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.

Epitalon-Related Bulk Drug Substances (Epitalon (Free Base) and Epitalon Acetate)

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FDA Evaluation of Epitalon-Related Bulk Drug Substances (Epitalon (Free Base) and Epitalon Acetate)

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TO: Pharmacy Compounding Advisory Committee

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

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List of Abbreviations

Abbreviation	Term
6-sulfatoxymelatonin	6-SMT
AE	adverse event
AEDG	Ala-Glu-Asp-Gly
API	active pharmaceutical ingredient
BDS	bulk drug substance
BET	bacterial endotoxins test
CAS No	Chemical Abstract Service Number
CoA	Certificate of Analysis
CQA	critical quality attributes
FAERS	FDA Adverse Events Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
HFCS	Human Foods Complaint System
INN	International Nonproprietary Name
IUPAC	International Union of Pure and Applied Chemistry
MF	Molecular Formula
MW	Molecular Weight
NF	National Formulary
NIH	National Institutes of Health
OTC	over the counter
PG	pineal gland
ROA	route of administration
SC	subcutaneous
SHR	spontaneously hypertensive rat
SL	sublingual
UNII	Unique Ingredient Identifier
USAN	United States Adopted Name
USP	United States Pharmacopeia

I. INTRODUCTION

The Food and Drug Administration (FDA, the Agency, or we) received nominations for epitalon-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] The nominators provided inconsistent information in the nomination packages regarding the specific BDS proposed. Specifically, it is unclear in both packages whether the nomination was for epitalon (free base) or epitalon acetate. Epitalon (free base) and epitalon acetate are different active pharmaceutical ingredients (APIs) and hence are considered different BDSs. Please see additional information in Section II.A. The nominations were withdrawn[2] and FDA is evaluating the substances at its discretion.

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

Epitalon-related BDSs were evaluated for use in insomnia.[3,4] The epitalon-related drug products proposed in the nominations are 10 mg/mL and 3000 mcg/mL for subcutaneous (SC) injection.

Epitalon is also known as epithalon and/or by its amino acid components Alanine-Glutamic Acid-Aspartic Acid-Glycine (Ala-Glu-Asp-Gly);[5,6] these terms will be used interchangeably throughout this evaluation consistent with the term used in each reference.

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[1] Nominations that had been submitted include: Nomination from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0286) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0286; Nomination from LDT Health Solutions, Inc., on behalf of International Peptide Society (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 epitalon (free base) and epitalon acetate on its own initiative, FDA considered information submitted in these nominations as part of this evaluation.

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

[3] 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.

[4] Epitalon-related BDSs were nominated for other uses; however, for reasons described in Section II.C, FDA only evaluated the use of insomnia.

[5] See information for unique ingredient identifier (UNII) code O65P17785G in FDA's Global Substance Registration System (GSRS), accessed 2/29/2024, https://precision.fda.gov/uniisearch/srs/unii/O65P17785G.

[6] The nominators stated that other common names for epitalon include epithalamin(e); however, FDA considers epitalon and epithalamin as different substances. Epithalamin is a polypeptide complex extracted from the pineal gland (Khavinson and Morozov 2003). Epitalon is a tetrapeptide synthesized based on the study of the amino acid content of epithalamin; epitalon is considered a "synthetic analog" of epithalamin with similar biologic effects (Khavinson and Linkova 2012). Epithalamin(e) is not listed as a synonym for epitalon (UNII code O65P17785G) in FDA's GSRS. This evaluation pertains only to epitalon-related BDSs.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for epitalon (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, effectiveness, and safety in compounding of these substances. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing epitalon (free base) or epitalon 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]

Epitalon 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 for similarly situated products. Inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN[9], USAN, IUPAC[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 epitalon-related BDSs also introduce risks because of the inability to determine which BDS a particular reference standard is referencing.

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[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 certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

[8] A United States Adopted Name (USAN) is a unique, nonproprietary name assigned by the USAN Council for drugs sold in the United States. Use of a common name that lacks meaning or formal definition may contribute to the BDS being not well characterized because there is no basis for a long-term understanding of the composition of the BDS nor an expectation that the common name will always identify the same specific chemical structure and form. The USAN naming convention overcomes this problem by helping physicians, pharmaceutical manufacturers of active ingredients and finished dosage forms, and pharmacists ensure that patients receive the intended drug with consistent chemical identity.

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

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

A BDS or 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 ester forms 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.

As an initial matter, Table 1 below summarizes available identifying information obtained from the public domain for each BDS.

Table 1. Summary of Basic Characteristics of Epitalon Free Base and Epitalon Acetate.

Characteristics	Epitalon (Free Base)	Epitalon Acetate
UNII Code	O65P17785G	Not available
CAS No.	307297-39-8	307297-40-1
MF/MW (g/mol)	$C_{14}H_{22}N_4O_9$/ 390.35	$C_{14}H_{22}N_4O_9.C_2H_4O_2$/ 450.40
Chemical Structure	H-Ala-Glu-Asp-Gly-OH	H-Ala-Glu-Asp-Gly-OH.CH_3CO_2H
Supplier[10]	Yes	Yes
Active Moiety	Epitalon (free base)	Epitalon (free base)

CAS = Chemical Abstract Service

Two nominations were submitted, which, as discussed above, were later withdrawn. The nominators provided inconsistent information about the different epitalon BDSs in their nomination packages. Due to these inconsistencies, it is unclear which epitalon-related BDS the nominators intended to nominate. For example, the Certificate of Analysis (CoA) submitted with each nomination refers to one BDS by name in the title and a different BDS by the molecular weight/formula. All chemistry-related information about the BDSs provided by both nominators is summarized in Table 2.

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[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 Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."). An API is defined in FDA regulations at 21 CFR 207.1, which states "*Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."

[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.

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

Nominator	**1**	**2**
Nominated BDS	Epitalon	Epitalon
BDS per UNII code	O65P17785G *(matches Epitalon (free base))*	Not Provided
CoA	CoA provided for Epitalon acetate	CoA provided for Epitalon acetate
CAS No.	307297-39-8 (provided in the CoA) *(matches Epitalon (free base))*	307297-40-1 (provided in the CoA) *(matches Epitalon acetate)*
MF	C14H22N4O9 (provided in the CoA) *(matches Epitalon (free base))*	C14H22N4O9 (provided in the nomination) *(matches Epitalon (free base))* C16H26N4O11 (provided in the CoA) *(matches Epitalon acetate)*
MW	390.35 *(provided in CoA) (matches Epitalon (free base))*	390.35 *(provided in CoA and in the nomination) (matches Epitalon (free base))*
Chemical Name	H-Ala-Glu-Asp-Gly-OH *(matches Epitalon (free base))*	H-Ala-Glu-Asp-Gly-OH *(matches Epitalon (free base))*
Proposed Products	Subcutaneous Injection 10 mg/mL	Subcutaneous Injectable 3,000 mcg/mL

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

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

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

- Injection

For an injection product, in general, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET), and foreign particulates are considered 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 injections. Evaluation of the solubility of the BDS is also critical to ensure that no BDS precipitates are formed in the compounded drug product.

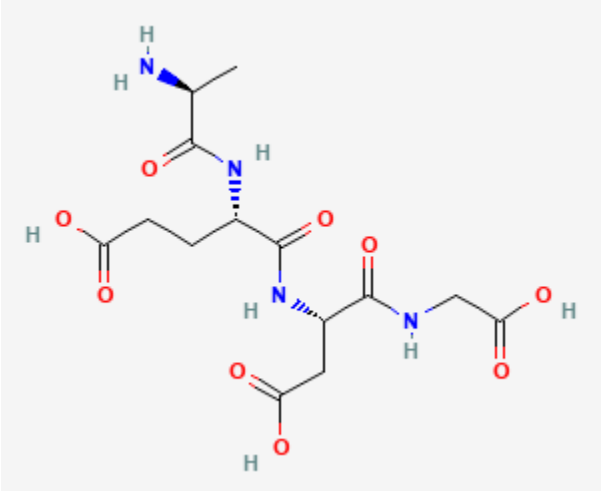
There is no USP drug substance monograph for epitalon (free base) or its acetate salt form. We reviewed physical and chemical characterization-related information provided by the nominators and performed a literature search for additional information on epitalon (free base) and its acetate form. Databases searched for information on epitalon (free base) and its acetate form in

preparation of this section included Researchgate.net, SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. *Epitalon (Free Base)*

Epitalon (free base) is reported to be a synthetic tetrapeptide (L-Alanine-L-Glutamate-L-Aspartate-L-Glycine) that can be extracted from the pineal gland (PG). The chemical structure of epitalon (free base) is shown in Figure 1.[13] The melting point of epitalon (free base) is 198.0°C - 202.0°C. The molecular formula of epitalon (free base) is $C_{14}H_{22}N_4O_9$, and its molecular weight is 390.35 g/mol. There is no CoA available for epitalon (free base) in the nominations.

Figure 1. The Structure of Epitalon (Free Base).



a. Stability of the API and Likely Dosage Forms

It is reported that lyophilized epitalon (free base) is stable at room temperature for 3 weeks. However, it is recommended to be stored desiccated below -18°C, because exposure to moisture greatly decreases the long-term stability of lyophilized peptides. Upon reconstitution, epitalon (free base) in solution should be stable for 2-7 days stored at 4°C and below -18°C for future use.[14]

FDA notes that peptides such as epitalon (free base) can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Such methods involve equipment that may not be available in a compounding facility. Hence, peptides may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product

[13] https://pubchem.ncbi.nlm.nih.gov/compound/Epitalon. Accessed 3/31/2025.
[14] https://www.prospecbio.com/epitalon. Accessed 3/31/2025.

aggregation. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

The above-mentioned issues also apply to the evaluation of epitalon acetate under subsection II.A.2.a.

b. Probable Routes of API Synthesis

Epitalon (free base) was first synthesized in the late 1980s by researchers under the direction of Professor Vladimir Khavinson from the Saint Petersburg University, Russia.[15] Epitalon (free base) is a synthetic peptide, which may be identified as the putative active component of a bovine pineal gland extract known as epithalamin.

There are several suppliers of epitalon (free base).[16,17]

c. Likely Impurities[18]

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 epitalon (free base). For most synthetic peptides, solid-phase synthesis methods are widely used by industry for peptide synthesis. The solid-phase synthesis 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 include starting materials (e.g., typically protected amino acids, isomeric impurities, free amino acids) and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid-phase peptide synthesis process-related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

There were no CoAs for epitalon (free base) in the nomination packages. We conducted literature searches and found that CoAs for epitalon (free base) only contain purity testing

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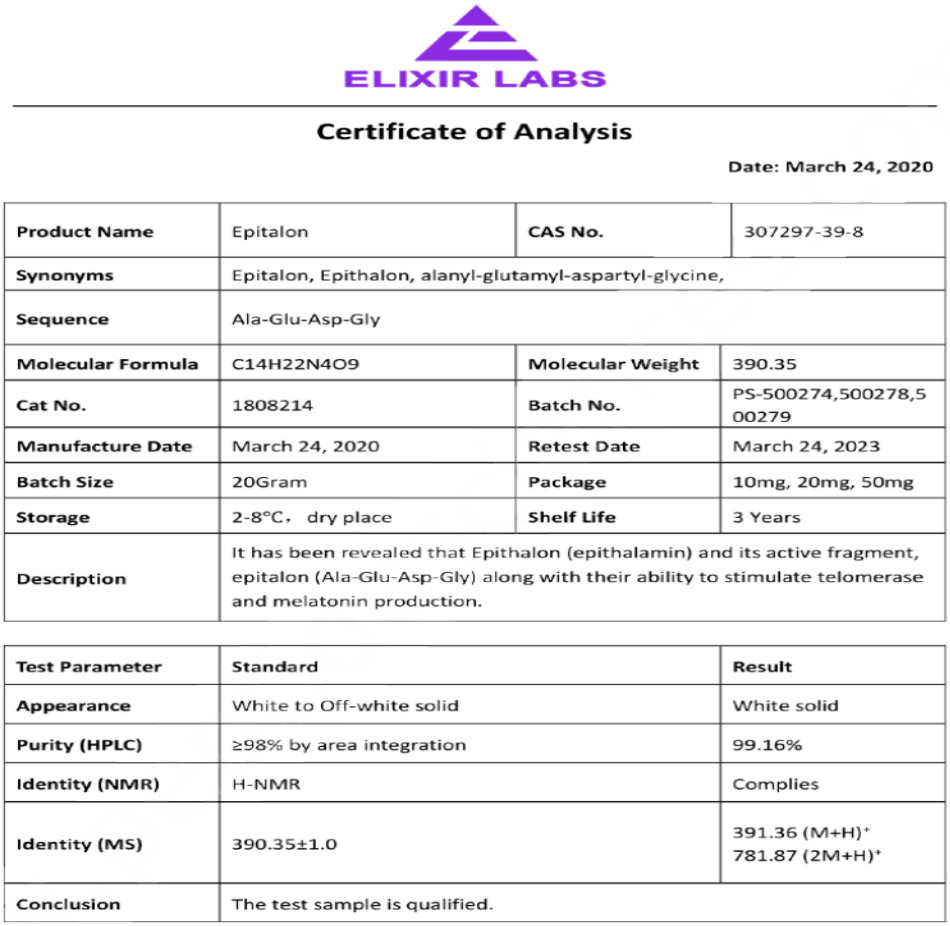
[15] https://www.researchgate.net/publication/370060637_Epitalon. Accessed 3/31/2025.
[16] https://www.chemicalbook.com/ChemicalProductProperty_EN_CB12518304.htm. Accessed 3/28/2025.
[17] https://pubchem.ncbi.nlm.nih.gov/compound/Epitalon. Accessed 3/27/2025.
[18] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section D.1. as part of the safety assessment of the substance.

results, an example of which is shown below (Figure 2).[19] There is no information about the impurity limits/testing results in the CoA to demonstrate quality control of impurity profile of epitalon (free base).

