FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

October 29, 2024

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.

Ipamorelin-Related Bulk Drug Substances (Ipamorelin (free base) and Ipamorelin Acetate)

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FDA Evaluation of Ipamorelin-Related Bulk Drug Substances (Ipamorelin (free base) and Ipamorelin acetate)

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TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

FDA received nominations for ipamorelin-related bulk drug substances for inclusion on the list of bulk drug substances (BDSs) that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] There are two nominators of ipamorelin-related BDSs: Wells Pharmacy Network and LDT Health Solutions. Each nominator provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear in both packages whether the nomination is for ipamorelin acetate or ipamorelin (free base). Ipamorelin acetate and ipamorelin (free base) are different BDSs. Please see additional information in section II.A.

Peptides such as ipamorelin have specific considerations that differentiate them from small molecule drugs due to their composition, which may include immunogenic potential, peptide self-association and aggregation, the potential for peptide-related impurities, and challenges in characterization. Although it is unclear whether the nominators intended to nominate ipamorelin acetate or ipamorelin (free base), due to FDA's significant safety concerns related to the use of certain peptides in compounded drug products, FDA has decided to evaluate both on its own initiative.

Ipamorelin (free base) and ipamorelin acetate were evaluated for the following uses: growth hormone deficiency (GHD) and postoperative ileus (POI).[2,3] The ipamorelin-related drug product proposed in the nominations is a 2000 mcg/mL lyophilized powder for subcutaneous (SC) injection.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for ipamorelin (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 both ipamorelin (free base) and

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[1] Nomination of "ipamorelin acetate" from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0283) can be accessed at https://www.regulations.gov/document/FDA-2015-N-3534-0283. Nomination of "ipamorelin" from LDT Health Solutions Inc. (Document ID: FDA-2018-N-2973-0002) can be accessed at https://www.regulations.gov/document/FDA-2018-N-2973-0002.

[2] 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.

[3] Consistent with past practice, FDA in its discretion opted to evaluate the unnominated use of postoperative ileus. See Final Rule entitled List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act, February 19, 2019 (84 FR 4696, 4701); Notice of Proposed Rulemaking entitled List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act, December 16, 2016 (81 FR 91071, 91075). Postoperative ileus is a serious condition, as it is associated with significant postoperative morbidity and prolonged hospitalization following major abdominal surgery. Additionally, the nominator cited a publication by Beck et al. (2014) that provided sufficient information for the Agency to evaluate whether the substance is appropriate for use in compounded drug products containing ipamorelin-related bulk drug substances.

ipamorelin 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?[4]

As discussed above, FDA received nominations for ipamorelin-related BDSs that were not clear about which BDS was being nominated.

A BDS or active pharmaceutical ingredient (API)[5] 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.[6] 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.

[4] 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).

[5] The terms BDS and active pharmaceutical ingredient (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."

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

Table 1. Summary of Basic Information on Ipamorelin Free Base and Ipamorelin Acetate.

	Ipamorelin (free base)	**Ipamorelin Acetate**
UNII Code	Y9M3S784Z6	Not available
CAS No	170851-70-4	1258196-85-8*
MF/MW (g/mol)	$C_{38}H_{49}N_9O_5$/711.9	$C_{38}H_{49}N_9O_5 \cdot xCH_3COOH$/NA
Chemical Structure	H-Aib-His-D-2Nal-D-Phe-Lys-NH_2	H-Aib-His-D-2Nal-D-Phe-Lys-NH2 x·CH_3COOH
Supplier[7]	Yes	Yes
Active Moiety	Ipamorelin (free base)	Ipamorelin (free base)

* https://www.biosynth.com/p/FI159334/1258196-85-8-ipamorelin-acetate. However, the CAS number for Ipamorelin Acetate is used as that for Ipamorelin in some public references.

There are two nominators of ipamorelin-related BDSs: Wells Pharmacy Network and LDT Health Solutions. The nominators provided inconsistent information about the different ipamorelin BDSs in their packages. Due to inconsistencies in the nomination packages, it is unclear which ipamorelin-related BDS each of the nominators intended to nominate. For example, the Certificate of Analysis (CoA) submitted with each nomination package 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 are summarized in Table 2.

Table 2. Summary of Information Submitted in Two Nominations.

Nominator	**Wells Pharmacy Network**	**LDT Health Solutions**
Nominated BDS	Ipamorelin Acetate	Ipamorelin
BDS per UNII code	Y9M3S784Z6 *(matches Ipamorelin free base)*	Y9M3S784Z6 *(matches Ipamorelin free base)*
CoA	CoA provided for Ipamorelin Acetate	CoA provided for Ipamorelin Acetate
CAS No.	170851-70-4 *(matches Ipamorelin free base)*	170851-70-4 *(matches Ipamorelin free base)*
MF	$C_{38}H_{49}N_9O_5$ *(provided in the CoA) (matches Ipamorelin free base)*	$C_{38}H_{49}N_9O_5$ *(provided in the CoA) (matches Ipamorelin free base)*
MW	711.9 *(provided in the CoA) (matches Ipamorelin free base)*	711.9 *(provided in the CoA) (matches Ipamorelin free base)*
Chemical Name	H-Aib-His-D-2Nal-D-Phe-Lys-NH_2 *(matches Ipamorelin free base)*	H-Aib-His-D-2Nal-D-Phe-Lys-NH_2 *(matches Ipamorelin free base)*
Active Moiety in Clinical References	Ipamorelin Free Base	Ipamorelin Free Base

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

Italics in the table above represents FDA opinion.

Due to FDA's significant safety concerns related to this nomination/BDS, FDA is choosing to concurrently evaluate both BDSs (ipamorelin (free base) and ipamorelin 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

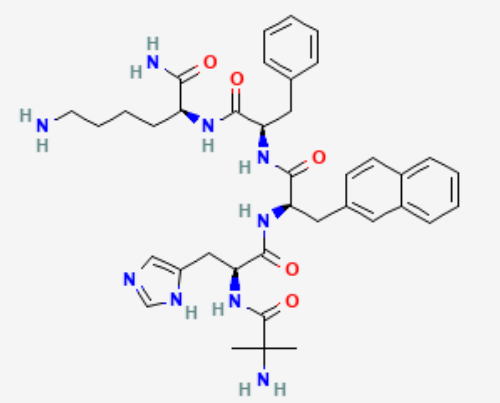
For an injection product, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET) and foreign particulates are critical safety factors. For this reason, bioburden load (i.e., microbial enumeration test) and BET are critical for the BDSs to be used in compounding injections.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

There is no USP drug substance monograph for ipamorelin 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 ipamorelin (free base) and its acetate form. Databases searched for information on ipamorelin (free base) and its acetate form in preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. Ipamorelin (Free Base)

Ipamorelin (free base) is a pentapeptide hormone (Aib-His-D-2-Nal-D-Phe-Lys-NH_2) containing non-proteinogenic amino acids, including Aib (Aminoisobutyric acid) and Nal (naphthylalanine) as shown in Figure 1. The melting point of ipamorelin (free base) is 144-147°C. The molecular formula of ipamorelin (free base) is $C_{38}H_{49}N_9O_5$ and its molecular weight is 711.85 g/mol. There is no CoA for ipamorelin (free base) in the nomination.

Figure 1. The Structure of Ipamorelin (free base).[8]



a. Stability of the API and likely dosage forms

It is reported that lyophilized ipamorelin (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 will greatly decrease long-term stability of lyophilized peptides. Upon reconstitution, ipamorelin (free base) in solution is stable for 2-3 weeks stored at 4°C and for 3-4 months at -20°C.[9]

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

b. Probable routes of bulk drug substance synthesis

Ipamorelin (free base) was first synthesized by researchers at Novo Nordisk in the mid-1990s (EP 0736039 B1). In 1998, ipamorelin (free base) was described to be synthesized by using the fluorenyl methoxycarbonyl protecting (Fmoc) strategy on an Applied Biosystems Model 431A peptide synthesizer, which employs Hexafluorophosphate Benzotriazole Tetramethyl Uronium (HBTU) mediated couplings in N-methylpyrrolidone (NMP) and UV monitoring of the

[8] Ipamorelin | C38H49N9O5 | CID 9831659 - PubChem (nih.gov). Accessed 07/07/2024.
[9] https://www.prospecbio.com/ipamorelin. Accessed 07/07/2024.

deprotection of the Fmoc protection group (Raun et al. 1998). The crude ipamorelin (free base) was then purified using semi-preparative reversed phase high-performance liquid chromatography (RP-HPLC) to a purity of >95%. The final product of ipamorelin (free base) was characterized by amino acid analysis, analytical RP-HPLC and by plasma desorption mass spectroscopy. In addition, proton nuclear magnetic resonance (^{1}H-NMR) analysis was performed to support the proposed structure of ipamorelin (free base).

c. Likely impurities[10]

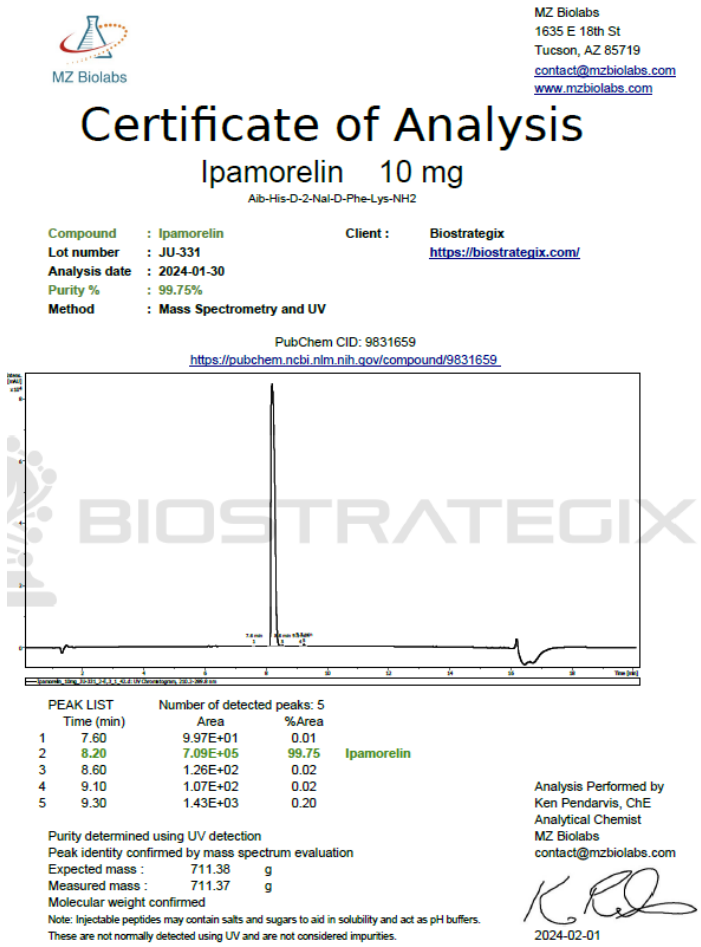
Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including ipamorelin (free base). For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials, 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.

Because there is no CoA for ipamorelin (free base) in the nomination packages, we conducted literature searches and found that CoAs for ipamorelin (free base) only contain a purity testing result similar to that shown below as an example[11]. There is limited or no information on the impurity limits/testing results as attribute control in the CoA to demonstrate quality control of impurity profile of ipamorelin (free base).

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

[10] 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 nominated bulk drug substance, available nonclinical toxicity data for these impurities are discussed in the Nonclinical Assessment at Section D.1. as part of the safety assessment of the substance.

[11] https://cdn.shopify.com/s/files/1/0614/4111/4267/files/COA_Ipamorelin_10mg_JU-331_2024-02-01.pdf?v=1706830918. Accessed 07/07/2024.



