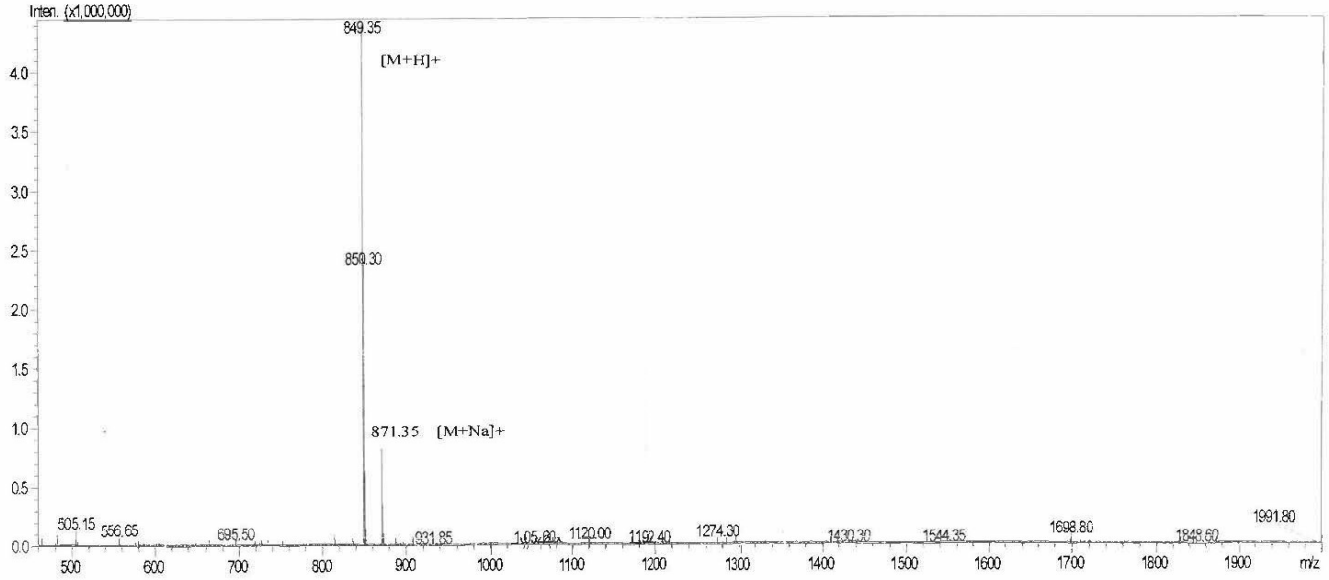
Gradient :	A	B
0.1min	89%	11%
25.0min	64%	36%
25.1min	0%	100%
30.0min	stop	

Flow rate:1.0ml/min
Wavelength(nm):220
Volume:10ul



Peak No.	Ret Time	Height	Area	Conc.
1	8.447	4272.969	35580.598	0.6262
2	12.053	2338.700	7124.397	0.1254
3	12.222	454447.375	5632620.000	99.1261
4	12.908	880.549	6949.908	0.1223
				100.00

MS Spectrum



Acquired by	:Sullivan
Data Acquired	: 2018/11/06
Injection Volume	: 1
Sample Name	: DSIP
Mw	:848.83
Lot No.	: 31618-DSIP

Probe	:ESI	Probe bias	:+4.5kv
Nebulizer Gas Floe	:1.5L/min	Detector	:1.2kv
CDL	:-20.0v	T.Flow	:0.2ml/min
CDL Temp	:250℃	B.conc	:50%H2O/50%ACN
Block Temp	:400℃		

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?	EMIDELTIDE
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?	Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu $C_{35}H_{48}N_{10}O_{15}$ CAS: 62568-57-4
What is the common name of the substance?	DSIP, Delta Sleep Inducing Peptide, SCHEMBL5523007
Does the substance have a UNII code?	YN28Z5YZ73
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?	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?	NO
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?	Subcutaneous Injectable
What strength(s) will be compounded from the nominated substance?	1,000 mcg/ml (1 mg/mL)
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous Injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Schneider-Helmert, D., Schoenenberger, G.A. The influence of synthetic DSIP (delta-sleep-inducing-peptide) on disturbed human sleep. *Experientia* **37,** 913–917 (1981). https://doi.org/10.1007/BF01971753 Schneider-Helmert D. Effects of delta-sleep-inducing peptide on 24-hour sleep-wake behaviour in severe chronic insomnia. *Eur Neurol*. 1987;27(2):120-129. doi:10.1159/000116143 Bes F, Hofman W, Schuur J, Van Boxtel C. Effects of delta sleep-inducing peptide on sleep of chronic insomniac patients. A double-blind study. *Neuropsychobiology*. 1992;26(4):193-197. doi:10.1159/000118919 Schneider-Helmert D, Gnirss F, Monnier M, Schenker J, Schoenenberger GA. Acute and delayed effects of DSIP (delta sleep-inducing peptide) on human sleep behavior. *Int J Clin Pharmacol Ther Toxicol*. 1981;19(8):341-345. Larbig W, Gerber WD, Kluck M, Schoenenberger GA. Therapeutic effects of delta-sleep-inducing peptide (DSIP) in patients with chronic, pronounced pain episodes. A clinical pilot study. *Eur Neurol*. 1984;23(5):372-385. doi:10.1159/000115716 Nakamura A, Nakashima M, Sugao T, Kanemoto H, Fukumura Y, Shiomi H. Potent antinociceptive effect of centrally administered delta-sleep-inducing peptide (DSIP). *Eur J Pharmacol*. 1988;155(3):247-253. doi:10.1016/0014-2999(88)90510-9