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

[19] https://elixirlabsco.com/wp-content/uploads/2023/02/CoA_Epithalon_Final.pdf?srsltid=AfmBOooUWcuwshX1yA20J5eYG0YtOKocbBWVkT2nQgB0mYFlBEE54Ebs. Accessed 3/28/2025.

Figure 2. Example of a CoA for Epitalon (Free Base).



ELIXIR LABS

Certificate of Analysis

Date: March 24, 2020

Product Name	Epitalon	**CAS No.**	307297-39-8
Synonyms	Epitalon, Epithalon, alanyl-glutamyl-aspartyl-glycine,		
Sequence	Ala-Glu-Asp-Gly		
Molecular Formula	C14H22N4O9	**Molecular Weight**	390.35
Cat No.	1808214	**Batch No.**	PS-500274,500278,500279
Manufacture Date	March 24, 2020	**Retest Date**	March 24, 2023
Batch Size	20Gram	**Package**	10mg, 20mg, 50mg
Storage	2-8°C， dry place	**Shelf Life**	3 Years
Description	It has been revealed that Epithalon (epithalamin) and its active fragment, epitalon (Ala-Glu-Asp-Gly) along with their ability to stimulate telomerase and melatonin production.		

Test Parameter	**Standard**	**Result**
Appearance	White to Off-white solid	White solid
Purity (HPLC)	≥98% by area integration	99.16%
Identity (NMR)	H-NMR	Complies
Identity (MS)	390.35±1.0	391.36 $(M+H)^+$ 781.87 $(2M+H)^+$
Conclusion	The test sample is qualified.	

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

Epitalon (free base) is a white to off-white lyophilized powder. There is limited reliable aqueous solubility data in the literature. Due to its limited solubility in water, it may not be possible to compound epitalon (free base) injection at 3 mg/mL using water as the solvent.

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

Because no CoA was provided in the nominations for epitalon (free base), it is unclear whether a bioburden load (microbial enumeration test) and/or BET is in place to control the microbiological quality of the BDS, proposed for compounding an injectable dosage form. Endotoxin testing is considered a CQA to control microbiological quality of a BDS intended for an injection product. Also, there is no information about residual solvent testing. No such relevant information was identified from the public domain.

Conclusions: Epitalon (free base) is reported to be a peptide of four amino acids. As reported in the literature, epitalon (free base) is expected to be stable under storage conditions below -20°C.

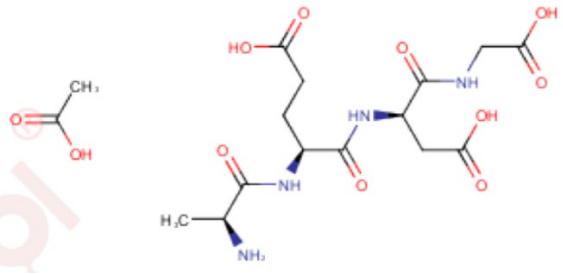
Epitalon (free base) is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, USAN, IUPAC), and (2) data/information relevant to certain critical quality attributes for establishing its identity, purity, and quality for its intended use in the proposed dosage form (injection) were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information includes but are not limited to having specific tests on the Certificate of Analysis for the critical quality attributes that are relevant to characterizing peptide related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins) and other critical quality attributes as dictated either by the dosage form or route of administration (injection). Also, the stability, pharmacological activity, and immunogenic properties of peptides such as epitalon (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

Further, FDA is concerned about the potential for immunogenicity of epitalon (free base) when compounding an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in Section II.A.1.c. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. Therefore, we cannot rule out potential immunogenicity issues associated with these impurities and peptide-related aggregates. In addition, due to its limited solubility, it may be difficult to compound epitalon (free base) injection at 3 mg/mL using water as the solvent.

2. Epitalon Acetate

Epitalon acetate is reported to be a salt of epitalon (free base) peptide of four amino acids. Figure 3 illustrates the structure of epitalon acetate. The molecular formula of epitalon acetate is $C_{14}H_{22}N_4O_9 \bullet C_2H_4O_2$. The nominator provided a CoA for epitalon acetate with quality control attribute testing results, including identification, peptide purity, water content, amino acid composition, acetic acid content, impurities (total impurities and largest single impurity), and residual organic solvents. There are no testing results for the quality control attributes on impurities (no information regarding individual impurities that can be present), aggregates, and bioburden load (microbial enumeration test) and/or bacterial endotoxin levels.

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



a. Stability of the API and Likely Dosage Forms

Based on the CoA provided by the nominator, long-term storage conditions for epitalon acetate are "in a sealed container at 2°C to 8°C in a fridge or freezer". Additionally, epitalon acetate is reported to remain stable up to three years when stored at -20°C and one year in solvent at -80°C.[21]

FDA notes that peptides such as epitalon acetate can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Such methods involve equipment that may not be available in a compounding facility. Hence, peptides may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

b. Probable Routes of API Synthesis

Epitalon (free base) is a synthetic peptide, which may be identified as the putative active component of a bovine pineal gland extract known as epithalamin. Then, the epitalon (free base) can be converted into epitalon acetate.

[20] https://www.targetmol.com/compound/epitalon_%28acetate%29. Accessed 3/31/2025.
[21] https://www.targetmol.com/compound/epitalon_%28acetate%29. Accessed 3/31/2025.

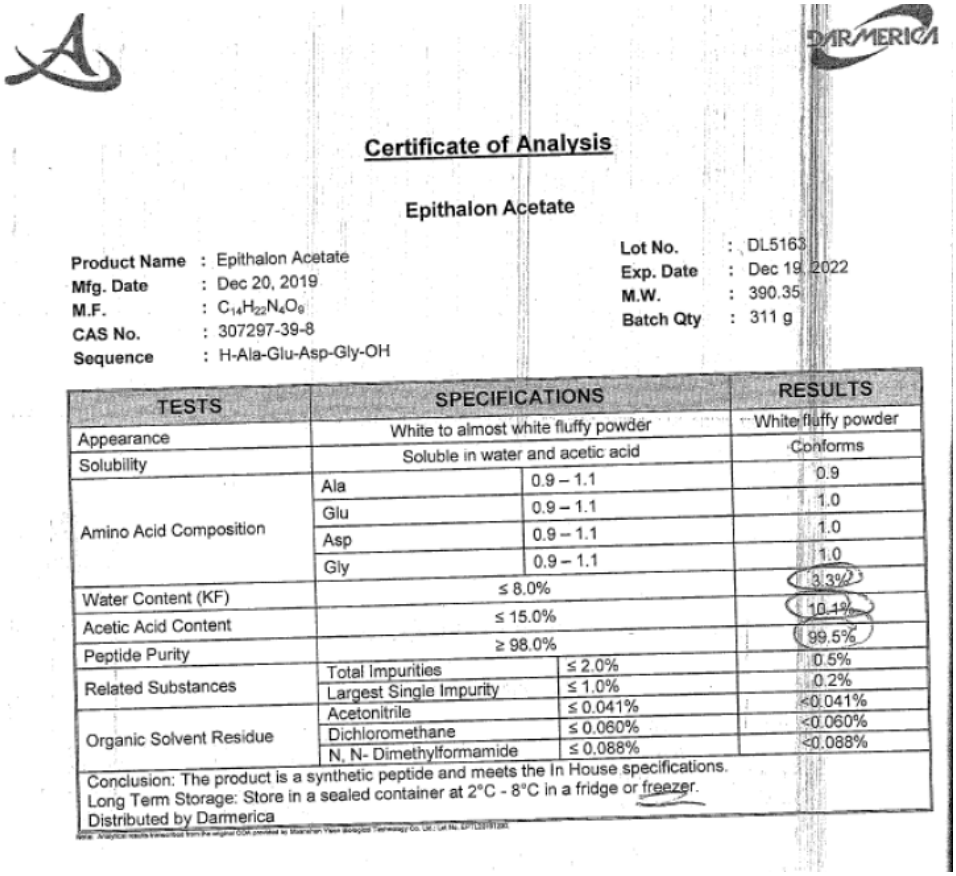
c. Likely Impurities[22]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including epitalon acetate. For most synthetic peptides, solid-phase synthesis methods are 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 include starting materials (e.g., typically protected amino acids, isomeric impurities, free amino acids) and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid-phase peptide synthesis process-related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

In the CoA provided by the nominator, a purity test limit of ≥98% with the testing result of 99.5% is listed for epitalon acetate. A general impurity attribute (total impurities of not more than 2.0% and largest single impurity of no more than 1.0%) control is included to demonstrate the impurity profiles as shown below in Figure 4. However, no information regarding the nature of individual impurities that can be present at up to the 1.0% level is provided.

[22] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. If likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) are identified in the CoAs or the literature of a nominated bulk drug substance, available nonclinical toxicity data for those impurities are discussed in the Nonclinical Assessment at Section D.1. as part of the safety assessment of the substance.

Figure 4. Example of a CoA for Epitalon Acetate.



Certificate of Analysis

Epithalon Acetate

Product Name : Epithalon Acetate
Mfg. Date : Dec 20, 2019
M.F. : $C_{14}H_{22}N_4O_9$
CAS No. : 307297-39-8
Sequence : H-Ala-Glu-Asp-Gly-OH

Lot No. : DL5163
Exp. Date : Dec 19, 2022
M.W. : 390.35
Batch Qty : 311 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to almost white fluffy powder		White fluffy powder
Solubility	Soluble in water and acetic acid		Conforms
Amino Acid Composition	Ala	0.9 – 1.1	0.9
	Glu	0.9 – 1.1	1.0
	Asp	0.9 – 1.1	1.0
	Gly	0.9 – 1.1	1.0
Water Content (KF)	≤ 8.0%		3.3%
Acetic Acid Content	≤ 15.0%		10.1%
Peptide Purity	≥ 98.0%		99.5%
Related Substances	Total Impurities	≤ 2.0%	0.5%
	Largest Single Impurity	≤ 1.0%	0.2%
Organic Solvent Residue	Acetonitrile	≤ 0.041%	<0.041%
	Dichloromethane	≤ 0.060%	<0.060%
	N, N- Dimethylformamide	≤ 0.088%	<0.088%

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

Because there is a lack of information regarding potential impurities that can be present in epitalon acetate and a lack of information on the potential for peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide-related aggregates, especially when administered by injection routes of administration (ROAs) because injectable ROAs may present a particular risk for immunogenicity.

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

Epitalon acetate is a white to almost white fluffy powder. Because the BDS would be solubilized prior to administration, particle size and polymorphism are not considered CQAs that affect performance of the proposed injection dosage form. However, FDA is concerned about the potential for immunogenicity of epitalon acetate when administered by injection ROAs due to the potential for aggregation as well as potential peptide-related impurities, as discussed under the impurity section. The nominated SC ROA is generally associated with an increased risk for immunogenicity compared to other parenteral ROAs.