MZ Biolabs
1635 E 18th St
Tucson, AZ 85719
contact@mzbiolabs.com
www.mzbiolabs.com

Certificate of Analysis

Ipamorelin 10 mg

Aib-His-D-2-Nal-D-Phe-Lys-NH2

Compound	: Ipamorelin	Client :	Biostrategix
Lot number	: JU-331		https://biostrategix.com/
Analysis date	: 2024-01-30		
Purity %	: 99.75%		
Method	: Mass Spectrometry and UV		

PubChem CID: 9831659
https://pubchem.ncbi.nlm.nih.gov/compound/9831659

PEAK LIST — Number of detected peaks: 5

	Time (min)	Area	%Area	
1	7.60	9.97E+01	0.01	
2	8.20	7.09E+05	99.75	Ipamorelin
3	8.60	1.26E+02	0.02	
4	9.10	1.07E+02	0.02	
5	9.30	1.43E+03	0.20	

Purity determined using UV detection
Peak identity confirmed by mass spectrum evaluation
Expected mass : 711.38 g
Measured mass : 711.37 g
Molecular weight confirmed
Note: Injectable peptides may contain salts and sugars to aid in solubility and act as pH buffers.
These are not normally detected using UV and are not considered impurities.

Analysis Performed by
Ken Pendarvis, ChE
Analytical Chemist
MZ Biolabs
contact@mzbiolabs.com

2024-02-01

d. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Ipamorelin (free base) is white lyophilized powder. It is slightly soluble in water at 0.0032 mg/mL.[12] Because the API has limited solubility in water, it is impossible to formulate the proposed injectable dosage form at the concentration of 2 mg/mL.

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

FDA did not identify additional relevant information regarding the physical and chemical characterization of ipamorelin (free base).

Conclusions: Ipamorelin (free base) is a five amino acids peptide containing unnatural amino acids. Generally, less is known about the safety and biological properties of peptides that contain unnatural amino acids, including regarding the structure and chromatographic behavior for

[12] https://go.drugbank.com/drugs/DB12370. Accessed 07/07/2024.

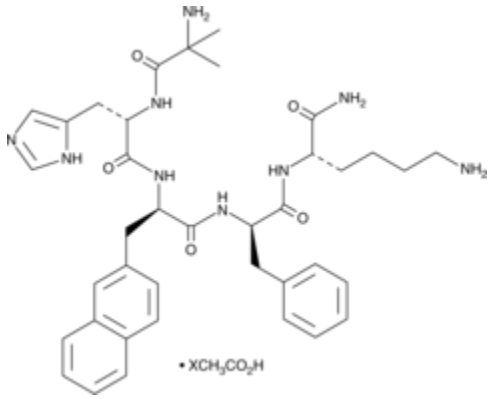
purification of unnatural amino acids and their derivatives, as well as any impact on a peptide's propensity to aggregate, which may add to the complexity of the characterization of ipamorelin (free base). As reported in the literature, ipamorelin is expected to be stable under reported storage conditions (below -18°C).

Ipamorelin (free base) is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to ipamorelin (free base), including impurities, aggregates, and bacterial endotoxins, were not found in the publicly available scientific literature, and the nomination packages lacked CoAs, which are offered as evidence to establishing identity, purity, and impurity profiles of the substance. In addition, due to limited water solubility of ipamorelin (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with the concentration of 2 mg/mL.

2. Ipamorelin Acetate

The molecular formula of ipamorelin acetate is $C_{38}H_{49}N_9O_5$ x($C_2H_4O_2$) and its structure shows in Figure 2. The nominator provided a CoA for ipamorelin acetate with testing attribute results, including identification, assay, water content and acetate content. There is no testing result for the control on impurities, aggregates, and bioburden/endotoxin levels.

Figure 2. The Structure of Ipamorelin Acetate. [13]



a. Stability of the API and likely dosage forms

Based on the CoA provided by the nominator, long-term storage conditions for ipamorelin acetate are "in a sealed container at 2°C to 8°C in a fridge or freezer". Additionally, ipamorelin acetate is reported to remain stable up to 4 years when stored at -20°C.

FDA notes that peptides such as ipamorelin acetate can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients etc.), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity. Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field

[13] https://www.caymanchem.com/product/39813/ipamorelin-(acetate). Accessed 07/07/2024.

flow fractionation. Hence, peptides may require more and/or specific analytical in-process and final product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation. Product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions.

b. Probable routes of bulk drug substance synthesis

Ipamorelin (free base) was synthesized as mentioned in II.A.1.b (EP 0736039 B1). Then, the free base can be converted into acetate form of ipamorelin.

c. Likely impurities[14]

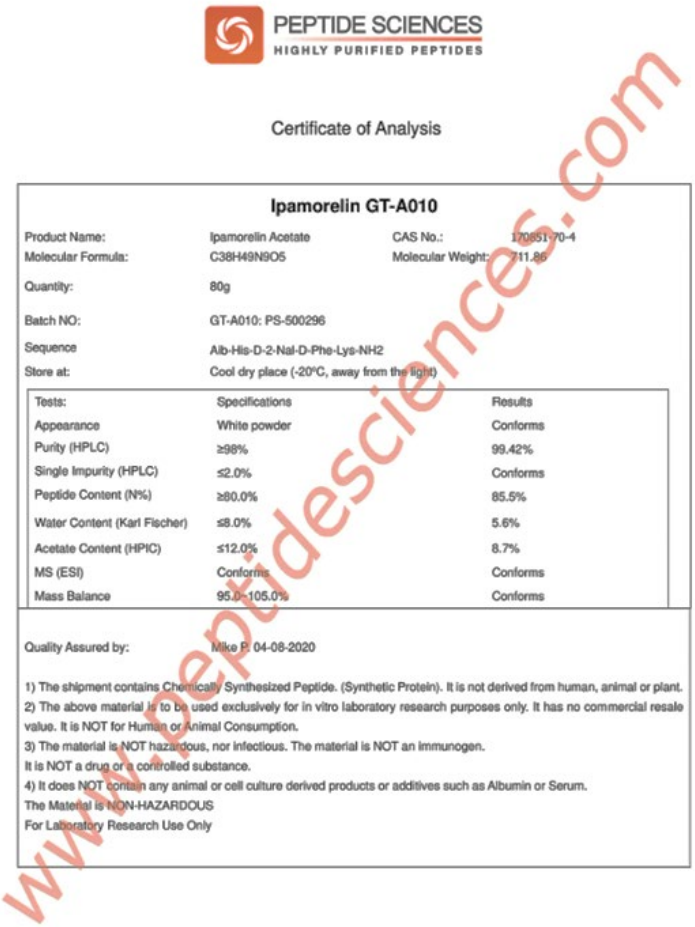
Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including ipamorelin acetate. For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials, 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 in the nomination package, there is only a purity test limit of ≥95% with the testing result of 99.72%, and there is no impurity attribute control to demonstrate the impurity profiles.

We further conducted a literature search and could only find a single impurity limit of less than 2%, in a CoA from Peptide Science as shown below[15] However, even here, there is no information regarding the nature of individual impurities that can be present at up to 2.0% level.

[14] 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.

[15] https://www.peptidesciences.com/ipamorelin-5mg#coa. Accessed 02/05/2024.



PEPTIDE SCIENCES
HIGHLY PURIFIED PEPTIDES

Certificate of Analysis

Ipamorelin GT-A010

Product Name:	Ipamorelin Acetate	CAS No.:	170851-70-4
Molecular Formula:	C38H49N9O5	Molecular Weight:	711.86
Quantity:	80g		
Batch NO:	GT-A010: PS-500296		
Sequence	Aib-His-D-2-Nal-D-Phe-Lys-NH2		
Store at:	Cool dry place (-20°C, away from the light)		

Tests:	Specifications	Results
Appearance	White powder	Conforms
Purity (HPLC)	≥98%	99.42%
Single Impurity (HPLC)	≤2.0%	Conforms
Peptide Content (N%)	≥80.0%	85.5%
Water Content (Karl Fischer)	≤8.0%	5.6%
Acetate Content (HPIC)	≤12.0%	8.7%
MS (ESI)	Conforms	Conforms
Mass Balance	95.0~105.0%	Conforms

Quality Assured by: Mike P. 04-08-2020

1) The shipment contains Chemically Synthesized Peptide. (Synthetic Protein). It is not derived from human, animal or plant.
2) The above material is to be used exclusively for in vitro laboratory research purposes only. It has no commercial resale value. It is NOT for Human or Animal Consumption.
3) The material is NOT hazardous, nor infectious. The material is NOT an immunogen.
It is NOT a drug or a controlled substance.
4) It does NOT contain any animal or cell culture derived products or additives such as Albumin or Serum.
The Material is NON-HAZARDOUS
For Laboratory Research Use Only

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

d. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Ipamorelin acetate is a white to off-white solid powder. It is soluble in water at 5 mg/mL.[16] Because the BDS is soluble in water and would be solubilized prior to administration, particle size and polymorphism are not considered critical quality attributes that affect performance for the proposed injection dosage form.

[16] https://www.peptidesciences.com/ipamorelin-5mg#coa. Accessed 06/03/2024.

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

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

Conclusions: Ipamorelin acetate is a salt form of a peptide consisting of five amino acids. Ipamorelin acetate contains unnatural amino acids. Generally, less is known about the safety and biological properties of peptides that contain unnatural amino acids, including regarding the structure and chromatographic behavior for purification of unnatural amino acids and their derivatives, as well as any impact on a peptide's propensity to aggregate, which may add to the complexity of the characterization of ipamorelin acetate. As reported in the literature, ipamorelin acetate is expected to be stable under reported storage conditions (below -20°C).

Ipamorelin acetate is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to ipamorelin acetate were not found in the publicly available scientific literature, and the provided CoA, which was offered as evidence to establishing identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, and bacterial endotoxins). The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.D.2.d., FDA is concerned about the potential for immunogenicity of ipamorelin acetate when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as ipamorelin acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

B. Has the substance been used historically in compounding?

This evaluation focuses on ipamorelin (free base) and ipamorelin acetate for SC injection and its use in GHD and POI; however, FDA looked generally for information on the historical use of ipamorelin (free base) and ipamorelin acetate in compounding. Information about use may not specify specific attributes of the product, such as route of administration. Databases searched for information on both substances for this evaluation included PubMed, EMBASE, Google/Google Scholar, Natural Medicines, GlobalEdge, Cochrane Library, United States Pharmacopeia – National Formulary, European Pharmacopoeia, Chinese Pharmacopoeia, Indian Pharmacopoeia, and Japanese Pharmacopoeia. FDA also considered the report provided by M-CERSI.[17] It is often unclear whether the ipamorelin discussed in this section is the salt formulation or the free

[17] M-CERSI: Ipamorelin acetate summary report: https://archive.hshsl.umaryland.edu/bitstream/handle/10713/14873/Ipamorelin%20acetate_Final_2020_12.pdf?sequence=1&isAllowed=y. Although the title of this report refers to ipamorelin acetate, it is often unclear whether the ipamorelin discussed in this report is the salt formulation or the free base.

base and whether it was compounded or not. Therefore, FDA will consider the information discussed in this section in its evaluation of both the free base and salt form as appropriate.

1. Length of time the substance has been used in compounding

The nominator did not provide historical use data. Literature shows that ipamorelin was first identified in 1998 from a series of compounds lacking the central dipeptide Ala-Trp of growth hormone-releasing peptide (GHRP)-1 (Raun et al. 1998). Although ipamorelin has been used in the past, there is insufficient information available to determine how long ipamorelin has been used in compounding. According to outsourcing facility (OF) reports submitted to the FDA between 2017 and 2023, OFs have compounded both single and multiple active ingredient drug products containing ipamorelin in injection dosage forms since at least 2017.[18]

2. The medical condition(s) it has been used to treat

In Beck et al. 2014, the authors evaluated the safety and efficacy of ipamorelin administered intravenously for POI following abdominal surgery. However, it is unclear if the study used the compounded formulation of ipamorelin.

A 2017 review by Stakenborg et al. listed ipamorelin as a "potential pharmacological strategy" that has been used for POI (Stakenborg et al. 2017). Ipamorelin acetate has also been studied in patients with small and/or large bowel resection (ClinicalTrials.gov identifier NCT01280344) (M-CERSI Report, 2020).