	Khvatova EM, Samartzev VN, Zagoskin PP, Prudchenko IA, Mikhaleva II. Delta sleep inducing peptide (DSIP): effect on respiration activity in rat brain mitochondria and stress protective potency under experimental hypoxia. *Peptides*. 2003;24(2):307-311. doi:10.1016/s0196-9781(03)00040-8 Khvatova EM, Rubanova NA, Prudchenko IA, Mikhaleva II. Effects of delta-sleep inducing peptide (DSIP) and some analogues on the activity of monoamine oxidase type A in rat brain under hypoxia stress. *FEBS Lett*. 1995;368(2):367-369. doi:10.1016/0014-5793(95)00661-r Helena Walleus, Erik Widerlöv & Rolf Ekman (1985) Decreased concentrations of delta-sleep inducing peptide in plasma and cerebrospinal fluid from depressed patients, Nordisk Psykiatrisk Tidsskrift, 39:sup11, 63-67, DOI: 10.3109/08039488509101959 Anders Bjartell, Rolf Ekman, Frank Sundler & Erik Widerlöv (1988) Delta sleep-inducing peptide (DSIP): An overview of central actions and possible relationship to psychiatric illnesses, Nordisk Psykiatrisk Tidsskrift, 42:2, 111-117, DOI: 10.3109/08039488809103215 Westrin A, Ekman R, Träskman-Bendz L. High delta sleep-inducing peptide-like immunoreactivity in plasma in suicidal patients with major depressive disorder. *Biol Psychiatry*. 1998;43(10):734-739. doi:10.1016/s0006-3223(97)00254-0 Backmund M, Meyer K, Rothenhaeusler HB, Soyka M. Opioid detoxification with delta sleep-inducing peptide: results of an open clinical trial. *J Clin Psychopharmacol*. 1998;18(3):257-258. doi:10.1097/00004714-199806000-00016 Dick P, Costa C, Fayolle K, Grandjean ME, Khoshbeen A, Tissot R. DSIP in the treatment of withdrawal syndromes from alcohol and opiates. *Eur Neurol*. 1984;23(5):364-371. doi:10.1159/000115715 Popovich IG, Voitenkov BO, Anisimov VN, et al. Effect of delta-sleep inducing peptide-containing preparation Deltaran on biomarkers of aging, life span and spontaneous tumor incidence in female SHR mice. *Mech Ageing Dev*. 2003;124(6):721-731. doi:10.1016/s0047-6374(03)00082-4
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?	Narcolepsy, opiate withdrawal, paradoxical sleep disorders, insomnia

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

Delta Sleep-Inducing Peptide (DSIP) Acetate

Product Name : Delta Sleep-Inducing Peptide (DSIP) Acetate
Mfg. Date : May 08, 2020
M.F. : $C_{35}H_{48}N_{10}O_{15}$
CAS No. : 62568-57-4
Sequence : H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-OH

Lot No. : DL5269
Exp. Date : May 07, 2023
M.W. : 848.814
Batch Qty : 94 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water and acetic acid		Conforms
Amino Acid Composition	Trp	0.9 – 1.1	0.9
	Ala	1.8 – 2.2	1.9
	Gly	2.7 – 3.3	2.8
	Asp	0.9 – 1.1	1.0
	Ser	0.9 – 1.1	1.0
	Glu	0.9 – 1.1	1.1
Water Content (KF)	≤ 8.0%		5.7%
Acetic Acid Content (HPLC)	≤ 15.0%		2.8%
Peptide Purity (HPLC)	≥ 98.0%		98.9%
Related Substances	Total Impurities	≤ 2.0%	1.1%
	Largest Single Impurity	≤ 1.0%	0.6%
Organic Solvent Residue	Acetonitrile	≤ 410ppm	< 410 ppm
	Dichloromethane	≤ 600ppm	<600 ppm
	N,N-Dimethylformamide	≤ 880ppm	< 880 ppm