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 load is a critical BDS quality control attribute for an injection product. No such relevant information for epitalon acetate was identified in the public domain. In addition, there is no residual solvent testing in the nomination.

FDA did not identify additional relevant information regarding the physical and chemical characterization of epitalon acetate.

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

Epitalon 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., INN, USAN, IUPAC), and (2) data/information relevant to certain critical quality attributes for establishing its identity, purity, and quality for its intended use in the proposed dosage form (injection) were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information includes but are not limited to having specific tests on the Certificate of Analysis for the critical quality attributes that are relevant to characterizing peptide related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins) and other critical quality attributes as dictated either by the dosage form or route of administration (injection). We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as epitalon acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

Further, FDA is concerned about the potential for immunogenicity of epitalon acetate when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities section II.A.1.c*. Injectable routes of administration may present a particular risk for immunogenicity (systemic versus local) compared to other dosage forms. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

B. Has the Substance Been Used Historically in Compounding?

This evaluation focuses on epitalon (free base) and epitalon acetate for SC injection and their use in insomnia; however, FDA searched generally for information on the historical use of epitalon (free base) and epitalon acetate in compounding. Databases searched for information on both substances for this evaluation included PubMed, Embase, GlobalEdge, NatMed Pro database,

USP/NF, FDA Adverse Event Reporting System (FAERS) public dashboard,[23] Google, Compounding Today, European Pharmacopeia, Japanese Pharmacopeia, and the Outsourcing Facility Product Reporting Database.[24] It is often unclear whether the references discussed in this section were referring to epitalon as the salt form or the free base and whether it was compounded or not. Therefore, FDA will consider the information discussed in this section in its evaluation for both the free base and salt form, as appropriate.

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

The nominators stated that epitalon[25] has been used to compound drug products but did not provide any additional information regarding the historical use of epitalon in compounding. The nominators submitted 23 articles[26] but none of the articles discussed the use of a compounded formulation of epitalon.[27]

Using available data, the extent to which epitalon has been used in compounding is unclear. After conducting a literature search, epitalon appears to have first been synthesized in 1999 due to the limited availability of calf pineal gland needed to produce epithalamin (Anisimov et al. 2001b).[28] Based on a press release from the office of the U.S. Attorney for the Eastern District of Kentucky,[29] a pharmacy compounded and distributed products containing epitalon from 10/25/18 to 4/1/20, but it is unclear which form of epitalon was being used to compound the products. No studies were found in which epitalon was used as a compounded drug product and no outsourcing facility has reported compounding drug products containing epitalon to FDA.

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[23] Available at https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. Accessed 12/3/2025.
[24] Available at https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/. Accessed 12/3/2025.
[25] As noted previously, the form of epitalon (i.e., epitalon (free base), epitalon acetate) that was nominated is unclear. Therefore, when the nominators state that epitalon has been used to compound drug products, it is unclear to which form of epitalon they are referring.
[26] Twenty-six unique articles were submitted by the nominators but two of the articles were published in Russian only (Korkushko et al. 2007; Slepushkin et al. 1983) and one article (Khavinson 1997) was not able to be found. The remaining 23 articles (Anisimov 2001; Anisimov et al. 2001a; Anisimov et al. 2002a; Anisimov et al. 2002b; Anisimov et al. 2002c; Anisimov and Khavinson 2010; Goncharova et al. 2001; Goncharova et al. 2004; Gumen et al. 2006; Hekimi et al. 2011; Khavinson et al. 2001; Khavinson 2001a; Khavinson 2001b; Khavinson et al. 2002a; Khavinson et al. 2003; Khavinson and Morozov 2003; Khavinson et al. 2004; Khavinson and Linkova 2012; Korkushko et al. 2004; Korkushko et al. 2006; Korkushko et al. 2011; Labunets et al. 2007; Malinin and Khavinson 2005) were reviewed.
[27] None of the articles submitted discussed the use of epitalon. Seven of the articles submitted (Anisimov et al. 2001a; Khavinson and Morozov 2003; Korkushko et al. 2004; Korkushko et al. 2006; Korkushko et al. 2011; Labunets et al. 2007; Slepushkin et al. 1983) discussed the use of epithalamin; however, we note that epitalon and epithalamin are different substances.
[28] Epithalamin is a polypeptide complex extracted from the pineal gland and extracted from natural raw materials of animal origin (Anisimov et al. 2001b). Epitalon is a tetrapeptide that is synthesized from epithalamin (Kozina et al. 2007)
[29] See https://www.justice.gov/usao-edky/pr/nicholasville-compounding-pharmacy-and-its-owner-plead-guilty-unlawful-distribution. Accessed 12/3/2025.

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

After conducting a literature search, three studies were found in which epitalon was administered to humans. In two studies, epitalon was administered sublingually to subjects who worked night shifts to determine the effect on the expression of circadian genes (Khavinson et al. 2021) and the effect on the excretion level of 6-sulfatoxymelatonin (6-SMT)[30] (Ivko et al. 2021); the studies did not use a compounded formulation of epitalon. In the other study, epitalon was administered as a parabulbar injection in patients with congenital retinitis pigmentosa; it is unclear whether a compounded formulation of epitalon was used (Khavinson et al. 2002b). Epitalon received an orphan drug designation for the treatment of retinitis pigmentosa on September 2, 2010 (Vanhee et al. 2015). However, the orphan drug designation was withdrawn/revoked on January 6, 2016.[31]

Epitalon is marketed online by several wellness clinics and concierge medicine practices for use as an anti-aging agent, with some websites stating it is often referred to as "the fountain of youth."[32] The websites state that epitalon increases the production of telomerase which, according to these websites, results in a wide range of potential benefits including slowing down and reversing the signs of aging; increasing lifespan; improving skin health and appearance; healing injured and deteriorating muscle cells; promoting deeper sleep and improving sleep quality; restoring and normalizing melatonin levels; preventing age-related diseases such as cancer, heart disease, and dementia; improving brain health; treating symptoms of diabetes; boosting the immune system; improving eye health; increasing energy levels and improving mood; increasing resilience to emotional stress; reducing lipid oxidation and reactive oxygen species; and enhancing overall wellness.[33] Some of the sites provide administration and dosing information stating that epitalon is typically administered as an SC injection[34] or oral supplement[35] with doses ranging from 5 mg to 10 mg per day.[36] Some of the sites recommend using epitalon in cycles[37] with one site recommending using epitalon every 4 months.[38]

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[30] 6-Sulfatoxymelatonin is a metabolite of melatonin. It is referred to in the publication as "6-sulphateoximelatonin" and "6-COMT."
[31] See https://www.accessdata.fda.gov/scripts/opdlisting/oopd/. Accessed 12/3/2025.
[32] See, e.g., https://www.myconciergemd.com/epitalon-peptide/. Accessed 12/3/2025.
[33] See, e.g., https://www.transformyou.com/epithalon, https://www.myconciergemd.com/epitalon-peptide/, https://www.bodyrejuvenationmd.com/lifespan-longevity-anti-aging/epitalon-the-longevity-peptide/, https://www.genemedics.com/epithalon, https://focalpointvitality.com/epitalon-peptide/, and https://neuronmedical.com/age-reversal-therapy/. Accessed 12/3/2025.
[34] See, e.g., https://www.myconciergemd.com/epitalon-peptide/ and https://focalpointvitality.com/epitalon-peptide/. Accessed 12/3/2025.
[35] See https://www.myconciergemd.com/epitalon-peptide/ and https://www.bodyrejuvenationmd.com/lifespan-longevity-anti-aging/epitalon-the-longevity-peptide/. Accessed 12/3/2025.
[36] See, e.g., https://www.myconciergemd.com/epitalon-peptide/ and https://www.bodyrejuvenationmd.com/lifespan-longevity-anti-aging/epitalon-the-longevity-peptide/. Accessed 12/3/2025.
[37] See, e.g., https://www.myconciergemd.com/epitalon-peptide/ and https://www.bodyrejuvenationmd.com/lifespan-longevity-anti-aging/epitalon-the-longevity-peptide/. Accessed 12/3/2025.
[38] See https://neuronmedical.com/age-reversal-therapy/. Accessed 12/3/2025.

3. How Widespread Its Use Has Been

No outsourcing facility has reported compounding drug products containing epitalon to FDA. Some wellness clinics that market the use of epitalon state that they obtain epitalon from a compounding pharmacy;[39] however, through a Google search, FDA was not able to identify any pharmacies that compound products containing any form of epitalon. Several websites were found that market epitalon products including 10 mg, 20 mg, 25 mg, 50 mg vials; 3 mg and 3.3 mg capsules; and an oral spray[40] with several of the sites stating that the product is intended for research use only.[41]

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

Epitalon is not recognized in either the European (11.8th edition) or Japanese (18th edition) Pharmacopeia. There are no approved products containing epitalon in Canada, Australia, the United Kingdom, Belgium, Ireland, France, Norway, Germany, Spain, and Italy. Additionally, there are no products containing epitalon that have been authorized for use in the European Union by the European Medicines Agency.

Conclusions: It is often unclear whether the epitalon discussed in the sources considered for this section is the salt form or the free base. The extent to which any form of epitalon has been used in compounding is unclear. Publicly available information suggests that epitalon has been used in compounding since at least 2018;[42] however, no pharmacies were found that compound products containing epitalon. Websites were found that sell products that contain epitalon, but it is unclear if these are compounded products. At the time of this evaluation, currently available data and published literature is too limited for FDA to understand the historical use of any form of epitalon in 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, DailyMed, Drugs@FDA, ClinicalTrials.gov, relevant professional healthcare organization websites, and various online clinical references and websites, such as information from the National Institutes of Health (NIH). In addition to a comprehensive review of pertinent information from these databases, this section provides a discussion of the proposed use.

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[39] See https://www.transformyou.com/peptide-therapy. Accessed 12/3/2025.
[40] See, e.g., https://myvidawellness.com/us/product/epitalon-the-anti-aging-peptide/, https://www.corepeptides.com/peptides/epitalon-25mg/, https://www.limitlesslifenootropics.com/, https://www.peptidesciences.com/epithalon-epitalon-20mg, https://www.almightypeptides.com/product/epitalon-peptide-10-mg/, and https://club120.com/products/epitalon. Most sites do not provide administration instructions. Accessed 12/3/2025.
[41] See https://www.corepeptides.com/peptides/epitalon-25mg/, https://www.limitlesslifenootropics.com/, and https://www.peptidesciences.com/epithalon-epitalon-20mg. Accessed 12/3/2025.
[42] See https://www.justice.gov/usao-edky/pr/nicholasville-compounding-pharmacy-and-its-owner-plead-guilty-unlawful-distribution. Accessed 12/3/2025.

References submitted by the nominator and those identified by FDA do not always clearly identify whether the epitalon form administered in the clinical studies was a salt form or the free base. Therefore, throughout this section, the substance will be generally referred to as epitalon unless otherwise specified as free base or acetate salt.

As mentioned above, epitalon is also known as epithalon and/or by its amino acid components Ala-Glu-Asp-Gly; these terms will be used interchangeably consistent with the term used in each reference.

We evaluated epitalon (free base) and epitalon acetate for the use of insomnia and considered available data to support effectiveness.

Epitalon-related BDSs were also proposed for the following uses: anti-aging, longevity, lengthening telomeres in human cells, promotion of deeper sleep, delay and prevention of age-related diseases such as dementia, anti-oxidant by reducing lipid oxidation and reactive oxygen species along with normalizing T cell function, improvement of skin health and appearance, healing of injured and deteriorating muscle cells, restores and normalizes melatonin levels in older people who have lost some pineal gland function due to aging, resistance to emotional stress, and paradoxical sleep disorder. However, FDA did not evaluate these proposed uses because the nominations did not include sufficient information for FDA to evaluate whether the substances are appropriate for these uses in compounded drug products. See 80 FR 65765 for information necessary to fully evaluate a substance.