The M-CERSI report evaluated the current and historical use of ipamorelin acetate. The report drew on three distinct data resources (a literature review, outreach to medical specialists and specialty organizations, and a survey). According to the M-CERSI report, the subject matter experts (SMEs) were not familiar with the use of ipamorelin acetate for POI. Several stated that they could see the potential, but their practice does not involve procedures that put the patient at risk of POI. In addition, several SME urologists discussed ipamorelin acetate being used for patients with GHD due to its properties as a ghrelin agonist and somatostatin inhibitor[19]. One SME stated that there is "a "trending" synergistic combination of ipamorelin acetate with CJC-1295[20], which essentially acts as a growth hormone-releasing hormone (GHRH) analog". (M-CERSI Report, 2020).[21]

Results from a Google search using the terms *ipamorelin compounding* or *ipamorelin compounding pharmacy* or *ipamorelin compounding pharmacy 503A* indicate that many

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

[19] M-CERSI report did not provide additional details whether these patients with GHD were pediatric or adult patients.

[20] CJC-1295 is referred to as "Tetra-substituted GRF (1-29)" or CJC without DAC (drug affinity complex).

[21] M-CERSI report did not include information about administration of other FDA-approved hGH treatments in patients with GHD or whether use of ipamorelin (with or without CJC-1295) led to any improvements.

compounding pharmacy websites compounded ipamorelin products alone or in combination of with CJC-1295 or sermorelin acetate. The websites assert several uses of the substance, mostly compounded as injectable or oral troche formulations, including weight management, hormone replacement therapy, increasing vitality and mental clarity, strengthening the cardiovascular and immune system, increasing sex drive, improving recovery and repair from injuries, regenerating nerve tissues, improving cognition and memory and addressing aging-related issues such as lean muscle loss, skin laxity, poor sleep patterns and reduced bone density release.[22]

FDA identified numerous clinics such as wellness clinics and medical clinics that marketed ipamorelin. For example, these clinics marketed various uses of ipamorelin, including weight loss management, anti-aging purposes, inflammatory conditions, building muscles, boosting energy levels, and improving sleep cycle.[23] Ipamorelin is also marketed to increase collagen production and cell regeneration, increase bone density, "enhance flexibility and joint health" , "increase lean muscle mass", improve cognitive function, and "promote better recovery from injury".[24] Ipamorelin is marketed in combination with other peptides such as sermorelin and CJC-1295.[25] One website states that when ipamorelin is combined with CJC-1295, there is a "3-5 fold increase in growth hormone release over ipamorelin alone."[26]

3. How widespread its use has been

According to OF product reports submitted to FDA, an OF reported compounding single-API injections that included ipamorelin 0.6 mg/mL and ipamorelin 1.5 mg/mL, as well as compounded products for injection that include combinations of multiple APIs, including sermorelin 1.5 mg and ipamorelin 1.5 mg/mL, from the second half of 2017 to the first half of 2019. Another OF reported compounding injections, from the second half of 2019 to the first half of 2020, that included ipamorelin 0.015 g and the following compounded products for injection that are in combination with multiple APIs: sermorelin 0.005 g and ipamorelin 0.005 g, and ipamorelin 0.015 g/mL and growth hormone-releasing hormone (GHRH)[27] 0.006 g/mL. Outsourcing facilities last reported compounding products containing ipamorelin in 2020, with no reports thereafter.[28]

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[22] Wells Pharmacy Network https://wellsrx.com/advantageprogram, Wells Advantage Program-WP Pharma https://wppharmalabs.com/?page_id=70860, CompoundRx Partners. https://compoundrx.net/peptides-1, Tailor Made Compounding https://imcwc.com/wp-content/uploads/2019/08/CJC-1295-Ipamorelin.pdf , and ReviveRx product catalog https://reviverx.com/product-catalog/. Accessed 07/31/2023

[23] Vitality Sciences. What is Ipamorelin Acetate ? | Ipamorelin Acetate Peptide (vitality-sciences.com) . Accessed 08/09/2024 and Medwin Family medicine & Rehab. https://medwinfamily.com/ipamorelin-injections/. Accessed 07/31/2023.

[24] Re-new Institute https://re-newinstitute.com/peptide-therapy/ipamorelin/ and PRAMAH Aesthetics https://pramahtampa.com/peptide-therapy/ipamorelin/. Accessed 06/07/2024.

[25] PRAMAH Aesthetics https://pramahtampa.com/peptide-therapy/ipamorelin/. Accessed 07/22/2024.

[26] Envizion Medical https://www.envizionmedical.com/blog/peptide-therapy-cjc-1295-ipamorelin. Accessed 07/22/2024.

[27] The OF reported this substance as "GHRH receptor." However, FDA believes this to be an error and interprets it as "GHRH."

[28] Wayback Reporting. https://wayback.archive-it.org/7993/20171114123637/https:/www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm , https://wayback.archive-it.org/7993/20180908073717/https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCo

A Google search indicates that ipamorelin is offered extensively in the U.S. in medical spas (med spas)/wellness "clinics" and medical concierge services.[29] Although websites often do not describe or clearly state that ipamorelin is compounded, this is likely to be the case because there are no FDA-approved drug products containing ipamorelin (free base) or ipamorelin acetate. One of the medical clinics indicated that it "partners with FDA-regulated compounding pharmacies to bring consumers the highest quality products out on the market."[30]

Regarding the dosage forms of ipamorelin marketed by these clinics, one company offers ipamorelin as SC injections, rapid dissolve tablets (RDT), and sublingual troches.[31] Another wellness clinic markets ipamorelin acetate as available in different formulations including oral, nasal, intravenous (IV) solutions, and SC solutions (supplied as a dose of 150 mcg per day via single injections).[32] And yet another wellness clinic website markets ipamorelin as available in formulations of 15 mg injections, 300 mg and 500 mg oral troches, and 750 mg RDT. Additionally, some wellness clinic and medical spa websites market ipamorelin as available for delivery through the mail directly to the consumer for self-administration.[33] Concierge services are also marketed as available to consumers.[34] A compounding pharmacy website also offers "CJC-1295/ipamorelin (lyo) 6/6 mg vial," "ipamorelin/sermorelin acetate (lyo) 15/18 mg vial," and "ipamorelin/sermorelin acetate (lyo) 15/9 mg vial for hormone replacement therapy."[35]

Ipamorelin acetate has been used in sports as a doping agent. The use of growth hormone peptides, for example, has been reported since the 1980s for improving athletes' performance during competition or increasing their muscle mass solely for aesthetic purposes, as in the case of bodybuilding due to its anabolic and lipolytic effects (Gomez-Guerrero et al. 2022). Cox et al. (2015) stated that substances including ipamorelin have been detected in vials confiscated from athletes in Germany, Belgium, and Australia. In the USA, ipamorelin has been detected in confiscated vials. Ipamorelin is on the list of prohibited substances under section S2.4 of the World Anti-Doping Agency (WADA).[36]

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mpounding/ucm393571.htm , https://wayback.archive-it.org/7993/20190423031057/https:/www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm , https://wayback.archive-it.org/7993/20190423031057/https:/www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm , and https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm .

[29] Concierge MD: Peptide Therapy. https://conciergemdla.com/anti-aging-medicine/peptide-therapy/#ipamorelin , Revitalized Health https://rhsupplements.com/peptides/cjc-1295-ipamorelin and TransformYou https://www.transformyou.com/ipamorelin. Accessed 07/31/2023.

[30] Apollo Virtual Health peptide health https://apollovh.com/peptide-therapy/. Accessed 07/31/2023.

[31] Re-new institute https://re-newinstitute.com/peptide-therapy/ipamorelin/. Accessed 07/31/2023.

[32] Vitality Sciences https://vitality-sciences.com/peptides/ipamorelin-acetate-anti-aging-peptide/#top. Accessed 07/31/2023.

[33] Revitalized Health https://rhsupplements.com/peptides/cjc-1295-ipamorelin and TransformYou https://www.transformyou.com/ipamorelin. Accessed 07/31/2023.

[34] Concierge MD: Peptide therapy https://conciergemdla.com/anti-aging-medicine/peptide-therapy/#ipamorelin. Accessed 07/31/2023.

[35] ReviveRx product catalog https://reviverx.com/product-catalog/. Accessed 07/31/2023.

[36] WADA was established in 1999 as an international independent agency to lead a collaborative worldwide movement for doping-free sport. See https://www.wada-ama.org/en/who-we-are. WADA, 2022, Prohibited Substances, World Anti-Doping Agency Prohibited List. See https://www.wada-ama.org/sites/default/files/2023-05/2023list_en_final_9_september_2022.pdf. Accessed 07/13/2023.

4. Recognition of the substance in other countries or foreign pharmacopeias

A search of the National Medical Registries, European Medicines Agency website, European Pharmacopoeia (11.3 Edition, 2023), Chinese Pharmacopoeia (10th Edition, 2015), Indian Pharmacopoeia (2010), and the Japanese Pharmacopoeia (18th Edition) did not show any monograph listings for either ipamorelin or ipamorelin acetate. The Australian government Advisory Committee on Medicines Scheduling (ACMS) recommended, and confirmed, adding ipamorelin to the Poisons standards, under performance and image enhancing drugs (PIEDs) for which possession without authority is illegal (e.g., possession other than in accordance with a legal prescription).[37]

Conclusions: It is often unclear whether the ipamorelin discussed in the sources considered for this section is the salt formulation or the free base. Available literature indicates that ipamorelin was first identified in 1998. There is some evidence of compounded ipamorelin's use in humans. Based on OF reporting data, compounding with ipamorelin can be traced back to at least 2017, but it appears to have stopped in 2020. Ipamorelin has been studied for use in POI after abdominal surgery. It has been marketed for use in weight loss management, anti-aging, inflammatory conditions, sleep cycle improvement, and bodybuilding. Internet search results show that compounders have been preparing ipamorelin in injectable, nasal, and oral formulations. These formulations of ipamorelin are increasingly being marketed by medical spas and wellness clinics.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites.

The clinical articles submitted by the nominator and those identified by FDA do not always clearly identify whether the ipamorelin form administered in the clinical studies was a salt formulation or the free base. Therefore, throughout this section, FDA used the information available in the databases consulted to identify the ipamorelin form used in the studies as free base, acetate salt, or unspecified form.

Ipamorelin (free base) and ipamorelin acetate was evaluated for the following uses: growth hormone deficiency and postoperative ileus. In addition to a comprehensive review of pertinent information from the databases, this section provides a brief overview of the conditions, list reports of clinical evidence and anecdotal reports of effectiveness or lack of effectiveness of

[37] The website did not specify the form of ipamorelin (i.e., ipamorelin acetate or ipamorelin (free base)). See Australian Government performance and image enhancing drugs https://www.tga.gov.au/resources/publication/scheduling-decisions-interim/scheduling-delegates-interim-decisions-and-invitation-further-comment-accsacms-february-2016/27-performance-and-image-enhancing-drugs, Accessed 07/31/2023. The Australian Poisons Standard is a record of classification of medicines and chemicals into Schedules for inclusion in the relevant legislation of the States and Territories. There are 10 Schedules that have increasingly restrictive regulatory controls with progression from Schedule 1 through 10. There are also 13 Appendices which describe exemptions or additional restrictions placed on some substances. See https://www.legislation.gov.au/F2024L00095/latest/text. Accessed 06/07/2024.

ipamorelin (free base) and ipamorelin acetate for the conditions, relevant regulatory history, and a discussion of the proposed use(s) of ipamorelin (free base) and ipamorelin acetate.

1. Growth Hormone Deficiency (GHD)

Overview of proposed use

GHD is a disorder characterized by inadequate secretion of growth hormone (GH) from the pituitary gland. GH stimulates linear growth (increased height) during childhood. In adulthood, GH improves body composition, including muscle mass and bone strength, and quality of life (Molitch et al. 2011).[38]

GHD onset can be from birth (congenital) or during childhood or adulthood (acquired). Acquired GHD may develop after any process that can damage the pituitary gland or surrounding brain area (e.g., brain tumor, surgery). Other cases of GHD have no known or diagnosable cause (idiopathic) and may be childhood- or adult-onset.[39] Signs and symptoms of GHD vary depending on age of onset and etiology. Symptoms of GHD during childhood may include low blood glucose levels in infants and toddlers, growth failure, short stature, and maturation delays. GHD in adulthood can result in symptoms such as reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, lipid abnormalities, insulin resistance, and impaired cardiac function.[40]

Diagnosis of GHD in children and adults typically involves assessment of signs and symptoms, and at least two GH stimulation tests using different provocative agents to stimulate pituitary secretion of GH. If GH levels do not rise to a certain level, it suggests GHD.[41,42] A random GH level is not useful to diagnose GHD because GH levels fluctuate throughout the day.[43] Insulin-like growth factor (IGF-1) levels are helpful in GHD screening;[44] however, IGF-1 alone is not reliable for the diagnosis of GHD (Ibba et al. 2020).[45] Imaging and additional laboratory tests may also be utilized for GHD screening and diagnosis.