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

94.3% × 97.2% × 98.9%
= 90.65% A
10/8/25

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

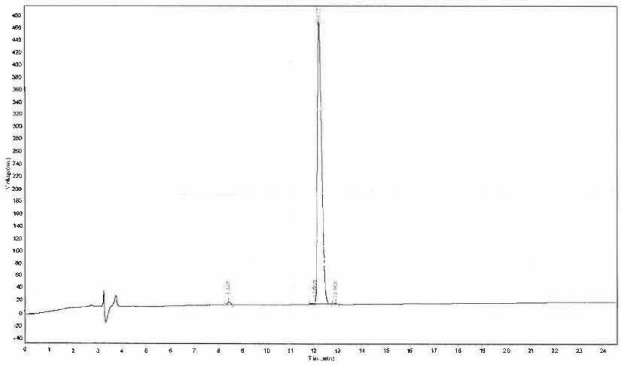
	Name	Title	Signature	Date
Prepared by	Sai Rasane	Quality Assistant		05/29/2020
Released by	Wilnelia Hernandez	Quality Assistant	WHR	06/01/2020

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

Structure: DSIP
Lot NO :31618-DSIP
Number :0200049
Column :250*4.6mm,Kromasil-C18-5um
Solvent A:0.1%TFA in 100%water
Solvent B:0.1%TFA in 100%acetonitrile

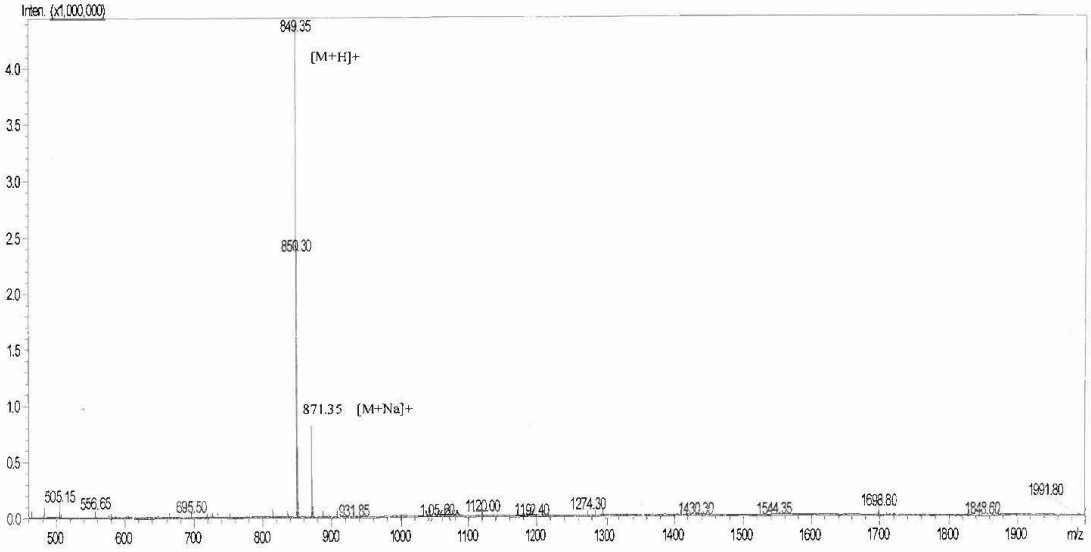
Gradient :	A	B
0.1min	89%	11%
25.0min	64%	36%
25.1min	0%	100%
30.0min	stop	

Flow rate:1.0ml/min
Wavelength(nm):220
Volume:10ul



Peak No.	Ret Time	Height	Area	Conc.
1	8.447	4272.969	35580.598	0.6262
2	12.053	2338.700	7124.397	0.1254
3	12.222	454447.375	5632620.000	99.1261
4	12.908	880.549	6949.908	0.1223
				100.00

MS Spectrum



Acquired by	:Sullivan
Data Acquired	: 2018/11/06
Injection Volume	: 1
Sample Name	: DSIP
Mw	:848.83
Lot No.	: 31618-DSIP

Probe	:ESI	Probe bias	:+4.5kv
Nebulizer Gas Floe	:1.5L/min	Detector	:1.2kv
CDL	:-20.0v	T.Flow	:0.2ml/min
CDL Temp	:250℃	B.conc	:50%H2O/50%ACN
Block Temp	:400℃		