1. Insomnia

Insomnia is a common sleep disorder associated with trouble falling asleep, staying asleep, or getting good quality sleep, despite adequate time and the right environment to sleep well. Insomnia can result in daytime sleepiness and impact daily activities, memory, and concentration. Risk factors for insomnia include age, occupation, lifestyle, and stress. Short-term insomnia may last for days or weeks.[43] Chronic insomnia is diagnosed when symptoms occur at least three times a week for three months or longer.[44, 45]

To diagnose insomnia, healthcare providers assess sleep habits and other symptoms, risk factors, health history, and family history, as well as evaluate for other medical problems that may affect sleep. Additional tests, such as polysomnography to evaluate for other sleep problems (e.g., sleep apnea, periodic limb movement disorder) may be performed (Rundo and Downey 2019). There are no routine laboratory studies necessary in the evaluation of chronic insomnia; however, selected tests may be indicated to evaluate for comorbidities.[46]

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[43] See: What Is Insomnia?, NIH National Heart, Lung, and Blood Institute, accessed 3/26/2025, https://www.nhlbi.nih.gov/health/insomnia.
[44] International Classification of Sleep Disorders-Third Edition: Highlights and Modifications (Sateia 2014).
[45] See: Substance Abuse and Mental Health Services Administration. Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health [Internet], accessed 3/26/2025, https://www.ncbi.nlm.nih.gov/books/NBK519704/table/ch3.t36/.
[46] See: Evaluation and Diagnosis of Insomnia in Adults. UpToDate, accessed 3/20/2024, https://www.uptodate.com/contents/evaluation-and-diagnosis-of-insomnia-in-adults.

Treatment strategies include implementing healthy sleep habits, cognitive behavioral therapy, and pharmacologic treatment. Pharmacologic therapy options may include medications from drug classes including benzodiazepine receptor agonists, melatonin receptor agonists, orexin receptor antagonists, and benzodiazepines.[47] Over-the-counter (OTC) products that contain antihistamines have also been used for relief of occasional sleeplessness.[48] Studies evaluating pharmacologic treatment of insomnia generally evaluate objectively and subjectively assessed sleep outcomes such as sleep latency, sleep duration, and number of awakenings.[49,50]

In addition, studies have evaluated the role of endogenous melatonin in insomnia and other primary sleep disorders. Melatonin is a hormone produced by the brain's pineal gland, which is one of several brain structures involved with sleep.[51,52] Endogenous melatonin is important for matching the body's circadian rhythm to the external cycle of light and darkness, and plays a key role in the sleep-wake cycle.[53,54] Endogenous melatonin production declines with age due to different factors, including calcification of the pineal gland, which is very common.[55] However, low melatonin levels have not been consistently associated with insomnia in elderly adults (Youngstedt et al. 1998).

The American Academy of Sleep Medicine (AASM)[56] has published practice guidelines on the treatment of chronic insomnia. Epitalon (free base) and epitalon acetate are not mentioned in the guideline (Sateia et al. 2017).

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

The nominations for epitalon-related BDSs cited one publication that mentioned epitalon use in humans (Khavinson and Linkova 2012). Our search of published medical literature did not retrieve publications discussing efficacy of epitalon-related BDSs administered in patients with

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[47] Alternative therapies for the conditions being considered are discussed in Section II.C.1.c
[48] See: Insomnia. Treatment, NIH National Heart, Lung, and Blood Institute, accessed 3/6/2024, https://www.nhlbi.nih.gov/health/insomnia/treatment.
[49] See, e.g., label for Ambien (zolpidem tartrate) oral tablet, new drug application (NDA) 019908/S-47, accessed 3/25/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019908.
[50] Sleep latency is defined as the duration of time between when the lights are turned off as the patient attempts to sleep, until the time the patient actually falls asleep (Shrivastava et al. 2014).
[51] See: Brain Basics: Understanding Sleep, NIH National Institute of Neurologic Disorders and Stroke, accessed 3/9/2024, https://www.ninds.nih.gov/health-information/public-education/brain-basics/brain-basics-understanding-sleep.
[52] See: Melatonin. Cleveland Clinic website, accessed 3/9/2024, https://my.clevelandclinic.org/health/articles/23411-melatonin.
[53] See: Brain Basics: Understanding Sleep, NIH National Institute of Neurologic Disorders and Stroke, accessed 3/9/2024, https://www.ninds.nih.gov/health-information/public-education/brain-basics/brain-basics-understanding-sleep.
[54] See: Melatonin. Cleveland Clinic website, accessed 3/9/2024, https://my.clevelandclinic.org/health/articles/23411-melatonin.
[55] See: Melatonin. Cleveland Clinic website, accessed 3/9/2024, https://my.clevelandclinic.org/health/articles/23411-melatonin.
[56] See: Practice Guidelines, American Academy of Sleep Medicine website, accessed 5/28/2024, https://aasm.org/clinical-resources/practice-standards/practice-guidelines/. The guideline for the pharmacologic treatment of chronic insomnia in adults was published in 2017 by Sateia et al.

insomnia, or clinical studies reporting use of these substances via the proposed SC ROA. We retrieved one clinical study that discusses the ability of the peptide to restore epiphyseal melatonin production in humans (Ivko et al. 2021).

- Khavinson and Linkova 2012 is a literature review of the morphology, molecular, and functional aspects of pineal gland aging and states that, "[t]he effect of a course of epithalamine or epithalon administration on the melatonin-forming function of the PG [pineal gland] depends on the initial degree of preservation of this function in elderly subjects. PG peptide preparations had no significant effect in elderly subjects with unchanged function of the PG or in young subjects. The MT [melatonin] concentration increased by a factor of two under the effect of epithalamine and epithalon in elderly subjects with involution changes in the PG. These data prove the modulatory effect of PG peptide preparations on the melatonin-forming function of the PG during its aging."[57]

- Ivko et al. 2021 is a randomized, placebo-controlled study that evaluated the effect of sublingual (SL) Ala-Glu-Asp-Gly ("AEDG peptide") on the urinary excretion of the melatonin metabolite 6-SMT[58] and the expression of clock genes in blood cells in healthy women ages 40-50 years (n = 75) primarily working night shifts. Subjects were divided into two groups based on levels of urinary excretion of 6-SMT: subjects with an "age-appropriate normal value" (n = 35, control) and subjects with 6-SMT "at the level of elderly people" with "reduced melatonin production" (n = 40).[59] The 40 subjects with low 6-SMT levels were divided in two groups and for 20 days, received either:

    - Placebo 3 SL sprays (0.9% NaCl solution) twice a day (Group 1), or
    - AEDG 3 SL sprays (Epitalon Solution-Spray Nanopep, France) twice a day (1 mL corresponded to a daily administration of 0.5 mg peptide/day; volume of each spray not described) (Group 2)

The authors observed that baseline levels of urinary 6-SMT were 1.7 times lower in Group 1 (placebo) as compared to control (normal value for age), and levels did not change with placebo treatment. In Group 2 (AEDG), 6-SMT levels were similar to Group 1 at baseline and increased 1.7-fold after treatment; per authors, "AEDG peptide restored the epiphyseal melatonin formation to a normal, age-appropriate value." The authors also noted that subjects receiving AEDG "demonstrated distinct positive dynamics of psycho-emotional and general physical condition in 83% of cases," as compared to 25% in placebo; however, no details were provided about how psycho-emotional and general physical condition were assessed. In addition, the authors observed changes in levels of clock genes after AEDG administration.

Authors concluded that AEDG peptide has a "geroprotective effect" and can stimulate melatonin synthesis and indirectly regulate the expression of proteins encoded by the clock genes. The publication did not specify blinding, and additional limitations include short duration and small

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[57] The cited source of this information, a reference titled *Pineal Gland: Correction in Aging* by Korkushko et al. 2006, was in the Russian language and we were unable to locate the reference in English.
[58] 6-Sulfatoxymelatonin is a metabolite of melatonin. It is referred to in the publication as "6-sulphateoximelatonin" and "6-COMT."
[59] Reference intervals for 6-SMT and details regarding age stratification were not provided in the publication.

study size. The study did not evaluate sleep outcomes and did not discuss clinical applicability of study results or potential therapeutic effect for insomnia or other sleep disorders. In addition, AEDG peptide was administered via SL ROA in the study while the proposed ROA is SC.

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

Chronic insomnia increases the risk of high blood pressure, coronary heart disease, diabetes, and cancer.[60] Insomnia is associated with multiple other adverse health outcomes, such as psychiatric disorders, suicide, and self-medication with alcohol and other substances.[61]

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

There are multiple FDA-approved and/or OTC monograph drug products that treat the same medical condition as that proposed for the epitalon-related compounded drug products (i.e., insomnia).[62] The following are oral pharmacotherapies by drug class with examples for each:[63]

- Benzodiazepine receptor agonists (e.g., eszopiclone [Lunesta][64], zaleplon [Sonata][65], zolpidem tartrate oral tablet [Ambien][66], zolpidem tartrate sublingual tablet[67])
- Benzodiazepines (e.g., quazepam [Doral][68], triazolam [Halcion][69])
- Melatonin receptor agonists (e.g., ramelteon [Rozerem][70]
- Orexin receptor antagonists (e.g., suvorexant [Belsomra][71])

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[60] See: What Is Insomnia?, NIH National Heart, Lung, and Blood Institute website, accessed 3/5/2024, https://www.nhlbi.nih.gov/health/insomnia.
[61] See: Risk Factors, Comorbidities, and Consequences of Insomnia in Adults, UpToDate, accessed 3/5/2024, https://www.uptodate.com/contents/risk-factors-comorbidities-and-consequences-of-insomnia-in-adults.
[62] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[63] See: Insomnia. Treatment, NIH National Heart, Lung, and Blood Institute website, accessed 3/9/2024, https://www.nhlbi.nih.gov/health/insomnia/treatment. See also: Practice Guidelines, American Academy of Sleep Medicine website, accessed 5/28/2024, https://aasm.org/clinical-resources/practice-standards/practice-guidelines/.
[64] See label for Lunesta (eszopiclone) oral tablet, NDA 021476/S-38, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=021476.
[65] See label for Sonata (zaleplon) oral capsule, NDA 020859/S-16, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=020859.
[66] See label for Ambien (zolpidem tartrate) oral tablet, NDA 019908/S-47, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019908.
[67] See label for zolpidem tartrate sublingual tablet, ANDA 204299, accessed 3/9/2024, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=6db679f6-b1f8-4fbf-9e87-9cef4650c45a.
[68] See label for Doral (quazepam) oral tablet, NDA 018708/S-29, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=018708.
[69] See label for Halcion (triazolam) oral tablet, NDA 017892/S-57, accessed 5/29/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=017892.
[70] See label for Rozerem (ramelteon) oral tablet, NDA 021782/S-22, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=021782.
[71] See label for Belsomra (suvorexant) oral tablet, NDA 204569/S-8, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=204569.

- Heterocyclics (e.g., doxepin hydrochloride [Silenor][72])
- Antihistamines (e.g., doxylamine succinate [Unisom][73] and diphenhydramine hydrochloride[74])

Conclusion: Based on available information, we conclude that there is a lack of evidence to support the effectiveness of epitalon (free base) or epitalon acetate for the proposed use of insomnia, a disorder which increases the risk for serious conditions. Available clinical information discusses the effects of epitalon-related BDSs on melatonin or melatonin metabolite levels. However, we did not identify studies evaluating the use of these substances in patients with insomnia, particularly when administered via the proposed SC ROA. The potential therapeutic effect of changes in melatonin levels induced by these substances is unclear without a corresponding evaluation of clinical outcomes. In addition, there are currently multiple FDA-approved drug products with established efficacy indicated for insomnia.

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

1. Nonclinical Assessment

The nominators submitted nonclinical information. Specifically, they submitted a list of 10 articles describing nonclinical studies of epitalon. Most articles discuss pharmacological properties of epitalon (Anisimov and Khavinson 2010; Goncharova et al. 2001; Gumen et al. 2006; Khavinson 2001a; Khavinson et al. 2001; Khavinson et al. 2003; Khavinson et al. 2004; Malinin and Khavinson 2005), and two articles discuss the effects of epitalon on the incidence of spontaneous tumors in mice (Anisimov et al. 2002a; Anisimov and Khavinson 2010).

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

The studies discussed in this section do not clearly identify the specific form of epitalon (free base or salt) used in the different experiments. Throughout this section, we refer to epitalon as it is referred to in the cited articles.

a. General Pharmacology of the Drug Substance

Epitalon (free base), the active moiety of epitalon (free base) and epitalon acetate, is a synthetic tetrapeptide derived from the amino acid composition of low-molecular weight peptides in epithalamin, an extract originally obtained from the pineal gland of cattle (Khavinson 2002). Figure 5 illustrates the amino acid sequence of epitalon.