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[38] Human Growth Hormone (HGH). Cleveland Clinic website. https://my.clevelandclinic.org/health/articles/23309-human-growth-hormone-hgh. Accessed 11/29/2023.

[39] Growth Hormone Deficiency. Endocrine Society Website. https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Accessed 07/21/2023.

[40] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed 06/30/2023.

[41] Two provocative tests are typically required for diagnosis of GHD in children (Grimberg et al. 2016). In adults, recommendations for provocative testing may vary depending on the context (e.g., two provocative tests are suggested for idiopathic GHD diagnosis, while provocative testing may be optional in the presence of three or more pituitary hormone deficiencies) (Molitch et al. 2011).

[42] Growth Hormone Deficiency. Endocrine Society Website. https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Accessed 07/21/2023. Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed 06/30/2023.

[43] Human Growth Hormone (HGH). Cleveland Clinic website. https://my.clevelandclinic.org/health/articles/23309-human-growth-hormone-hgh. Accessed 11/29/2023.

[44] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed 06/30/2023.

[45] IGF-1 levels can be influenced by factors such as nutritional status and presence of chronic illness or organ failure (Ibba et al. 2020). While IGF-1 level alone is not diagnostic of GHD, situations such as low IGF-1 level in adult

In children, the diagnosis of pediatric GHD is based on a combination of criteria including biochemical evaluation of the GH/IGF-1 axis that includes IGF-1 levels and two provocative tests (insulin, glucagon, arginine, clonidine, or L-dopa) (Grimberg et al. 2016; Collett-Solberg et al. 2019).

GHD can be complete (inability to secrete GH) or partial. A threshold result on GH provocative testing that "distinguishes normal from partial GHD that responds to treatment has not been well established." There are no randomized controlled studies that correlate GH provocative testing results with subsequent GH treatment effects on final adult height (Grimberg et al. 2016).

For treatment, multiple recombinant human GH (rhGH) preparations are approved for adults with GHD, such as once-daily somatropin and once-weekly somatropins (somapacitan and lonapegsomatropin). In pediatric patients with open epiphyses, GH therapy is used to normalize annual growth velocity and final adult height and dosing is typically weight-based. The doses are titrated based on the growth response and not on IGF-1 levels. IGF-1 levels are obtained to monitor adherence and for safety reasons; the doses are recommended to be decreased if there are AEs and elevated IGF-1 levels (Grimberg et al. 2016). According to Molitch et al. (2011), in adults with GHD, GH therapy offers benefits in body composition parameters, exercise capacity, and quality of life. GH therapy in adults is titrated to according to clinical response, side effects and IGF levels (Molitch et al. 2011).

Studies for treatments of GHD in children generally evaluate endpoints such as height velocity and near-adult height. For treatment of adult GHD, studies generally evaluate endpoints that include changes in body composition (lean body mass and fat mass) and IGF-1.[46] All available FDA-approved rhGH products were approved by FDA for the treatment of children with growth failure due to GHD based on improvement in annualized height velocity and/or height standard deviation score (SDS), since long-term studies with earlier formulations of human GH (e.g., Humatrope, BLA 019640)[47] also demonstrated that the improvement in annualized height velocity translates into improvement in final height.

Ipamorelin (free base) and ipamorelin acetate act as growth hormone secretagogues (GHSs), a class of drugs that consists of a variety of synthetic peptide or non-peptide agents that stimulate endogenous GH release (Sinha et al. 2020). Because ipamorelin (free base) and ipamorelin acetate activate ghrelin receptors on pituitary somatotrophs and in the hypothalamus to stimulate GH release from the pituitary (see Section II.D.1), some residual endogenous pituitary GH secretion must be preserved (i.e., partial and not complete GHD) in order for ipamorelin (free base) or ipamorelin acetate to increase circulating GH; ipamorelin (free base) or ipamorelin acetate would not be expected to increase circulating GH in individuals with absent pituitaries or severely damaged somatotrophs (Chapman et al. 1997).

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patients with evidence of panhypopituitarism (e.g., three or more other pituitary hormone deficiencies) may make provocative testing optional (Molitch et al. 2011).

[46] See Section II.C.1.c regarding availability of approved therapies.

[47] See prescription label for Humatrope (somatropin) for injection for SC use, BLA 019640. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019640s108lbl.pdf, Accessed 08/22/2024.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

The nominator cited a publication by Gobburu et al. (1999) to support the use of ipamorelin (unspecified form) for GHD, which was a randomized, placebo-controlled, dose escalation study characterizing PK and PD of ipamorelin in 48 healthy male subjects (refer to section II.D.2.a. for more details). The study did not report any effectiveness data on either diagnosis of GHD or treatment of GHD.

We did not find additional publications in the medical literature or databases that were consulted in the preparation of this section to evaluate effectiveness of ipamorelin (free base) or ipamorelin acetate for treatment of GHD.

Professional society guidelines for GHD diagnosis or treatment from the American Association of Clinical Endocrinologists and American College of Endocrinology (Yuen et al. 2019), including Pediatric Endocrine Society (Grimberg et al. 2016) and an Endocrine Society Clinical Practice Guideline on the evaluation and treatment of adult GHD (Molitch et al. 2011) do not mention ipamorelin (free base) or ipamorelin acetate.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

GHD is a serious disease. In children, untreated GHD may result in low blood glucose levels (in infants and toddlers) and is associated short stature and slowed height growth. Untreated GHD in adulthood may potentially cause serious medical conditions as it may increase risk for lipid abnormalities, heart disease, and fractures. [48,49]

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the compounded drug product(s) containing ipamorelin-related BDSs. [50] The following list includes currently available FDA-approved drug products indicated for use in the treatment of GHD in adults and growth failure in children due to inadequate secretion of endogenous GH.

[48] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed 11/04/2023.
[49] See: Growth Hormone Deficiency. Endocrine Society website. https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Accessed 11/04/2023. The Endocrine Society is a not-for-profit organization dedicated to enhancing the understanding of hormonal communication at the molecular, cellular, and systems levels in order to promote improved prevention, diagnosis, and treatment of endocrine disorders. See: https://rarediseases.org/non-member-patient/endocrine-society/. Accessed 11/04/2023.
[50] 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 therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

Examples of FDA-approved drug products indicated for GHD diagnosis and treatment include:

Diagnosis (GH Stimulation Testing):

- Arginine hydrochloride, IV (R-Gene 10),[51] an amino acid for diagnosis of pediatric and adult GHD
- Macimorelin acetate, oral (Macrilen),[52] a GH secretagogue (GHS) receptor agonist for diagnosis of adult GHD

GHD Treatment:

- Somatropin SC: a daily recombinant human growth hormone (rhGH) for the treatment of adults with GHD and growth failure in children due to inadequate secretion of endogenous GH (multiple FDA-approved somatropin products including Humatrope,[53] Genotropin,[54] Norditropin Flexpro,[55] Omnitrope,[56] Saizen,[57] and Zomacton[58])
- Lonapegsomatropin-tcgd, SC (Skytrofa):[59] a weekly pegylated human GH analog for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous GH
- Somapacitan-beco, SC (Sogroya):[60] a weekly human GH analog for the treatment of adults with GHD and pediatric patients with growth failure due to inadequate secretion of endogenous GH
- Somatrogon-ghla SC (Ngenla injection):[61] a weekly human GH analog for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous GH

[51] See prescription label for R-Gene 10 (Arginine Hydrochloride Injection) for IV use, NDA 016931/S-31. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016931s031lbl.pdf. Accessed 06/30/2023.
[52] See prescription label for Macrilen (macimorelin) for oral solution, NDA 205598. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205598s000lbl.pdf. Accessed 06/30/2023.
[53] See prescription label for Humatrope (somatropin) for injection for SC use, BLA 019640/S-105. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed 08/21/2023.
[54] See prescription label for Genotropin (somatropin) injection for SC use, BLA 020280/S-88. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020280s088lbl.pdf. Accessed 08/21/2023.
[55] See prescription label for Norditropin Flexpro (somatropin) injection for SC use, BLA 021148/S-53. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021148s053lbl.pdf. Accessed 08/21/2023.
[56] See prescription label for Omnitrope (somatropin) injection for SC use, BLA 021426/S-22. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021426s022lbl.pdf. Accessed 08/21/2023.
[57] See prescription label for Saizen (somatropin) injection for SC use, BLA 019764/S-86. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019764s086lbl.pdf. Accessed 08/21/2023.
[58] See prescription label for Zomacton (somatropin) injection for SC use, BLA 019774/S-51. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/180717s048s049s050s051lbl.pdf. Accessed 08/21/2023.
[59] See prescription label for Skytrofa (lonapegsomatropin-tcgd) for injection, for subcutaneous use, BLA 761177/S-1. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761177s001lbl.pdf. Accessed 06/30/2023.
[60] See prescription label for SOGROYA (somapacitan-beco) injection, for subcutaneous use, BLA 761156/S-5. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761156s005lbl.pdf. Accessed 06/30/2023.
[61] See prescription label for Ngenla (somatrogon-ghla), BLA 761184. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761184Orig1s000Corrected_lbl.pdf. Accessed 12/13/2023.

The nominators' proposed use for ipamorelin is to treat GHD. It is not clear whether the intent is to treat GHD in adults or children or both, or patients with complete or partial GHD, or both. Additionally, if the intent is to treat GHD in children, it is not clear whether this means the treatment of GHD in children generally, for which no product has been approved, or more specifically the treatment of short stature in children with GHD, the only one of many aspects of GHD in children for which products that improve GH levels have been approved. Among GHSs such as ipamorelin, only sermorelin (Geref, NDA 020443) was approved for the treatment of short stature associated with GHD in pediatric patients.[62] There are no GHSs that have been approved for the treatment of either adult- or childhood-onset GHD in adults.

Patients with GHD will most likely not respond to GHSs, including ipamorelin (free base) and ipamorelin acetate, unless these patients have partially preserved pituitary function (partial GHD). Patients with complete GHD will not respond to GHSs. A GH threshold on standard diagnostic tests that distinguishes normal pituitary function from partial GHD has not been established.

Regarding FDA-approved products containing human growth hormone (hGH), the indicated population is all patients with GHD regardless of time of onset, i.e., adult- or childhood-onset. The effectiveness of hGH formulations is not dependent on the criteria required for the effectiveness of GHSs noted above, as hGH formulations replace endogenous GH itself, and thus are effective in patients with either absent or partially preserved pituitary function.

Conclusions for GHD:
Based on available clinical information, FDA has not identified data to support the effectiveness of ipamorelin (free base) or ipamorelin acetate for the diagnosis or treatment of GHD in children or adults. Clinical practice guidelines for health professionals do not mention ipamorelin (free base) or ipamorelin acetate for the treatment of GHD in adults or in children with growth failure due to inadequate secretion of endogenous GH, or the diagnosis of GHD. GHD is a serious condition and there are multiple FDA-approved drug products for use in the treatment of GHD in adults and growth failure in children due to inadequate secretion of endogenous GH.

2. Postoperative Ileus (POI)

Overview of proposed use
POI is a transient cessation of coordinated bowel motility after surgical intervention which prevents effective transit of intestinal contents or tolerance of oral intake (Barletta and Senagore 2014). POI may contribute to significant postoperative morbidity, including delayed enteral nutrition, patient discomfort, and prolonged hospitalization. Postoperative hypomotility may affect all parts of the gastrointestinal (GI) tract, however, most data support that colonic dysfunction is the most contributing factor that limits resolution of POI. The colon is usually the

[62] Geref was approved for a preselected subpopulation of pediatric patients with GHD who respond to a Geref stimulation test (as per the label, "children who do not adequately respond (i.e., peak GH level < 2 ng/mL) should be excluded from Geref therapy"). However, the Geref stimulation test is not a validated test for the diagnosis of partial GHD and GH thresholds used for the diagnosis might now be different due to different modern GH assays' sensitivity since the time of Geref approval. In addition, treatment with Geref was indicated only for pediatric subjects with idiopathic GHD, thus patients with other GHD etiologies (e.g., surgery, congenital, infections, etc.) are not eligible for the treatment.

final portion of GI tract to regain normal motility, which usually occurs within 72 hours after surgery (Behm and Stollman 2003). The pathophysiology of POI is not fully understood; however, it is widely considered to be a multifactorial process involving a combination of pathways and mechanisms (Behm and Stollman 2003; Drake and Ward 2016).

The use of opioid analgesia, paralytic enteric nervous system reflexes and inflammation following surgery are thought to play key roles on GI motility (Drake and Ward 2016). POI commonly presents as a constellation of symptoms that reflect disrupted bowel motility and function and includes abdominal distention and bloating, nausea, vomiting, persistent abdominal pain, reduction of bowel sounds, inability to tolerate solid food, and delayed passage or inability to pass flatus or stool. These symptoms cause significant patient discomfort and may be associated with more severe clinical consequences if prolonged (Delaney et al. 2005). Therefore, prevention of POI is important to improve patient comfort, decrease length of hospital stay, and limit the healthcare costs associated with recovery (Carroll and Alavi 2009). An analysis of the Premier's Perspective Comparative Database, a repository of US hospital administrative data, showed that the mean length of stay of patients with POI versus those without one was 11.5 days vs. 5.5 days and the mean cost of the inpatient stay was US $18,877 vs. US $9,640, respectively (Bugaev N et al. 2019).

Current approaches to the management of POI are either preventive or supportive comprised of non-pharmacological as well as pharmacological strategies (Buchler et al. 2008). Early reintroduction of nutrition, and potentially gum chewing, can stimulate the digestive system to facilitate GI recovery. In addition, laparoscopic surgery, epidural anesthesia, and avoiding fluid excess have been associated with shorter recovery times and lower POI rates in some studies (Beck et al. 2014). Therapeutic options for managing POI also remain limited. To date, alvimopan is the only FDA-approved drug for management of POI.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

We found only one article (Beck et al. 2014) that reported a clinical study evaluating efficacy of ipamorelin (unspecified form) in subjects with POI when administered via intravenous (IV) route of administration. We did not find additional data on effectiveness of ipamorelin (free base) or ipamorelin acetate for other clinical uses or when administered via the proposed SC route of administration or other routes of administration.

Beck et al. (2014) conducted a prospective, proof-of-concept, phase 2, multi-center, randomized, double-blind, placebo-controlled study of IV ipamorelin (unspecified form) in postoperative subjects after abdominal surgery. The objective of the study was to evaluate upper GI recovery (as measured by food toleration) following abdominal surgery among 117 hospitalized adult subjects undergoing small and large bowel resection by either open laparotomy or laparoscopic left colon resection. After excluding subjects who withdrew consent and failed to meet the postoperative entry criteria, 114 subjects received randomly allocated study drug IV ipamorelin (unspecified form) 0.03 mg/kg (n = 56) or matching placebo (n = 58) twice daily beginning on postoperative day (POD) 1 and continued until POD 7 or hospital discharge, whichever occurred first.

The primary efficacy endpoint was time from first dose of study drug to tolerance[63] of a standardized solid meal without nausea or vomiting (indicating recovery of upper GI tract). The standardized solid meal was served twice daily beginning on postoperative day (POD) 2 along with twice daily study drug. The following secondary endpoints were also evaluated:

- Time to first bowel movement (recovery of lower GI tract)
- Time when patient is ready for hospital discharge based on recovery of GI function
- Time to recovery of GI function (GI-2)[64]
- Time to discharge order written, appetite and nausea assessment and vomiting episodes

Additional endpoints included NG tube insertions, length of hospital stay (LOS), time to passage of first flatus, and time to bowel sounds.

The primary efficacy endpoint of median time to first tolerated meal from first dose of study drug was 25.3 hours in the ipamorelin group and 32.6 hours in the placebo group (Table 3). Although there was reduction of 7.3 hours in the median time to tolerating first meal after surgery (indicating recovery of upper GI tract) the results were reported not to be statistically significant. Similarly, there was no reported differences between study groups for secondary efficacy endpoints to characterize upper and lower GI function, like the time to recovery of GI function (GI-2) or reductions in LOS (Table 3). However, in subgroup analysis stratified by surgery types, study found subjects on ipamorelin showed shorter bowel recovery times in subjects undergoing open laparotomy.

Authors concluded that the overall study results should be interpreted with caution due to several study limitations including small sample size for analyzing treatment effect and strict exclusion criteria that may have eliminated some subjects with most potential to get benefit from treatment for POI (e.g., history of Crohn's disease, complex bowel resections, irritable bowel syndrome).

[63] Author defined meal tolerance as consumption of 75% of standardized meal during the 30 min consumption period with (1) no episodes of vomiting while eating or within 1 hour of consumption period, and (2) no worsening of the nausea scale score by >1 point when assessed 1 hour after the meal consumption period.

[64] GI-2 is a composite endpoint defined as time to recovery of upper GI tract as demonstrated by tolerance of solid food and of and lower GI tract as demonstrated by first bowel movement. GI-2 is a clinically meaningful endpoint because it represents the most objective and clinically relevant measure of treatment response in patients undergoing surgeries that include a bowel resection.

Table 3. Median times from first dose to endpoints (MITT population).

Median time to:	Ipamorelin 0.03 mg/kg (n=56)	Placebo (n=58)	Treatment difference	Treatment HR	95 % CI of HR	p value
Tolerance of meal, h	25.3	32.6	−7.3	1.34	0.90, 1.98	*0.15*[a]
First BM, h	63.0	71.6	−8.6	1.35	0.87, 2.10	*0.18*[a]
RFD, h	59.1	71.4	−12.3	1.20	0.82, 1.77	*0.35*[a]
GI-2, h	63.3	75.5	−12.2	1.27	0.81, 1.99	*0.29*[a]
DOW, h	79.8	79.8	0	1.16	0.79, 1.72	*0.44*[a]
LOS, days	5	6	−1	NC	NC	*0.29*[b]
Flatus, h	45.1	46.8	−1.7	1.22	0.80, 1.84	*0.35*[a]
Bowel sounds, h	23.3	7.7	15.6	0.59	0.30, 1.14	*0.11*[a]

BM bowel movement, *CI* confidence interval, *DOW* discharge order written, *GI-2* recovery of gastrointestinal function, *HR* hazard ratio, *LOS* length of hospital stay, *MITT* modified intent-to-treat, *NC* not calculated, *RFD* ready for discharge based on gastrointestinal function

[a] Cox proportional hazards model

[b] ANCOVA

Of note, Ishida et al. (2020) reported about clinical development of ipamorelin (unspecified form) in the treatment of POI based on the study published by Beck et al. 2014. The authors stated that "in patients undergoing bowel resection, ipamorelin did not shorten the time to first meal intake compared with placebo. This phase II clinical trial did not show any significant difference in measurable colonic functions between ipamorelin and placebo. Due to these disappointing results, its development was discontinued."

We did not identify any clinical studies evaluating ipamorelin (free base) or ipamorelin acetate for the treatment of POI via the proposed SC ROA.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Postoperative ileus following major abdominal surgery is associated with significant postoperative morbidity, reduced patient satisfaction, and prolonged hospitalization. Increased hospital LOS caused by POI can increase healthcare costs, lost productivity and increase complications (Buchler et al. 2008).

c. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition as FDA has evaluated for the proposed compounded drug product(s) containing ipamorelin-related BDSs. [65] The following list includes currently available FDA-approved drug products indicated for POI.

To date, alvimopan[66] is the only FDA-approved drug for accelerating time to upper and lower GI recovery following bowel resection. Accelerating GI recovery and decreasing hospital LOS are important objectives for management of POI.

[65] 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 therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

[66] See prescription label for Entereg (alvimopan capsule), NDA 021775/S-18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021775s018lbl.pdf. Accessed 06/30/2023.

There are FDA-approved drug products that have been used to treat some of the POI-associated symptoms. These drugs fall into three categories based on mechanism of actions: stimulation of gastrointestinal mu-opioid receptors (methylnaltrexone[67]), minimizing sympathetic inhibition (metoclopramide[68], neostigmine[69]), and decreasing inflammation (celecoxib[70]).

Conclusions for POI:
FDA has not identified data to support the effectiveness of ipamorelin (free base) or ipamorelin acetate for postoperative ileus. The only published study evaluating effectiveness of ipamorelin (unspecified form) for this condition used an IV infusion and did not show significant differences between ipamorelin and placebo in the primary and secondary efficacy analyses. Development of ipamorelin as a potential treatment for postoperative ileus was reportedly discontinued because of the study's disappointing results. POI is a serious condition, and there is an FDA-approved drug, alvimopan, for the management of postoperative ileus following bowel resection surgery. Other FDA-approved products have also been used for managing POI-associated morbidity.

Overall Conclusions on Effectiveness: We conclude based on available clinical information that the evidence of effectiveness for GHD or POI is limited for any ROA, and there are no data to support the effectiveness of ipamorelin (free base) or ipamorelin acetate for the proposed SC route of administration for these medical conditions. Professional society guidelines do not discuss use of ipamorelin-related bulk drug substance for GHD or POI. Growth hormone deficiency and postoperative ileus are serious conditions, and there are FDA-approved therapies for treating adults with all forms of GHD, growth failure in children due to inadequate secretion of endogenous GH (whether due to complete or partial GHD), and for the treatment of postoperative ileus.

D. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The nominators submitted nonclinical information with the nomination. Specifically, the nominators provided articles that report the pharmacological properties of GHRPs, including ipamorelin (Ankersen et al. 1999; Dieguez and Casanueva 2000; Johansen 2008; Khatib et al. 2014; Hansen et al. 2001; Raun et al. 1998). The nominator-submitted articles do not include data to inform safety considerations for the potential therapeutic use of ipamorelin (free base) or ipamorelin acetate.

[67] See prescription label for Relistor (methylnaltrexone bromide injection), NDA 021964. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021964s019,208271s003lbl.pdf. Accessed 06/30/2023.
[68] See prescription label for Reglan (metoclopramide tablet), NDA 017854. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017854s062lbl.pdf. Accessed 06/30/2023.
[69] See prescription label for Bloxiverz (neostigmine methylsulfate injection), NDA 204078. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204078Orig1s014lbl.pdf. Accessed 06/30/2023.
[70] See prescription label for Celebrex (celecoxib capsule), NDA 020998. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020998s056lbl.pdf. Accessed 06/30/2023.

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

The nonclinical articles submitted by the nominator and those identified by FDA do not always clearly identify whether the ipamorelin form used in a nonclinical study was a salt or the free base. Therefore, throughout this section, FDA uses the information available in the published articles to identify the ipamorelin form used in the studies as free base, acetate salt, or unspecified form.

a. General pharmacology of the drug substance

Ipamorelin, in the form of free base or acetate salt, is a synthetic pentapeptide (Figure 3) that acts as a ghrelin mimetic. Primarily via activation of ghrelin receptors in GHRH-positive neurons in the hypothalamus, ipamorelin[71] stimulates growth hormone release from the anterior pituitary without major effects on adrenocorticotropic hormone or cortisol levels (Hansen et al. 2001; Raun et al. 1998). The exact amino acid sequence and chirality are critical determinants of the affinity of growth hormone-releasing peptides such as ipamorelin for ghrelin receptors and for the pharmacological actions of these peptides as agonists or antagonists at ghrelin receptors (Ferro et al. 2017).

Figure 3. Amino Acid Sequence of Ipamorelin.

Note: The sequence is shown from the C-terminal amino acid (Aib) to the N-terminal amino acid (L-Lys). Aib: α-methylalanine; L-His: L-histidine; D-2-Nal, (2-naphthyl)-D-alanine; D-Phe: D-phenylalanine; L-Lys: L-lysine.