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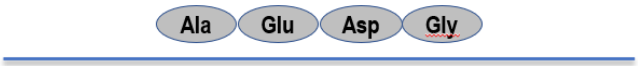
[72] See label for Silenor (doxepin hydrochloride) oral tablet, NDA 022036/S-6, accessed 3/9/2024, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022036.
[73] See label for Unisom SleepTabs (doxylamine succinate) oral tablet, ANDA 040167, accessed 3/9/2024, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f591d52f-5610-4517-a96f-1ed63deb00bc.
[74] See OTC Monograph M010: Nighttime Sleep Aid Drug Products for OTC Human Use, accessed 3/9/2024, https://dps.fda.gov/omuf/monographsearch/monograph_m010.

Figure 51. Amino Acid Sequence of Epitalon.



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.

Considering that the pineal gland has a central role in the regulation of the sleep-wake cycle and other circadian rhythms (Erlich and Apuzzo 1985), researchers have hypothesized that epitalon could affect circadian rhythmicity. Most pharmacological studies of epitalon have been conducted and published by Dr. Khavinson's research group in Russia. This section focuses on nonclinical studies that have been published in English and report pharmacological effects of epitalon relevant to the clinical indication of insomnia evaluated in this memo.

Goncharova and collaborators conducted a study to assess the effects of epitalon on serum levels of melatonin and cortisol in young (6 to 8 years old) and old (20 to 26 years old) female Rhesus monkeys housed under natural light-dark cycles (8 a.m.-7 p.m.) (Goncharova et al. 2001). Melatonin is a pineal gland hormone that is involved in the control of the sleep-wake cycle; melatonin's levels are generally higher during the night compared to the day (Zisapel 2018). Cortisol is an adrenal gland hormone, and its levels also oscillate with the circadian cycle, being higher in the morning than in the evening (Thau et al. 2019).

In the study by Goncharova and collaborators, monkeys received a daily intramuscular injection of epitalon (2 µg/kg) or vehicle (saline – 0.9% NaCl – 0.2 mL/kg) for 10 days. All animals were treated at 9 a.m. each day and had their blood drawn immediately after the injections and 9 p.m. on the last treatment day. The main findings were as follows:

- In the control (saline-treated) group, serum melatonin levels in blood drawn at 9 a.m. were significantly higher than those measured in blood drawn at 9 p.m. in both the younger monkeys [morning: 30 ± 9 pg/mL; evening: 17 ± 7 pg/mL] and the older monkeys [morning: 15 ± 3 pg/mL; evening: 10 ± 2 pg/mL]. The higher melatonin levels measured in the blood collected at 9 a.m. than 9 p.m. are likely to reflect the higher production and release of melatonin during the night compared to the day.

- In the control group of younger monkeys, serum cortisol levels were markedly higher in the morning (~1,100 nmoles/L) than in the evening (~600 nmoles/L). However, the circadian regulation of serum cortisol levels appeared to be lost in the control group of older monkeys because their serum cortisol levels were comparable between morning and evening (~900 nmoles/L).

- In the older monkeys, epitalon significantly increased by more than 4-fold the evening serum melatonin levels and had no statistically significant effect on morning serum melatonin levels. In addition, epitalon significantly reduced by ~30% the evening serum cortisol levels and had no statistically significant effect on morning serum cortisol levels, restoring the circadian fluctuation of serum concentrations of cortisol.

- In the younger monkeys, epitalon had no significant effect on serum melatonin levels and reduced serum cortisol levels both in the morning and the evening.

The authors did not assess the dose-response relationship of the pharmacological responses induced by epitalon. In addition, the pharmacological responses on blood drawn were assessed in the morning and the evening from monkeys on the last day of their 10-day dose regimen. Therefore, it is unclear whether the observed effects of epitalon were acute (in response to the dose administered on the last treatment day) or developed with time during the 10-day treatment. Although epitalon-induced increase of serum melatonin levels could affect the sleep-wake cycle, the authors did not assess sleep behavior or electroencephalographic activity in epitalon- and saline-treated monkeys. Thus, the functional relevance of the finding that epitalon treatment of older monkeys increased evening serum levels of melatonin and decreased evening serum levels of cortisol is unknown. FDA identified no nonclinical pharmacological study assessing the effects of epitalon on sleep.

The mechanisms by which epitalon regulates levels of melatonin and, possibly, modulates circadian rhythms are unknown. Findings of an in-vitro study suggest that epitalon may not directly stimulate release of melatonin from the pineal gland (Djeridane et al. 2003). Specifically, according to data from that study, acute superfusion of pineal glands harvested from young (6-week-old) and old (24-month-old) rats with physiological solution containing epitalon (1, 10, or 100 µM) failed to increase the release of melatonin (Djeridane et al. 2003).

b. Pharmacokinetics/Toxicokinetics

A preliminary account of potential tissue distribution of epitalon was reported in a study of pregnant rabbits treated with a single intravenous dose of fluorescent-labeled epitalon (30 µg/kg) on gestation day 29 (Lapina et al. 2005). According to the study authors: (i) fluorescence could be detected one-hour post-dosing in maternal and fetal organs that included the liver, lungs, stomach, and intestines, and (ii) fluorescence signals in brain and placental tissues was weak and diffuse (Lapina et al. 2005). The findings should be interpreted with caution because the study lacks data to demonstrate that the fluorescence signals detected in tissue were specifically due to labeled epitalon.

At the time of this evaluation, the nominator did not submit, and FDA did not identify additional pharmacokinetic or toxicokinetic studies of epitalon (free base) and epitalon acetate.

c. Acute Toxicity[75]

At the time of this evaluation, the nominator did not submit, and FDA did not identify acute toxicity studies of epitalon (free base) and epitalon acetate.

[75] 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.

d. Repeat-Dose Toxicity[76]

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

e. Genotoxicity[77]

The potential for epitalon to induce genotoxicity was assessed in two studies that analyzed the frequency of chromosome aberrations in bone marrow cells harvested at the end of treatment of female mice (n = 4/treatment group) of different strains with vehicle (saline, 0.1 mL/animal/day, SC) or epitalon (1 µg/mouse/day, SC) for 5 consecutive days/month (Anisimov et al. 2003; Rosenfeld et al. 2002). The mouse strains used in the studies include the outbred spontaneously hypertensive rat (SHR) strain derived from the outbred Swiss mouse strain and the senescence-accelerated mouse strains SAMP-1 and SAMR-1. These three mouse strains are reported to have a high incidence of spontaneous tumors (Anisimov et al. 2003; Rosenfeld et al. 2002).

The data from SHR mice are identical in the two studies. However, Anisimov et al. stated that mice were treated between the ages of 3 and 12 months, and Rosenfeld et al. stated that mice were treated between the ages of 2 and 12 months (Anisimov et al. 2003; Rosenfeld et al. 2002).

Rosenfeld et al. (2002) reported that the frequencies of chromosome aberrations in vehicle-treated female SAMP-1 and SAMR-1 mice were 18.7 ± 9.51% and 10.3 ± 0.11%, respectively. By contrast, the frequencies of chromosome aberrations in epitalon-treated SAMP-1 and SAMR-1 mice were 15.0 ± 0.28% and 7.2 ± 0.08%, respectively. The results indicated that epitalon reduced the frequencies of chromosome aberrations by ~20% in the senescence-accelerated SAMP-1 mice and by ~30% in the SAMR-1 mice (Rosenfeld et al. 2002). Anisimov et al. (2003) and Rosenfeld et al. (2002) also reported that, at 12 months of age, epitalon-treated SHR mice had a 17% lower frequency of chromosome aberrations than vehicle-treated mice. The findings suggest that, at the tested dose (1 µg/mouse/day, SC), epitalon was not mutagenic.

The studies published by Anisimov et al. (2003) and Rosenfeld et al. (2002) are limited in their ability to inform the potential for epitalon to induce genotoxicity in part because they were conducted with a fixed dose of epitalon. In addition, FDA notes that the research group appears to use the frequency of chromosome aberrations measured in bone marrow cells from four saline-treated SHR mice as historical control data for this mouse strain, because the same

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[76] 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.

[77] 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.

frequency was used as control data in a different study assessing the genotoxic potential of another peptide – emideltide (Popovich et al. 2003).

Although there are methods to incorporate historical control data in nonclinical toxicological studies (Maringwa et al. 2007), the authors provide no analysis to validate the use of their data from four saline-treated SHR mice as historical control data for this strain in their laboratory. Therefore, the data from all studies should be interpreted with caution because the use of historical control data that are not fully representative of the larger population can impact the statistical data analysis and cause over or underestimation of statistical significance (Maringwa et al. 2007).

In a study conducted in 3-month-old white and grey mice (undefined mouse strains), treatment with a single dose of epitalon (5 µg/kg, SC) did not increase the occurrence of micronuclei in peripheral blood erythrocytes (Mylnikov et al. 2012). This finding suggests that, under the conditions of this study and at the fixed SC dose of 5 µg/kg, epitalon did not induce chromosomal breakage or damage to the mitotic apparatus. This study is limited in its ability to inform the genotoxic potential of epitalon because it assessed the effects of a fixed dose of the peptide on chromosomal integrity.

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

f. Developmental and Reproductive Toxicity[78]

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

g. Carcinogenicity[79]

Three studies assessed the effects of epitalon on age-related incidence of spontaneous malignant tumors in different mouse strains and on the lifespan of the mice (Anisimov et al. 2001b; Anisimov et al. 2002b; Anisimov et al. 2003). The overall experimental design was similar across the studies, as they were conducted by the same research group. In short, female mice

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[78] 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.

[79] 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.

were treated with a fixed SC dose of epitalon (0.1 μg/mouse/day corresponding to ~3-4 μg/kg/day or 1 μg/mouse/day corresponding to ~30-40 μg/kg/day) or vehicle (saline; 0.1 mL/mouse/day) for 5 consecutive days every month. The treatments continued throughout the lifespan of each mouse.

Table 3 provides an overview of the experimental design for each study, including mouse strain, animals' age at start of treatment, epitalon dose administered to the animals, and number of animals per group. It also provides a summary of the main findings of each study.

Table 3. Summary of Effects of Epitalon on Incidence of Spontaneous Tumors and Lifespan of Mice.

Study	General Study Design	Main Effects of Epitalon
Anisimov et al. 2001b	**Mouse Strain**: CBA[a] **Age:**[b] 6 months **Dose**: 0.1 μg/mouse/day, SC, 5 days/month **n** = 50 mice/group	• ↑ Body weight (5%) • ↓ Locomotor activity • ↓ Incidence of spontaneous tumors (mainly lung carcinoma; control: 10/50; epitalon: 2/50) • ↑ Mean lifespan (Control: 685 days; Epitalon: 721 days)
Anisimov et al. 2002b	**Mouse Strain**: FVB/N HER- 2/neu[c] **Age**: 2 months **Dose**: 1 μg/mouse/day, SC, 5 days/month **n** = 50 mice/group	• ↓ Cumulative number and maximum size of mammary tumors • ↓ Size of lung metastases • ↓ Expression of HER-2/neu mRNA in mammary tumors (by 3.7-fold)
Anisimov et al. 2003	**Mouse Strain**: Swiss-derived SHR[d] **Age**: 3 months **Dose**: 1 μg/mouse/day, SC, 5 days/month **n** = 50 mice/group	• ↑ Food consumption • Slowed down age-related switching-off of estrous function (based on histological assessments of vaginal swabs) • ↑ Lifespan of the last 10% survivors (Control: 709 days; Epitalon: 803 days) • ↓ Incidence of leukemia (Control: 6/50; Epitalon: 1/50)

[a] Inbred mouse strain.
[b] Age refers to the age of mice at the start of treatment.
[c] Transgenic mice carrying the mammary cancer gene human epidermal growth factor receptor 2 (HER-2/neu) in the FVB/N (Friend virus B/NIH) genetic background are known to develop spontaneous focal mammary adenocarcinomas beginning at about 4 months of age, with the majority of mice developing spontaneous tumors by 10 months of age (Reilly et al. 2000).
[d] Outbred mouse strain. ↓ and ↑ represent decrease and increase, respectively, from control (saline-treated mice).

One common finding of the three studies was the suppression of the development of spontaneous tumors by the intermittent treatment of mice with epitalon compared to vehicle (Table 3). In addition, in the 2001 and 2003 studies, the oncostatic effect of epitalon in mice was accompanied by prolongation of their lifespan (Table 3). Although results of the studies listed in Table 3 suggest that epitalon could have oncostatic and longevity-inducing properties, they should be

interpreted with caution because: (i) each study used a fixed dose of epitalon, and, as such, did not provide an assessment of dose-response relationships, and (ii) the three studies assessed the effects of epitalon only in female (not male) mice (Anisimov et al. 2001b; Anisimov et al. 2002b; Anisimov et al. 2003).