Ghrelin receptors are G-protein-coupled receptors that signal primarily via $G_{\alpha 11/q}$-mediated phospholipase activation (Dieguez and Casanueva 2000; Howard et al. 1996; Khatib et al. 2014). These receptors are expressed not only in different brain regions, but also in peripheral organs, including the thyroid, heart, lung, liver, kidney, pancreas, spleen, intestine, adrenal gland, testis, adipose tissue, and stomach (Kaiya et al. 2014; Yin et al. 2014).

The endogenous agonist of ghrelin receptors – ghrelin – was first isolated from the rat stomach and later demonstrated to be produced in the human stomach. Via ghrelin receptor activation in the stomach, ghrelin, and ghrelin receptor agonists such as ipamorelin stimulate both gastric acid secretion and gastric motility. Research also shows that ghrelin receptor activation facilitates vagal control of gastric motility (Masuda et al. 2000).

In a study of rats with surgically induced POI, hereafter referred to as POI rats, an acute treatment with ipamorelin (unspecified form; 0.1-1.0 mg/kg, IV) accelerated colonic transit and induced a dose-dependent increase of fecal pellet output, food intake, and body weight gain.

[71] In the nonclinical section, the word ipamorelin (without reference to the free base, a specific salt, or an unspecified form) is intended to refer to the active moiety.

Ipamorelin also normalized the contractile response induced by acetylcholine or by electric field stimulation in the gastric fundus of rats following abdominal surgery (Pietra et al. 2011).

In another study of POI rats, oral administration of ipamorelin (unspecified form; dose: 10 or 100 mg/kg) by gavage accelerated stomach emptying by about 12.4% and 41.6%, respectively, and IV administration of ipamorelin doses of 0.1, 0.25, and 1.0 mg/kg accelerated stomach emptying by 87.1%, 96.0%, and 93.1%, respectively. Stomach emptying was assessed by measurement of stomach phenol red content following IV administration of phenol red to the animals (Polvino 2011).

Additional experiments in POI rats revealed that a single bolus IV infusion of ipamorelin (free base dissolved in saline containing glacial acetic acid; dose: 0.1 or 1.0 mg/kg) immediately after surgery decreased time to first bowel movement but had no effects on fecal output, body weight gain, or food intake during a 48-h course of recovery from the surgically induced POI. The experiments also revealed that multiple IV infusions of ipamorelin (free base dissolved in saline containing glacial; dose: 0.1 or 1.0 mg/kg) delivered to POI rats for 2 days after the surgical procedure significantly accelerated colonic transit and increased cumulative fecal pellet output for 48 hours post-surgery. At 48 hours post-surgery, POI rats treated with multiple ipamorelin IV infusions of 1 mg/kg showed a large increase (~10%) in body weight compared to untreated POI rats (Polvino 2011; Venkova et al. 2009).

In a nonclinical study in which visceral hypersensitivity was induced in the colon of rats, ipamorelin (unspecified form; IV dose: 0.01, 0.1, or 1.0 mg/kg) caused a dose-dependent reduction in colonic hypersensitivity and somatic allodynia, with the effect becoming statistically significant at the dose of 1.0 mg/kg. In this study, colonic hypersensitivity was assessed as the visceromotor response to colorectal distension, and somatic mechanical allodynia was quantified by the number of ipsilateral paw withdrawals in response to mechanical stimuli applied with calibrated von Frey filaments (Mohammadi et al. 2020).

Nonclinical studies have also reported that, via activation of ghrelin receptors in the hypothalamus and in somatotroph cells in the anterior pituitary gland, ipamorelin can induce growth hormone (GH) secretion from the pituitary. For instance, results from in-vitro experiments conducted by Raun and collaborators demonstrated that ipamorelin concentration dependently increased the release of GH from rat pituitary cells in primary cultures (Raun et al. 1998). Although the authors reported that ipamorelin was a white amorphous powder that had been isolated as a trifluoroacetate (TFA) salt, it is unclear whether they used the free base or the TFA salt of ipamorelin in the experiments. In vitro, the GH secretagogue potency of ipamorelin was reported to be approximately 1.3 nM (Raun et al. 1998). In addition, in-vivo experiments further revealed that serum GH concentrations increased dose dependently in anesthetized male Sprague-Dawley rats and in awake female swine treated intravenously with different doses of ipamorelin. In vivo, the GH secretagogue potency of ipamorelin was approximately 80 nmol/kg in rats and 2.3 nmol/kg in swine (Raun et al. 1998).

The ability of ipamorelin (as free base or salt) to stimulate gastric motility and counter clinical signs of POI in rodents and the GHS activity of ipamorelin have attracted the interest of researchers for the potential clinical usefulness of this peptide for management of POI and GHD

in humans. However, pharmacological activation of ghrelin receptors in other organs and systems can also contribute to untoward effects of ghrelin receptor agonists.

Ghrelin receptors are expressed in brain regions known to process reward, including the ventral tegmental area (VTA) (Zigman et al. 2006), and ghrelin receptor agonists and antagonists have been shown to modulate pharmacological responses normally associated with drugs of abuse. Specifically, nonclinical pharmacological studies have reported that treatment of rats with ghrelin: (i) stimulates dopamine release in the VTA, a response typically evoked by drugs of abuse (Edvardsson et al. 2021), and (ii) increases heroin comsumption and seeking (Maric et al. 2012). Conversely, ghrelin receptor antagonists: (i) reduce ethanol intake, preference, and operant self-administration in mouse and rat models of alcohol dependence (Gomez et al. 2015), and (ii) suppress the rewarding properties of morphine in rats (Sustkova-Fiserova et al. 2014). These nonclinical findings are clinically relevant because a functional magnetic resonance imaging study reported that, during exposure to food images, IV infusions of ghrelin in healthy human subjects increased activity in the VTA and other reward-processing brain regions (Malik et al. 2008).

By virtue of activating ghrelin receptors in reward-processing brain regions, ipamorelin (free base or acetate), like ghrelin, could stimulate reward processing and potentially induce reinforcing and addictive behaviors typically associated with drugs of abuse. However, at the time of this evaluation, nonclinical studies were insufficient to demonstrate whether ipamorelin (free base or acetate) has reinforcing and addictive properties.

b. Pharmacokinetics/Toxicokinetics (TK)

According to a pharmacokinetic study conducted in adult male rats treated with an IV injection of ipamorelin acetate (dose with respect to free base: 1 mg/kg), plasma concentrations of ipamorelin peaked within 1-minute post-injection. The half-life of ipamorelin was approximately 27 minutes. The finding that 60-80% of ipamorelin was excreted unchanged suggested that the peptide chain in ipamorelin is reasonably resistant to metabolism. Ipamorelin was primarily excreted in urine (Johansen et al. 1998).

At the time of this assessment, FDA did not identify nonclinical studies assessing the pharmacokinetic profile of ipamorelin (free base) or ipamorelin acetate delivered via the nominated SC route of administration.

c. Acute toxicity[72]

At the time of this evaluation, FDA did not identify in the publicly available literature nonclinical acute toxicity studies with ipamorelin (free base) or ipamorelin acetate.

[72] 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[73]

At the time of this evaluation, FDA did not identify in the publicly available literature nonclinical repeat-dose toxicity studies with ipamorelin (free base) or ipamorelin acetate.

e. Genotoxicity[74]

At the time of this evaluation, FDA did not identify in the publicly available literature nonclinical genotoxicity studies with ipamorelin (free base) or ipamorelin acetate.

f. Developmental and reproductive toxicity[75]

At the time of this evaluation, FDA did not identify in the publicly available literature nonclinical developmental and reproductive toxicity studies with ipamorelin (free base) or ipamorelin acetate. However, a nonclinical study conducted in mice revealed that either ghrelin receptor activation (by systemic treatment with synthetic ghrelin) or ghrelin receptor inhibition (by systemic treatment with the ghrelin receptor antagonist D-Lys^3-GHRP6) has negative effects on fertilization, implantation, and embryofetal development (Luque et al. 2014). These findings are relevant because the effects of ghrelin could represent pharmacological class effects that may generalize to other ghrelin receptor agonists, of which ipamorelin (as free base or acetate salt) is an example.

In the study by Luque and collaborators, treatments consisted of SC injections of synthetic ghrelin (2 or 4 nmol/animal/day), D-Lys^3-GHRP6 (6 nmol/animal/day), or vehicle (0.9% NaCl). Female Albino Swiss mice (N:NIH) were assigned to one of the three experimental groups listed below such that the different treatments were administered at well-defined times during the fertilization (group 1), early embryonic development (group 2), and implantation periods (group 3) (n = 8-11 female mice/treatment/experimental group).

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[73] 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 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.

[74] 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.

[75] 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 because 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.

- Group 1: Mice were subjected to the different treatments starting from 1 week before to 12 hours after copulation and were euthanized at gestation day (GD) 18.
- Group 2: Mice were subjected to the different treatments since ovulation induction until 80 hours later, when the embryos were retrieved from oviducts/uterus.
- Group 3: Mice were subjected to the different treatments from GD 3 to 7 (peri-implantation) and were euthanized at GD 18.

In experimental groups 1 and 3, ghrelin (4 nmol/day) or the ghrelin receptor antagonist increased the percentage of atrophied fetuses as well as the percentage of females exhibiting this finding or a greater number of corpora lutea compared with fetuses. In experimental group 2, the ghrelin receptor antagonist reduced the fertilization rate, and either ghrelin or the antagonist, delayed embryo development. In experimental group 3, ghrelin (4 nmol/day) or the antagonist also reduced weight gain of fetuses and dams during pregnancy. Taken altogether the results indicated that systemic treatment of mice with either a ghrelin receptor antagonist (D-Lys^3-GHRP6) or a ghrelin receptor agonist (ghrelin) negatively affected fertilization and embryofetal development.

It remains to be determined whether ipamorelin (free base) or ipamorelin acetate, substances that like ghrelin act as ghrelin receptor agonists, can negatively impact fertilization and embryofetal development as ghrelin did in the studies discussed above.

g. Carcinogenicity[76]

At the time of this evaluation, FDA did not identify in the publicly available literature nonclinical studies to inform the carcinogenic potential of ipamorelin (free base) or ipamorelin acetate.

Conclusions: From the nonclinical pharmacological perspective, due to its primary mechanism of action as a ghrelin receptor agonist, ipamorelin (free base) or ipamorelin acetate may have behavioral reinforcing properties, which can contribute to development of addiction, and may also negatively affect reproductive health and pregnancy outcomes. At the time of this evaluation, nonclinical toxicity studies were too limited in scope and duration to inform safety considerations for potential clinical uses of ipamorelin (free base) or ipamorelin acetate.

[76] 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.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), ClinicalTrials.gov, and various online clinical references and websites.

The clinical articles submitted by the nominator and those identified by FDA do not always clearly identify whether the ipamorelin form administered in the clinical studies was a salt formulation or the free base. Therefore, FDA used the information available in the databases consulted to identify the ipamorelin form used in the studies as free base, acetate salt, or unspecified form.

a. Pharmacokinetic data

FDA did not identify PK or PD information for the proposed SC route of administration of ipamorelin (free base) or ipamorelin acetate. A study published by Gobburu et al. (1999) described PK/PD information for the intravenous route of administration. There is no PK/PD information for any other routes of administration.

Gobburu et al. (1999) conducted a randomized, placebo-controlled, dose escalation study to characterize the PK and PD profiles of ipamorelin (unspecified form) in healthy male subjects. Forty-eight subjects were enrolled. Five groups with 6 healthy male subjects per group received a range of ipamorelin doses 4.21, 14.04, 42.13, 84.27, and 140.45 nmol/kg over a 15-minute IV infusion and 2 subjects per group received placebo. Subjects underwent post dose PK and PD assessment at various time points to determine the plasma ipamorelin and growth hormone concentrations. The lowest dose of 4.21 nmol/kg group and placebo groups were not included in the PK/PD analysis due to negligible GH levels. Ipamorelin displayed linear pharmacokinetics based on the two-compartment model. Concentrations declined in a biexponential fashion with a short terminal half-life of about 2 hours, systemic clearance of 0.078 L/h/kg and a steady-state volume of distribution of 0.22 L/kg in healthy subjects. Similarly, a linear pharmacodynamic model described the stimulation of GH release in an episodic fashion dependent on the concentration of ipamorelin. The maximum rate of GH release was 694 mIU/L/h and GH concentrations rose to a sharp peak around 0.67 hour (maximum plasma GH concentration is about 465 mIU/L) and declined to very low concentration at all doses by 6 hours. Although the model showed that ipamorelin induced the release of GH at all dose levels, prolonged exposure to the peptide may not necessarily produce GH stimulation for long periods[77]. Based on the model presented, authors concluded that the study satisfactorily characterized the ipamorelin-GH concentration relationship at all doses. The study by Gobburu et al. (1999) did not state that there were any adverse events associated with ipamorelin. Of note, this trial was conducted in healthy subjects with intact hypothalamic-pituitary axis. Studies in subjects with GHD,

[77] Data observed for prolonged exposure to the peptide in this study has important relevance in subjects with partial GHD. If subjects with partial GHD initially retain some ability to produce endogenous GH in response to GHSs, as GHSs are dependent on pituitary responsiveness to increase GH production, there is concern that patients may lose responsiveness over time due to depletion of GH stores in subjects with partial GHD.

especially those with complete GHD may not be expected to show the same PK/PD profiles as the deficiency of endogenous GH would likely not improve in response to GHS stimulation.

b. Reported adverse reactions (FAERS, CAERS, and case reports and anecdotal cases assessing safety)

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for ipamorelin through September 30, 2023. The report considered information for ipamorelin (free base) and ipamorelin acetate. The search retrieved two reports of non-serious adverse events associated with products containing ipamorelin, as a single ingredient and in combination with sermorelin.[78] Both cases involved compounded products used in adults.

The first case reported was from a 32-year-old male after using a compounded nasal spray product containing single ingredient ipamorelin once daily for 17 days (dose not reported) for sinus headache.[79] Subject experienced increased lacrimation and headache that were assumed to be related to a product quality issue.

The second case reported was a 46-year-old male who used a compounded drug product containing a combination of ipamorelin and sermorelin for erectile dysfunction that was self-administered as subcutaneous injections to the abdomen for 2 months (dose not reported). Subject experienced arthralgia with left elbow joint pain. The pain did not resolve after stopping the injections; however, it became less severe. Because the compounded product contained two peptides, it is not possible to assess a potential relationship between ipamorelin specifically and the reported adverse event.

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A CAERS search looking for adverse events associated with products containing ipamorelin covering the period between January 1, 2004, through August 17, 2023, found no cases.

c. Clinical studies assessing safety

Only one article (Beck et al. 2014) discussed clinical evaluation of ipamorelin (unspecified form) in subjects with POI when administered via the intravenous (IV) route of administration, and that article was considered for assessment of safety. We did not find additional articles to inform our

[78] It is important to note that FAERS data have limitations. First, there is no certainty that the 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 ipamorelin (free base) or ipamorelin acetate based on FAERS data alone.

[79] Subject reported that the website (madisonjamesresearchchems.com) sold peptide product nasal sprays and did not disclose complete information about the products. There was no information that the nasal sprays were for research purposes only; it was not packaged in a sterile manner, and the website did not have a working phone number and sold online through Venmo to "avoid detection from authorities". At the time of this evaluation, the website provided by the reporter is non-functioning.

assessment of safety of ipamorelin (free base) and ipamorelin acetate for other clinical uses or when administered via other routes of administration.

Beck et al. (2014) evaluated the safety (and effectiveness) of IV ipamorelin (unspecified form) in the treatment of POI following abdominal surgery among 117 hospitalized adult subjects undergoing small and large bowel resection. For more details of this study refer to Section II.C.2.a.

Authors stated that most treatment-emergent adverse events (TEAEs) were mild to moderate in severity and were generally related to surgery or underlying disease. The most common TEAEs included nausea, vomiting, and abdominal distention. These were similar in both treatment groups, but numerically lower in subjects receiving ipamorelin. The TEAEs of hypokalemia (12.5% ipamorelin vs 3.4% placebo) and insomnia (10.7% ipamorelin vs 5.2% placebo) occurred more frequently in the ipamorelin group than the placebo group. Similarly, a higher proportion of subjects in the ipamorelin group experienced hyperglycemia at discharge (14.3% ipamorelin vs 8.6% placebo). Three subjects in the ipamorelin group discontinued the drug due to nausea, hypertension, or hypotension, and three subjects in the placebo group discontinued the drug due to hyponatremia, vomiting, nausea, or abdominal distention.

Serious adverse events (SAEs) including infection, anastomotic leak, and readmission due to complications of wound healing occurred in 10 subjects (17.9%) in the ipamorelin group and 9 subjects (15.5%) in the placebo group. More than one SAE may have occurred in these subjects with SAEs. Of the nineteen subjects with SAEs, twelve subjects experienced infection: six subjects (10.7%) received ipamorelin and six subjects (10.3%) received placebo; three subjects experienced anastomotic leak: two subjects (3.6%) received ipamorelin and 1 subject (1.7%) received placebo; twelve subjects were readmitted <30 days after initial procedure: seven subjects (12.5%) received ipamorelin and five subjects (8.6%) received placebo. Most SAEs occurred after subjects completed therapy.

Although authors reported that most subjects tolerated the study drug ipamorelin, serious adverse events including fatal SAEs were observed in the study. Two subjects treated with ipamorelin experienced fatal SAEs; they underwent bowel resection for colon cancer and developed postoperative complications of anastomotic leak.[80] The primary causes of death were from hyperkalemia in a subject with aortic clots, sepsis, perforated ulcer, and renal failure and sepsis in a subject with pneumonia.

Although it is unclear whether the deaths reported in the above study were related to ipamorelin, their occurrence in ipamorelin-treated subjects, along with the higher rates of hypokalemia and hyperglycemia reported in ipamorelin-treated subjects, raises safety concerns about the use of ipamorelin in compounding.

[80] Anastomotic leaks are reported in about 5% of anastomosis surgeries. About 75% of anastomotic leaks are associated with colectomy, removal of some part of the colon. See anastomotic leak in https://my.clevelandclinic.org/health/diseases/22324-anastomotic-leak#:~:text=How%20common%20are%20anastomotic%20leaks,your%20rectum%20or%20sigmoid%20colon).

There were no additional data on safety of ipamorelin (free base) or ipamorelin acetate reported in the databases that were consulted in the preparation of this section.

d. Other safety information

GHSs, such as ipamorelin (free base) or ipamorelin acetate, stimulate production of endogenous GH, which in turn stimulates production of IGF-1. There are known potential risks associated with elevated GH and IGF-1 levels, and these risks are included in all FDA-approved recombinant human GH (rhGH) products' labeling. Specifically, the warning and precautions section of the labels of currently approved rhGH products lists the following risks: increased risk of neoplasm, glucose intolerance and diabetes mellitus, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis in pediatric patients, progression of preexisting scoliosis in pediatric patients, and pancreatitis.[81] We are concerned that similar potential risks will be associated with the use of ipamorelin (free base) or ipamorelin acetate. In addition, there is a risk of QT prolongation associated with the use of the approved GHS macimorelin acetate (Macrilen oral solution[82]). There are insufficient data to conclude that ipamorelin (free base) or ipamorelin acetate, GHSs that stimulate the GH/IGF-1 axis, would not raise safety concerns similar to those associated with approved products that stimulate GH release.

Immunogenicity and aggregation concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[83] 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 ipamorelin (free base) and ipamorelin acetate), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC ROA. In general, SC ROA is associated with increased immunogenicity compared to IV ROA.

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

[81] See, e.g., label for Humatrope (somatropin) injection for SC use, BLA 019640/S-105. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed 08/21/2023.
[82] Macrilen is indicated for the diagnosis of adult GHD. See label for Macrilen (macimorelin acetate) oral solution, NDA 205598. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205598s000lbl.pdf. Accessed 12/12/2023.
[83] See FDA's guidance for industry. *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014), available at https://www.fda.gov/media/85017/download.

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

The nominators did not provide, and FDA did not identify clinical studies assessing immunogenicity or aggregation of ipamorelin (free base) or ipamorelin acetate. Although ipamorelin (free base) or ipamorelin acetate consists of five 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 ipamorelin (free base) or ipamorelin acetate does not present these risks.

e. Therapies that have been used for the condition(s) under consideration

There are FDA-approved drug products that treat the same medical condition that was nominated, and for the medical condition that was unnominated, as those proposed for the compounded drug product(s) containing ipamorelin-related BDSs.[84] See Sections II.C.1.c and II.C.2.c regarding currently available FDA-approved drug products indicated for growth hormone deficiency and postoperative ileus.

Conclusions: Based on available clinical information for ipamorelin (free base) and ipamorelin acetate, we conclude that the use of ipamorelin-related bulk drug substances in compounding may raise safety concerns. In a clinical study conducted in subjects with POI who received ipamorelin via the IV ROA, the following AEs were reported: hypokalemia, insomnia, hyperglycemia, nausea, vomiting, abdominal distention and death. However, it is unclear whether the two deaths were related to ipamorelin. Additionally, the nomination did not include, and FDA did not identify sufficient data to conclude that ipamorelin (free base) or ipamorelin acetate, would not present safety concerns similar to those associated with approved products that stimulate GH release, such as glucose intolerance and diabetes mellitus. While there is limited FAERS data available about compounded drug products containing ipamorelin, FDA's ability to interpret FAERS reports is limited by lack of information in the reports and confounding factors such as concomitant medications.

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

[84] 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.

The safety profile of compounded drug products containing ipamorelin (free base) or ipamorelin acetate can be negatively impacted by various factors that include but are not limited to the product formulation, peptide concentration, and conditions of storage favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. Even though ipamorelin (free base) or ipamorelin acetate is a peptide containing only 5 amino acids, FDA is concerned about the potential risk of immunogenicity because the immunogenic response may be enhanced when peptides like ipamorelin (free base) or ipamorelin acetate are administered via injectable ROAs, such as IV and SC, due to potential for aggregation as well as potential peptide-related impurities. The nomination did not include, and FDA did not identify, information about ipamorelin (free base) or ipamorelin acetate to suggest that the substances do not present these risks.

There are currently available FDA-approved drugs for diagnosis of GHD in children and adults, and for the treatment of GHD in adults and the treatment of short stature due to insufficient endogenous production of GH in children. Alvimopan is an FDA-approved product for the management of postoperative ileus.

III. CONCLUSION AND RECOMMENDATION

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

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

   1.1.
   Ipamorelin (free base) is a five amino acids peptide containing unnatural amino acids. Generally, less is known about the safety and biological properties of peptides that contain unnatural amino acids, including regarding the structure and chromatographic behavior for purification of unnatural amino acids and their derivatives, as well as any impact on a peptide's propensity to aggregate, which may add to the complexity of the characterization of ipamorelin (free base). As reported in the literature, ipamorelin is expected to be stable under reported storage conditions (below -18°C).

   Ipamorelin (free base) is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to ipamorelin (free base), including impurities, aggregates, and bacterial endotoxins, were not found in the publicly available scientific literature, and the nomination packages lacked CoAs, which are offered as evidence to establishing identity, purity, and impurity profiles of the substance. In addition, due to limited water solubility of ipamorelin (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with the concentration of 2 mg/mL.

1. 2.
Ipamorelin acetate is a salt form of a peptide consisting of five amino acids. Because ipamorelin acetate contains unnatural amino acids as mentioned above for ipamorelin (free base), it may add to the complexity of the characterization of the BDS. It is expected to be stable under recommended storage condition (below -20°C) as reported in the literature.

Ipamorelin acetate is not well-characterized from the physical and chemical characterization perspective because certain critical characterization data specific to ipamorelin acetate were not found in the publicly available scientific literature, and the provided CoA, which was offered as evidence to establishing identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, and bacterial endotoxins). The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section 2.D., FDA is concerned about the potential for immunogenicity of ipamorelin acetate when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as ipamorelin acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

2. Available literature indicates that ipamorelin was first identified in 1998 and there is some evidence of compounded drug products containing ipamorelin being used in humans. Based on OF reporting data, compounding with ipamorelin was reported from 2017 to 2020. It was studied for use in post-operative ileus after abdominal surgery. It has been marketed for use in weight loss management, anti-aging, inflammatory conditions, sleep cycle improvement, and bodybuilding in the injectable, nasal, and oral formulations. These formulations of ipamorelin are increasingly being marketed by medical spas and wellness clinics.