Considering reports that longer telomere lengths are associated with longer lifespans, the researchers hypothesized that epitalon-induced prolongation of lifespan could be due to effects of epitalon on telomere lengths (Khavinson et al. 2003; Malinin and Khavinson 2005). Telomeres are DNA-protein structures at both ends of each chromosome that prevent genomic instability by protecting the genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion (Rossiello et al. 2022). As cells divide, telomeres become shorter, and, when telomere length reaches a critical limit, cells undergo senescence and eventually die (Rossiello et al. 2022; Shammas 2011). Telomere length shortens with advancing age (Shammas 2011), and transgenic induction of telomerase activity in normal human cells in vitro extends their lifespan (Bodnar et al. 1998).

To test their hypothesis, researchers assessed telomere length in primary cultures of human fetal lung fibroblasts that were either untreated or incubated with epitalon (50 ng/mL) for 4 days (Khavinson et al. 2003; Malinin and Khavinson 2005). The authors reported that epitalon: (i) increased the expression and activity of telomerase (the enzyme that catalyzes the addition of telomere structures to the ends of chromosomes), and (ii) extended the mean and maximum lengths of telomeres (Khavinson et al. 2003; Malinin and Khavinson 2005). Their findings lend support to the hypothesis that epitalon-induced prolongation of lifespan could be due to epitalon-induced increase in telomerase activity, which, in turn, would extend telomere lengths and suppress cellular senescence (Anisimov and Khavinson 2010; Khavinson et al. 2003; Malinin and Khavinson 2005).

In addition to being mechanisms likely to contribute to the prolongation of the lifespan of animals reported in different studies (Table 3), increased telomerase activity and telomere lengthening could be mechanisms involved in the oncostatic properties of intermittent treatment with epitalon. Through a phenomenon referred to as telomere position effect, telomeres can suppress the expression of subtelomeric genes (Lee et al. 2021). Thus, as hypothesized by Dr. Khavinson's research group, by activating telomerase and lengthening telomeres, intermittent treatment with epitalon could suppress the expression of nearby cancer-related genes and prevent development of tumors (Khavinson et al. 2003; Malinin and Khavinson 2005). In-vitro studies have also reported that epitalon can act as an antioxidant (Yue et al. 2022) and an anti-inflammatory (Avolio et al. 2022), and these actions could also contribute to the potential antitumorigenic effects of intermittent treatment with epitalon.

It should be noted, however, that chronic continuous exposures to epitalon, by virtue of upregulating telomerase and extending telomere lengths beyond the upper boundary limits for cells to become immortalized and cancerous, could result in carcinogenicity. As described in the literature, long telomeres (generally >0.7x standard deviations of the mean lengths) have been associated with increased risks for malignant tumors (McNally et al. 2019). Caution is warranted when interpreting the results of the studies by Anisimov and colleagues because potential effects of epitalon on tumor development may depend on dose regimen and duration of treatment.

In general terms, in a typical study designed to assess the carcinogenic potential of a substance, male and female mice (or rats) are treated daily with the test article for a minimum of 2 years.[80] 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 studies by Anisimov and colleagues, the intermittent epitalon treatments resulted in exposures far shorter than 12 months. For instance, in the 2003 study by Anisimov and colleagues, epitalon was administered to mice for 5 consecutive days/month between 2 months of age and the end of their natural life (~24 months of age). Therefore, mice were exposed to epitalon for a maximum of 22 weeks (or ~5.5 months).

In November 2022, FDA published the guidance for industry *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals*, which discusses the use of a weight-of-evidence analysis to assess the human carcinogenic potential of pharmaceuticals.[81] This analysis considers, among other factors, the primary mechanisms of action, off-target actions, and pharmacokinetic profile of the substance, to inform whether a long-term (2-year) carcinogenicity study could add value to human risk assessment. Although data are not currently available to support a full weight-of-evidence analysis for epitalon, reports that epitalon can activate telomerase and lengthen telomeres raise concerns that continuous exposure to epitalon through the lifespan could enable cells to evade senescence and become cancerous.

At the time of this evaluation, FDA did not identify 2-year carcinogenicity studies with epitalon (free base) or epitalon acetate.

Conclusions: From the pharmacological perspective, findings that epitalon can increase serum levels of melatonin, a pineal gland hormone known to regulate sleep-wake cycle, suggest that epitalon could influence sleep-wakefulness. However, FDA did not identify nonclinical studies assessing the effects of epitalon on behavioral or electroencephalographic endpoints of sleep. In addition, the mechanisms by which epitalon regulates serum levels of melatonin in vivo remain unknown. From the toxicological perspective, nominator-submitted and FDA-identified studies reported that intermittent treatments of female mice from different strains with a fixed dose of epitalon did not increase the frequency of chromosome aberrations in bone marrow cells and suppressed the development of spontaneous tumors. Due to their limitations, which include the use of a fixed dose of epitalon, assessment of female mice only, and short-lasting exposure of mice to epitalon, these studies do not adequately inform the genotoxic or the carcinogenic potential of epitalon. This is concerning because, from the mechanistic standpoint, epitalon has the potential to be carcinogenic. Specifically, epitalon has been shown to activate telomerase and lengthen telomeres, and longer telomeres are generally associated with increased risk for cancer. In conclusion, at the time of this evaluation, nonclinical studies were too limited in scope and duration to inform safety considerations for potential clinical uses of epitalon (free base) or epitalon acetate.

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[80] See footnote 79.

[81] *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.

2. *Human Safety*

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FAERS, Human Foods Program[82] Human Foods Complaint System (HFCS)[83], ClinicalTrials.gov, relevant professional healthcare organization websites, and various online clinical references and websites, such as information from the NIH.

References submitted by the nominator and those identified by FDA do not always clearly identify whether the epitalon form administered was a salt formulation or the free base. Therefore, throughout this section, the substance will be generally referred to as epitalon or epitalon-related BDSs.

a. Pharmacokinetic Data

No pharmacokinetic data were found for epitalon (free base) or epitalon acetate.

b. Reported Adverse Reactions

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for epitalon through December 8, 2025. The search retrieved no reports.[84,85]

Human Foods Program collects reports of AEs and product complaint reports submitted to FDA for food, dietary supplements, and cosmetics in the HFCS. A search of HFCS was conducted for AEs associated with epitalon through December 5, 2025, and retrieved no cases.

c. Clinical Studies Assessing Safety

The nominations did not include, and our search of the published medical literature has not identified clinical studies assessing the safety of epitalon-related BDSs administered in humans.

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[82] Formerly Center for Food Safety and Nutrition (CFSAN).
[83] Formerly CFSAN Adverse Event Reporting System (CAERS).
[84] It is important to note that FAERS data have limitations. Reporting is voluntary. In general, there is no certainty that reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that may potentially occur with a product, especially for compounded products. Considering these limitations, FDA cannot make definitive conclusions regarding the safety of epitalon based on FAERS data alone. For additional information, see Questions and Answers on the FDA FAERS website, available at: https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Accessed 12/8/2025.
[85] Compounders under section 503A of the FD&C Act generally do not report adverse events to FDA. FDA encourages compounders, health care professionals, and consumers to report adverse events and product quality concerns associated with compounded drugs to FDA's MedWatch Adverse Event Reporting program. Unless an adverse event report is submitted to FDA, the Agency may not be aware of adverse events associated with a product compounded under section 503A.

Our search identified a study in which 20 subjects (ages 40 to 50 years) received SL Ala-Glu-Asp-Gly for 20 days (3 sprays twice daily, 1 mL corresponded to administration of 0.5 mg peptide/day) that did not report safety data (Ivko et al. 2021).

Our search identified an abstract by Korkushko et al. 2007 that noted that in the course of aging, both monkeys and people revealed decreased levels of melatonin. The abstract also noted the preparations of the PG (epitalon and epithalamin) have "no side effects" in elderly people. However, details such as ROA, dosing information, duration of administration, number of subjects and demographics, and methods of safety data collection were not provided in the abstract.[86]

d. Other Safety Information

Immunogenicity and Aggregation Concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[87] 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 epitalon (free base) and epitalon acetate), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC ROA. In general, the SC ROA is associated with increased immunogenicity compared to intravenous ROA.

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

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

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[86] We could not evaluate the full article by Korkorshko et al. 2007 because it was in the Russian language. We searched multiple databases and were unable to locate the full article in English.

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

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

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

There are FDA-approved drug products and/or OTC monograph drug products that treat the same medical condition as that proposed for the compounded drug products containing epitalon-related BDSs.[88] See Section II.C. for a discussion of alternative therapies.

Conclusions: Based on available information, we conclude that there are no clinical data to support the safety of epitalon (free base) or epitalon acetate when used in humans. FDA has not identified safety data regarding epitalon-related BDSs when administered to humans, particularly via the proposed SC ROA. SC ROA may present a particular risk for immunogenicity due to the potential for aggregation as well as potential peptide-related impurities. Therefore, there is a lack of important information regarding the use of these substances administered subcutaneously, including whether the drug would cause harm if administered to humans. In addition, there are currently available FDA-approved therapies for the treatment of insomnia; these drug products have well-characterized safety profiles and have been shown to be safe for their labeled use.

III. CONCLUSION AND RECOMMENDATION

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

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

   1.1.

   Epitalon (free base) is reported to be a peptide of four amino acids. As reported in the literature, epitalon (free base) is expected to be stable under storage conditions below -20°C.

   Epitalon (free base) is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not

[88] 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.

follow established chemical nomenclature standards (e.g., INN, USAN, IUPAC), and (2) data/information relevant to certain critical quality attributes for establishing its identity, purity, and quality for its intended use in the proposed dosage form (injection) were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information includes but are not limited to having specific tests on the Certificate of Analysis for the critical quality attributes that are relevant to characterizing peptide related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins) and other critical quality attributes as dictated either by the dosage form or route of administration (injection). Also, the stability, pharmacological activity, and immunogenic properties of peptides such as epitalon (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

Further, FDA is concerned about the potential for immunogenicity of epitalon (free base) when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities section II.A.1.c*. Injectable routes of administration may present a particular risk for immunogenicity (systemic versus local) compared to other dosage forms. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

1.2.

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

Epitalon 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., INN, USAN, IUPAC), and (2) data/information relevant to certain critical quality attributes for establishing its identity, purity, and quality for its intended use in the proposed dosage form (injection) were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information includes but are not limited to having specific tests on the Certificate of Analysis for the critical quality attributes that are relevant to characterizing peptide related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins) and other critical quality attributes as dictated either by the dosage form or route of administration (injection). We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as epitalon acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

Further, FDA is concerned about the potential for immunogenicity of epitalon acetate when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities section II.A.1.c*. Injectable routes of administration may present a particular risk for

immunogenicity (systemic versus local) compared to other dosage forms. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

2. It is often unclear whether the epitalon discussed in the sources considered for this section is the salt formulation or the free base. The extent to which any form of epitalon has been used in compounding is unclear. Publicly available information suggests that epitalon has been used in compounding since at least 2018;[89] however, no pharmacies were found that compound products containing epitalon. Websites were found that sell products that contain epitalon, but it is unclear if these are compounded products. At the time of this evaluation, currently available data and published literature is too limited for FDA to understand the historical use of any form of epitalon in compounded drug products.

3. Based on available information, we conclude that there is a lack of evidence to support the effectiveness of epitalon (free base) or epitalon acetate for the proposed use of insomnia, which increases the risk for serious conditions. Available clinical information discusses effects of epitalon-related bulk drug substance on melatonin or melatonin metabolite levels. However, we did not identify studies evaluating the use of these substances in patients with insomnia, particularly when administered via the proposed subcutaneous route of administration. The potential therapeutic effect of changes in melatonin levels induced by these substances is unclear without a corresponding evaluation of clinical outcomes. In addition, there are currently multiple FDA-approved drug products with established efficacy indicated for insomnia.

4. From the pharmacological perspective, findings that epitalon can increase serum levels of melatonin, a pineal gland hormone known to regulate sleep-wake cycle, suggest that epitalon could influence sleep-wakefulness. However, FDA did not identify nonclinical studies assessing the effects of epitalon on behavioral or electroencephalographic endpoints of sleep. In addition, the mechanisms by which epitalon regulates serum levels of melatonin in vivo remain unknown. From the toxicological perspective, nominator-submitted and FDA-identified studies report that intermittent treatments of female mice from different strains with a fixed dose of epitalon did not increase the frequency of chromosome aberrations in bone marrow cells and suppressed the development of spontaneous tumors. However, due to their limitations, which include the use of a fixed dose of epitalon, assessment of female mice only, and short-lasting exposure of mice to epitalon, these studies do not adequately inform the genotoxic or the carcinogenic potential of epitalon. This is concerning because, from the mechanistic standpoint, epitalon has the potential to be carcinogenic. Specifically, epitalon has been shown to activate telomerase and lengthen telomeres, and longer telomeres are generally associated with increased risk for cancer. In conclusion, at the time of this evaluation, nonclinical studies were too limited in scope and duration to inform safety considerations for potential clinical uses of epitalon (free base) or epitalon acetate.

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[89] See https://www.justice.gov/usao-edky/pr/nicholasville-compounding-pharmacy-and-its-owner-plead-guilty-unlawful-distribution. Accessed 9/4/2024.

> Based on available information, we conclude that there are no clinical data to support the safety of epitalon (free base) or epitalon acetate when used in humans. FDA has not identified safety data regarding epitalon-related bulk drug substances when administered to humans, particularly via the proposed subcutaneous route of administration. The subcutaneous route of administration may present a particular risk for immunogenicity due to the potential for aggregation as well as potential peptide-related impurities. Therefore, there is a lack of important information regarding the use of these substances administered subcutaneously, including whether these would cause harm if administered to humans. In addition, there are currently available FDA-approved therapies for the treatment of insomnia; these drug products have well-characterized safety profiles and have been shown to be safe for their labeled use.

On balance, the physicochemical characterization, limited information on historical use, lack of evidence of effectiveness, and lack of safety information identified for both epitalon (free base) and epitalon acetate weigh against their being added to the 503A Bulks List. In particular, the Agency's proposal regarding these substances is based on the fact that these substances are not well characterized from a physicochemical perspective, the lack of data to support safety of these substances when used in humans as well as additional concerns related to potential immunogenicity risk, the lack of evidence to support effectiveness for use in insomnia which is associated with multiple serious adverse health outcomes, and the availability of FDA-approved drug products that are indicated to treat this condition. Accordingly, we propose not adding epitalon (free base) or epitalon acetate to the 503A Bulks List.

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Epitalon-Related Bulk Drug Substances (Epitalon (Free Base) and Epitalon 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 With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Epitalon
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	H-Ala-Glu-Asp-Gly-OH
Common Name(s)	Epithalon, Epithalone, Epithalamine
UNII Code	O65P17785G
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of AX Pharmacueticals Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	Russian Pharmacopoeia
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Subcutaneous Injectable
Compounded Strengths	3,000 mcg/ml
Anticipated Routes of Administration	Subcutaneous Injection
Saftey & Efficacy Data	Anisimov, V., 2001. Experimental research on ageing in Russia. Experimental Gerontology, 36(7), pp.935–945. Available at: http://dx.doi.org/10.1016/s0531-5565(00)00262-x.
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Used Previously to compound drug products	Yes
Proposed use	Insomnia, Paradoxical sleep disorder,
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Added as an attachment

AX Pharmaceutical Corp

CERTIFICATE OF ANALYSIS

Epitalon Acetate

Lot Number	D262-17K24SH	**MFG Date**	Nov 24, 2017
Molecular Formula	$C_{16}H_{26}N_4O_{11}$	**Expiry Date**	Nov 23, 2019
CAS Number	307297-40-1	**Batch QTY**	10G
Storage: Keep frozen at -20ºC.			
Tests	**Specifications**		**Results**
Appearance	White to off-white powder		White powder
Identification	MS: Theoretical MW 390.35		Conform
Purity (HPLC)	≥ 98.0%		99.40%
Conclusion: The product complies with specifications **Original Reference No.**: 20171124			
Transcription: **Date:**	**Issued by:** **Date:**	**Approved by:** **Date:**	

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

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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?	Epitalon
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?	<u>IPUAC Name:</u> (4*S*)-4-[[(2*S*)-2-aminopropanoyl]amino]-5-[[(2*S*)-3-carboxy-1-(carboxymethylamino)-1-oxopropan-2-yl]amino]-5-oxopentanoic acid L-alanyl-L-alpha-glutamyl-L-alpha-aspartyl-glycine H-Ala-Glu-Asp-Gly-OH $C_{14}H_{22}N_4O_9$
What is the common name of the substance?	Epithalon Epithalone Epithalamin Epithalamine Epitalon 307297-39-8 UNII-O65P17785G O65P17785G
Does the substance have a UNII code?	O65P17785G
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?	Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Russian Pharmacopoeia
Has information been submitted about the substance to the USP for consideration of drug monograph development?	YES
What dosage form(s) will be compounded using the bulk drug substance?	Subcutaneous Injectable
What strength(s) will be compounded from the nominated substance?	10 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?	Anisimov, V., 2001. Experimental research on ageing in Russia. *Experimental Gerontology*, 36(7), pp.935–945. Available at: http://dx.doi.org/10.1016/s0531-5565(00)00262-x Korkushko, O.V. et al., 2011. Peptide Geroprotector from the Pituitary Gland Inhibits Rapid Aging of Elderly People: Results of 15-Year Follow-Up. *Bulletin of Experimental Biology and Medicine*, 151(3), pp.366–369. Available at: http://dx.doi.org/10.1007/s10517-011-1332-x. Khavinson VKh, Morozov VG. Peptides of pineal gland and thymus prolong human life. *Neuro Endocrinol Lett*. 2003;24(3-4):233-240. Malinin, V.V. & Khavinson, V.K., 2005. Effect of Epitalon on Telomerase Activity,Telomere Elongation and Proliferative Potential in Human Somatic Cells. *Gerontological Aspects of Genome Peptide Regulation*, pp.52–57. Available at: http://dx.doi.org/10.1159/000085319. Khavinson, V.K. et al., (2003). Epithalon peptide induces telomerase activity and telomere elongation in human somatic cells. *Bulletin of Experimental Biology and Medicine*, 135(6), 590-592.

	Anisimov VN, Khavinson VKh. Peptide bioregulation of aging: results and prospects. *Biogerontology*. 2010;11(2):139-149. doi:10.1007/s10522-009-9249-8 Khavinson VKh, Lin'kova NS. [Morphofunctional and molecular bases of pineal gland aging]. *Fiziol Cheloveka*. 2012 Jan-Feb;38(1):119-27. Russian. PMID: 22567846. Korkushko OV, Khavinson VKh, Shatilo VB, Magdich LV. Effect of peptide preparation epithalamin on circadian rhythm of epiphyseal melatonin-producing function in elderly people. *Bull Exp Biol Med*. 2004;137(4):389-391. doi:10.1023/b:bebm.0000035139.31138.bf Khavinson VKh, Bondarev IE, Butyugov AA, Smirnova TD. Peptide promotes overcoming of the division limit in human somatic cell. *Bull Exp Biol Med*. 2004 May;137(5):503-6. doi: 10.1023/b:bebm.0000038164.49947.8c. PMID: 15455129. Khavinson, V.K., et al., 2001. Reparative effect of epithalon on pineal gland ultrastructure in gamma-irradiated rats. *Bulletin of Experimental Biology and Medicine*, 131(1), 81-85. https://www.ncbi.nlm.nih.gov/pubmed/11329090. Gumen, A.V. et al., 2006. Production of lymphocyte-activating factors by mouse macrophages during aging and under the effect of short peptides. *Bulletin of Experimental Biology and Medicine*, 142(3), pp.360–362. Available at: http://dx.doi.org/10.1007/s10517-006-0366-y. Khavinson, V.K. et al., 2001. Tissue-specific effects of peptides. *Bulletin of Experimental Biology and Medicine*, 132(2), 807-808. https://www.ncbi.nlm.nih.gov/pubmed/11713572. Anisimov, V.N. et al., 2002. Epithalon Decelerates Aging and Suppresses Development of Breast Adenocarcinomas in Transgenic Her-2/neu Mice. *Bulletin of Experimental Biology and Medicine*, 134(2), 187-190. https://www.ncbi.nlm.nih.gov/pubmed/12459848.
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?	Anti-aging, Longevity • lengthening telomeres in human cells • Promotion of deeper sleep • Delay and prevention of age-related diseases such as dementia • anti-oxidant by reducing lipid oxidation and ROS (Reactive oxygen species) along with normalizing T cell function. • Improvement of skin health and appearance • Healing of injured and deteriorating muscle cells • Restores and normalizes melatonin levels in older people who have lost some pineal function due to aging • resistance to emotional stress
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

Certificate of Analysis

Epithalon Acetate

Product Name : Epithalon Acetate
Mfg. Date : Dec 20, 2019
M.F. : $C_{14}H_{22}N_4O_9$
CAS No. : 307297-39-8
Sequence : H-Ala-Glu-Asp-Gly-OH

Lot No. : DL5163
Exp. Date : Dec 19, 2022
M.W. : 390.35
Batch Qty : 311 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to almost white fluffy powder		White fluffy powder
Solubility	Soluble in water and acetic acid		Conforms
Amino Acid Composition	Ala	0.9 – 1.1	0.9
	Glu	0.9 – 1.1	1.0
	Asp	0.9 – 1.1	1.0
	Gly	0.9 – 1.1	1.0
Water Content (KF)	≤ 8.0%		3.3%
Acetic Acid Content	≤ 15.0%		10.1%
Peptide Purity	≥ 98.0%		99.5%
Related Substances	Total Impurities	≤ 2.0%	0.5%
	Largest Single Impurity	≤ 1.0%	0.2%
Organic Solvent Residue	Acetonitrile	≤ 0.041%	<0.041%
	Dichloromethane	≤ 0.060%	<0.060%
	N, N- Dimethylformamide	≤ 0.088%	<0.088%

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

Note: Analytical results extracted from the original COA provided by Shanghai Yisen Biological Technology Co. Ltd.; Lot No. EPTL20191205.

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

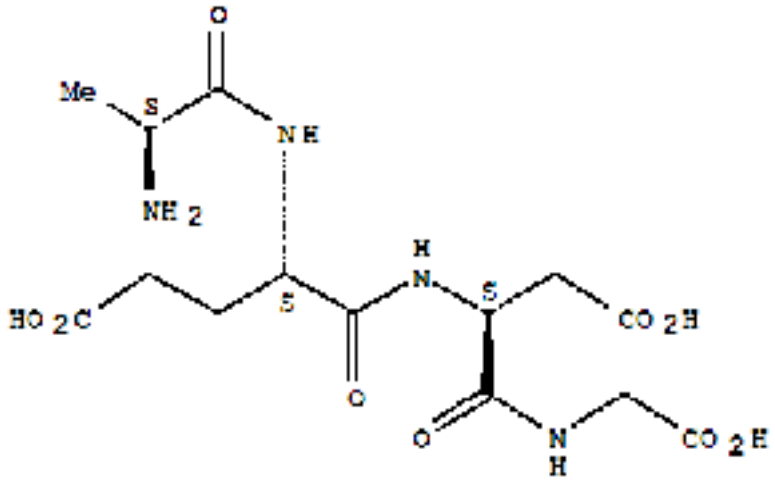
	Name	Title	Signature	Date
Prepared by	Sonia Liciaga	Operations Technician	Sonia Liciaga	03/26/2020
Released by	Wilnelia Hernandez	Quality Assistant	WHR	03/30/2020

$(0.967)(0.899)(0.995) = 0.8650$
86.5 %

9/1/20

Medical Professional Monograph

Epithalon



Sequence - Alanine-Glutamate-Asparagine-Glycine

Molecular Formula – C14H22N4O9

Molecular Weight – 390.349 g/mol g/mol

Indication and Usage Summary

- Upregulation of telomerase activity
- Complete normalization of anti-oxidant indices
- Reduction of peroxide lipid oxidation products
- Increased activity of glutathione peroxidase
- Improved melatonin and immunity (cellular and humoral)

- Improves insulin sensitivity
- Decreases LDL and VLDL
- Improves tissue repair
- Anti-tumor effects
- Decreases mortality and increases life expectancy

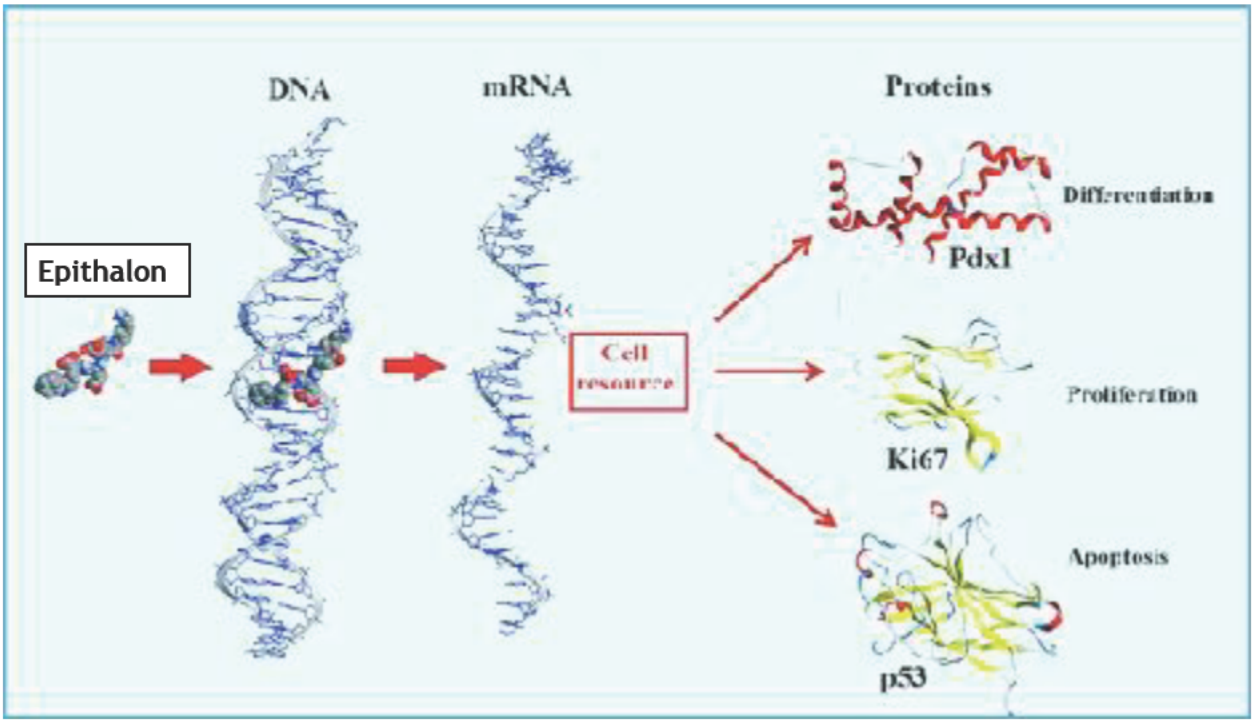
Description/Classification:

Epithalon is a short, 4 amino acid chain peptide used to regulate the cell cycle through upregulation of telomerase activity. It has been shown to have distinctive anti-aging and anti-tumor activity across many animal and human studies. Known as the synthetic version of the tetrapeptide epithalamin, which naturally occurs in the pineal gland in our body, Epithalon (also known as Epitalon or Epithalone) was first discovered in the late 1980's by Prof. Vladimir Khavinson from The Sankt Petersburg University, Russia. As the most prominent tasks of the pineal gland are to maintain different kind of processes in our body, such as to normalize the activity of anterior pituitary and to maintain the levels of calcium, gonadotropins, and melatonin, its activity is highly regulated by a series of feedback mechanisms. Epithalamin acts as an antioxidant and increases the resistance to stress and lowers the levels of corticosteroids. The life extension and anti-aging properties, amongst a variety of different clinical indications, of Epithalon are incredible.

Mechanism of Action

Epithalon regulates the cell cycle through up-regulation of telomerase activity. Upregulating telomerase activity has a vast amount of effects on the body because it allows all the cells in the body to be maintained due to inhibiting the shortening of telomeres, which are fundamentally involved in the aging process.[1] Telomerase is a RNA-dependent polymerase that elongates and maintains the length of telomeres by adding tandem repeats on the 3' end of chromosomes. Telomere elongation promotes indefinite cellular proliferation and that can promote neoplastic cells. However, it has been shown that maintaining proper telomere length acts as a prominent effector of anti-aging and inhibitor of tumorigenesis; and, this is precisely what epithalon does.

Epithalon has also been shown to affect the aging process by exerting an antioxidant effect.[2] This is implicated in the slowing of the aging process because cytotoxicity due to reactive oxygen species can lead to damaging DNA, leading to cellular death and/or mutations leading to the formation of cancerous cells.[3] It has also been reported to show significant anti-tumor effects in breast and colorectal cancer by inhibiting carcinogenic receptor expression and attenuation of metastasis.[45] Further, epithalon has been reported to play a key role in the regulation of important biomolecules such as cytokines, C-reactive protein, and other acute phase reactants to attenuate the inflammatory response.[6] This regulation of the inflammation process is pivotal to human health because dysregulation and potentiation can cause a broad spectrum of disorders including, but not limited to, rheumatoid arthritis, ulcerative colitis, amongst others. Lastly, it has been found that epithalon plays a very important role in the regulation of the endocrine system in the body. The vast amount of effect different hormones has in the body is fundamental to different processes in the body. And, any loss in hormones can result in different aspects of disease. But, in the realm of aging, we tend to lose production of hormones due to shortening of telomeres. So, epithalon can increase endogenous levels of hormones that we lose. For example, a study was done on elderly patients to determine the effect of epithalon administration on levels of melatonin, a natural regulator of the sleep cycle.[7] This study showed that levels of melatonin increased and restoration of sleep was achieved. Other studies have reported that epithalon has affects on other hormones such as gonadotropic hormones (FSG, LG, prolactin) to improve sexual and reproductive functions.[8]



Dosage

- IM General Dosing (Russian Protocol)
    - 100mg total
    - 10 mg IM daily for 10 days
    - Twice a Year
- or IM General Dosing (Ukraine Protocol)
    - 50 mg total
    - Use 10 mg every third day times 2 weeks
    - Twice a year

Note these Are IM protocols , this is a small peptide and Currently IPS protocol is a sub- q protocol

Clinical Indications

Aging Deceleration

Epithalon induces telomerase activity and telomere elongation in human somatic cells. It a study it was shown to induce a 33% increase in telomere elongation which is directly involved in the aging process.[9] There was a human trial done over a 12-year period with patients treated with epithalon and a placebo group. The results of this study demonstrated a 28% decrease in overall mortality with those treated with epithalamin, and a 2-fold decrease in cardiovascular mortality by decreasing the functional age and degree of cardiovascular aging.[10] Another study was done to show that those treated with thymalin and epithalamin over a 6-year period had a mortality rate that was 4.1 times lower than the control group.[11]

Tumor Suppression

There has been a lot of scientific research made and still is being made on the use of epithalon against cancer. It was found that epithalon has inhibitory effects on the development and growth of tumors with studies done on mammary tumors, colon carcinogenesis, prostate cancer just to name a few. Tumors exposed to epithalon have been shown to shrink in size. Treatment with epithalon stopped the metastases of tumors in mice and it has oncostatic properties, halting the spread of cancer. Due to its role in telomerase activity along with endocrine and immune function, epithalon has been implicated for its anti-tumor properties in hormone dependent cancer. A study was done a patients with uterus, cervix, and ovarian cancer and it was shown that treatment of epithalon restored cellular immunity, decreased recurrence and metastasis of the cancer, and decreased the size of tumors.[12]

Anti-Oxidant Effects

Research has shown that epithalon is a powerful antioxidant that eliminates oxygen-free radicals responsible for damaging and killing cells. This process, known as oxidative stress, is the root cause of a wide variety of age-related diseases. It is important to note that the human lifespan is inversely related to the number of oxygen-free radicals in the human body, and epithalon is responsible for slowing down and killing these killer radicals. Since free radicals are the main source of degenerative diseases, eliminating them prevents diseases such as cancer, dementia, Alzheimer's, muscle and joint pain, heart disease, and more.

Restoring Normal Sleep Patterns

As we age, melatonin content in our blood decreases considerably. Epithalon plays a key role in our bio-rhythm control and effects the endocrine, nervous and immune systems. In fact, reduced melatonin production leads to age-related neurodegenerative changes and certain diseases. Melatonin's importance is clear, however, supplementing melatonin, in some cases, can provoke considerable side-effects, such as neoplastic growth. Finding a suitable way to safely increase melatonin levels is an important endeavor. Epithalon stimulates production of melatonin through its action on the pineal gland, and this is why people taking epithalon have reported better sleep patterns and increased deep sleep, which is essential for the body to repair itself and strengthen the immune system.

Regulation of Inflammation

There are countless disorders that arise due to dysregulation of the immune system and inflammatory process. Therefore, obtaining therapies that have the ability to help regulate the inflammatory pathway through control of different mediators in the process can help treat disorders. Epithalon has extensively been shown to help regulate the function of mediators such as cytokines, C-reactive protein, and other acute phase reactants.

Insulin and Cholesterol

Due to epithalon's variety of activity amongst different cells in the endocrine system, amongst other systems, due to telomerase upregulation and pineal gland activation, it has been shown that epithalon significantly improves insulin sensitivity, glucose utilization, and overall cholesterol health.[13] In regard to cholesterol health, it has been shown to significantly decrease LDL and VLDL while significantly increasing levels of HDL.

Frequently Asked Questions (FAQs)

Is it okay to increase telomerase activity and telomere length even though it naturally decreases in your body as you age?

There have been studies that have shown that increasing telomerase activity and telomere length can result in over-proliferation of cells. However, there have been numerous studies that indicate there is a range of telomere activity that maintains healthy cells. This is critical to epithalon's unique activity because it restores telomerase activity and telomere length that is LOST in through the aging process; by that we mean it returns the telomere concentration and activity to NORMAL and HEALTHY levels.

[1] Khavinson VK, Bondarev IE, Butyugov AA. Epithalon peptide induces telomerase activity & telomere elongation in human somatic cells. Bull Exp Biol Med. 2003 Jun;135(6):590-2.

[2] Anisimov VN, Arutjunyan AV, Khavinson VK. Effects of pineal peptide preparation Epithalamin on free-radical processes in humans and animals. Neuro Endocrinol Lett. 2001;22(1):9-18.

[3] Hekimi S, Lapointe J, Wen Y. Taking a "good" look at free radicals in the aging process. Trends In Cell Biology. 2011;21(10) 569-76.

[4] Anisimov VN, Khavinson VK, Provinciali M, Alimova IN, Baturin DA, Popovich IG, et al. Inhibitory effect of the peptide epitalon on the development of spontaneous mammary tumours in HER-2/neu transgenic mice. Int J Cancer. 2002 Sep 1;101(1):7-10.

[5] Anisimov VN, Khavinson VK, Popovich IG, Zabezhinski MA. Inhibitory effect of peptide Epitalon on colon carcinogenesis induced by 1,2-dimethylhydrazine in rats. Cancer Lett. 2002 Sep 8;183(1):1-8.

[6] Labunets IF, Butenko GM, Korkushko OV, Shatilo VB. Effect of epithalamin on the rhythm of immune and endocrine systems functioning in patients with chronic coronary disease. Bull Exp Biol Med. 2007 Apr;143(4):472-5.

[7] Korkushko OV, Lapin BA, Goncharova ND, Khavinson VK, Shatilo VB, Vengerin AA, et al. Normalizing effect of the pineal gland peptides on the daily melatonin rhythm in old monkeys & elderly people. Adv Gerontol. 2007;20(1):74-85.

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[9] Epithalon Peptide induces Telomerase activity and Telomere elongation in Human somatic cells, Bulletin of Experimental Biology and Medicine,Vol 135,No.5,pp 692-695, June 2003

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[11] Neuro Endocrinol Lett. 2003 Jun-Aug;24(3-4):233-40.,Peptides of pineal gland and thymus prolong human life.,Khavinson VKh1, Morozov VG.

[12] Khavinson VKh, Bioregulating therapy as a new direction in Medicine,Proceedings of the National conference of Gerontology and Geriatrics;May 28-31, 1997 Bucharest, Romainia;1997 p205

[13] Peptide regulation of Aging.Proceedings of the 17th World Congress of the International Association of Gerontology,July 1-6 2001,Vancouver Canada, Gerontology 2001, 47(1) pg 545