3. We conclude based on available clinical information that the evidence of effectiveness for GHD or POI is limited for any ROA, and there are no data to support the effectiveness of ipamorelin (free base) or ipamorelin acetate for the proposed SC route of administration for these medical conditions. Professional society guidelines do not discuss use of ipamorelin-related bulk drug substance for GHD or POI. Growth hormone deficiency and postoperative ileus are serious conditions, and there are FDA-approved therapies for treating adults with all forms of GHD, growth failure in children due to inadequate secretion of endogenous GH (whether due to complete or partial GHD), and for the treatment of postoperative ileus.

4. From the nonclinical pharmacological perspective, due to its primary mechanism of action as a ghrelin receptor agonist, ipamorelin (free base) or ipamorelin acetate may have behavioral reinforcing properties, which can contribute to development of addiction, and may also negatively affect reproductive health and pregnancy

outcomes. At the time of this evaluation, nonclinical toxicity studies were too limited in scope and duration to inform safety considerations for potential clinical uses of ipamorelin (free base) or ipamorelin acetate.

Based on available clinical information for ipamorelin (free base) and ipamorelin acetate, we conclude that the use of ipamorelin-related bulk drug substances in compounding may raise safety concerns. In a clinical study conducted in subjects with POI who received ipamorelin via the IV ROA, the following AEs were reported: hypokalemia, insomnia, hyperglycemia, nausea, vomiting, abdominal distention and death. However, it is unclear whether the two deaths were related to ipamorelin. Additionally, the nomination did not include, and FDA did not identify sufficient data to conclude that ipamorelin (free base) or ipamorelin acetate, would not present safety concerns similar to those associated with approved products that stimulate GH release, such as glucose intolerance and diabetes mellitus. While there is limited FAERS data available about compounded drug products containing ipamorelin, FDA's ability to interpret FAERS reports is limited by lack of information in the reports and confounding factors such as concomitant medications.

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

The safety profile of compounded drug products containing ipamorelin (free base) or ipamorelin acetate can be negatively impacted by various factors that include but are not limited to the product formulation, peptide concentration, and conditions of storage favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. Even though ipamorelin (free base) or ipamorelin acetate is a peptide containing only 5 amino acids, FDA is concerned about the potential risk of immunogenicity because the immunogenic response may be enhanced when peptides like ipamorelin (free base) or ipamorelin acetate are administered via injectable ROAs, such as IV and SC, due to potential for aggregation as well as potential peptide-related impurities. The nomination did not include, and FDA did not identify, information about ipamorelin (free base) or ipamorelin acetate to suggest that the substances do not present these risks.

There are currently available FDA-approved drugs for diagnosis of GHD in children and adults, and for the treatment of GHD in adults and the treatment of short stature due to insufficient endogenous production of GH in children. Alvimopan is an FDA-approved product for the management of postoperative ileus.

On balance, physiochemical characterization, information on historical use, evidence of effectiveness, and safety information identified for both ipamorelin (free base) and ipamorelin acetate weigh against their being added to the 503A Bulks List. Although available data suggests that these substances have been used historically in compounding, FDA's proposal is based on the lack of data related to physiochemical characterization, identified safety concerns, and lack of data to support effectiveness. These substances are not well characterized from a physical and chemical characterization perspective, and endotoxin testing for injectable ROAs is lacking.

FDA also did not identify information that addresses additional concerns related to potential immunogenicity risk for ipamorelin (free base) or ipamorelin acetate, as described above. We do not have nonclinical and clinical safety data or effectiveness data for GHD or POI for the proposed SC ROA. Available clinical information indicates safety issues raised by the use of ipamorelin-related bulk drug substances, considering higher rates of hypokalemia, hyperglycemia and two deaths in ipamorelin (unspecified form) treated subjects. Although it is unclear whether the deaths reported in the above study were related to ipamorelin, their occurrence in ipamorelin-treated subjects raises safety concerns about the use of ipamorelin in compounding. The lack of data discussed above, safety issues raised by use of ipamorelin-related bulk drug substances, lack of evidence of effectiveness, and the existence of FDA-approved drugs to treat GHD and POI, particularly in light of these being serious conditions, weigh against ipamorelin-related bulk drug substance being added to the 503A Bulks List. Accordingly, we propose not adding ipamorelin acetate or ipamorelin (free base) to the 503A Bulks List.

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Ipamorelin-Related Bulk Drug Substances (Ipamorelin (free base) and Ipamorelin acetate) Nominations

International Peptide Society Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Ipamorelin
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-Aib-His-D-2Nal-D-Phe-Lys-NH2
Common Name(s)	Ipamorelin Acetate, 170851-70-4, NNC-260161
UNII Code	Y9M3S784Z6
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of Attix Pharmacueticals Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	No
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Subcutaneous Injectable
Compounded Strengths	2,000 mcg/ml
Anticipated Routes of Administration	Subcutaneous Injection
Saftey & Efficacy Data	Ankersen, Michael., et al. "Growth Hormone Secretagogues: Recent Advances and Applications." Therapeutic Focus, vol. 4, no. 11, 11 Nov. 1999, pp. 497–506.
	Dieguez, Carlos. "Ghrelin: A Step Forward In the Understanding of Somatotroph Cell Function and Growth Regulation ." *European Journal of Endocrinology* , no. 142, June 2000, pp. 413–417., doi:10.1530/eje.0.1420413.
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	Moulin, Aline., et al. "Recent Developments in Ghrelin Receptor Ligands." ChemMedChem, vol. 2, 2007, pp. 1242–1259., doi:10.1002/cmdc.200700015.
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	Pietra, Claudio., et al. "Preclinical Pharmacological Profile of Ipamorelin a Novel Gastroprokinetic for Intestinal Dysmotility ."*AGA Abstracts. Sal340* .
	Beck, David E., et al. "Prospective, Randomized, Controlled, Proff-of-Concept Study of the Ghrelin Mimetic Ipamorelin for the Management of Postoperative Ileus in Bowel Resection Patients ." *Int J Colorectal Dis* , vol. 29, 2014, pp. 1527–1534., doi:10.1007/s00384-014-2030-8.
	Raun, Kristen., et al. "Ipamorelin, The FIrst Selective Growth Hormone Secretagogue." *European Journal of Endocrinology* , vol. 139, 1998, pp. 552–561.
Used Previously to compound drug products	Yes
Proposed use	Growth Hormone Deficiency
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Added as an attachment

Attix Pharmaceuticals

APPROVED 1/12/18

Certificate of Analysis

Ipamorelin Acetate

Product Name : Ipamorelin Acetate
Batch No. : A3902A
M.W. : 711.85
Molecular Formula: $C_{38}H_{49}N_9O_5$
Mfg. Date : Jan 01, 2017
Exp. Date : Dec 30, 2019
CAS Number : 170851-70-4
Batch Qty : 19 g
Sequence : Aib-His-D-2-Nal-D-Phe-Lys-NH_2

TESTS (Method Reference)	SPECIFICATIONS	RESULTS
Appearance (CP-IP)	White or slightly yellowish powder	White powder
Mass Identity (CP-IP)	Monoisotopic mass 711.85 ± 1.0	711.4
Peptide Purity (By HPLC) (CP-IP)	≥ 95.0% by area integration	99.67%
Water Content (Karl Fisher) (CP-IP)	≤ 5.0%	2.5%
Conclusion: The product meets the specifications. Long Term Storage: Store in tight vials and in freezer.		

Note: Analytical results transcribed from the original COA provided by Chengdu Kaide Biopharm Co., Ltd. No.137, Jiaodongjiao, Dayi County, Chengdu, Sichuan, China. Lot Number: 20170101 COA available on Request.

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

	Name	Title	Signature	Date
Prepared by	James Mikos	Operations Coordinator		Jan 5/18
Approved by	Pak Hin Law	QA/QC Assistant		Jan 5/18

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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?	Ipamorelin Acetate
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?	• Amino Acid Sequence: • H-Aib-His-D-2-Nal-D-Phe-Lys-NH2 • IUPAC Name: • (2S)-6-amino-2-[(2R)-2-[(2R)-2-[(2S)-2-(2-amino-2-methylpropanamido)-3-(1H-imidazol-4-yl)propanamido]-3-(naphthalen-2-yl)propanamido]-3-phenylpropanamido]hexanamide
What is the common name of the substance?	• Ipamorelin Acetate • CAS#: 170851-70-4 • NNC-260161
Does the substance have a UNII code?	Y9M3S784Z6
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?	NO
Has information been submitted about the substance to the USP for consideration of drug monograph development?	YES
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	2,000 mcg/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?	Gobburu, J.V.S., Agersø, H., Jusko, W.J. et al. Pharmacokinetic-Pharmacodynamic Modeling of Ipamorelin, a Growth Hormone Releasing Peptide, in Human Volunteers. *Pharm Res* 16, 1412–1416 (1999). https://doi.org/10.1023/A:1018955126402 C. Y. BOWERS, G. A. REYNOLDS, D. DURHAM, C. M. BARRERA, S. S. PEZZOLI, M. O. THORNER, F. FORLONI, A. PINCHERA, G. FAGLIA, Growth Hormone (GH)-Releasing Peptide Stimulates GH Release in Normal Men and Acts Synergistically with GH-Releasing Hormone, *The Journal of Clinical Endocrinology & Metabolism*, Volume 70, Issue 4, 1 April 1990, Pages 975–982, https://doi.org/10.1210/jcem-70-4-975 P. B. JOHANSEN Pharmacokinetic evaluation of ipamorelin and other peptidyl growth hormone secretagogues with emphasis on nasal absorption Xenobiotica, vol. 28, no. 11, Dec. 1998, 1083-1092 | Published online: 22 Sep 2008 Raun, Kristen., et al. "Ipamorelin, The First Selective Growth Hormone Secretagogue." European Journal of Endocrinology , vol. 139, 1998, pp. 552–561 Beck, D.E., Sweeney, W.B., McCarter, M.D. et al. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. *Int J Colorectal Dis* 29, 1527–1534 (2014). https://doi.org/10.1007/s00384-014-2030-8 Ankersen M, et al. "Growth Hormone Secretagogues: Recent Advances and Applications." Therapeutic Focus, 4(11); 11 Nov. 1999:497–506.

	Dieguez C, Casanueva F. "Ghrelin: A Step Forward In the Understanding of Somatotroph Cell Function and Growth Regulation" *European Journal of Endocrinology*. No.142; June 2000:413–417. doi:10.1530/eje.0.1420413. Khatib N, Gaidhane S, Gaidhane AM, et al. Ghrelin: ghrelin as a regulatory Peptide in growth hormone secretion. *J Clin Diagn Res*. 2014;8(8):MC13-MC17. doi:10.7860/JCDR/2014/9863.4767 Hansen T, Ankersen M, Raun K, Hansen B. Highly potent growth hormone secretagogues: Hybrids of NN703 and ipamorelin, *Bioorganic & Medicinal Chemistry Letters*, 11(14); 2001:1915-1918. ISSN 0960-894X https://doi.org/10.1016/S0960-894X(01)00345-6.
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?	**Growth Hormone Deficiency**
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 Attachments**

Certificate of Analysis

Ipamorelin Acetate

Product Name	: Ipamorelin Acetate		**Lot No.**	: DL5453	
Mfg. Date	: Dec 06, 2019		**Exp. Date**	: Dec 05, 2022	
M.F.	: $C_{38}H_{49}N_9O_5$		**M.W.**	: 711.85	
CAS No.	: 170851-70-4		**Batch Qty**	: 755 g	
Sequence	: Aib-His-D-2-Nal-D-Phe-Lys-NH_2				

TESTS	SPECIFICATIONS	RESULTS
Appearance	White to off-white powder	White powder
Identification	711.85 ± 1	711.62
Solubility	Soluble in water or 1% acetic acid at a concentration of ≥ 1mg/ml to give a clear, colorless solution	Conforms
Water Content (KF)	≤ 5.0%	2.0%
Acetate Content	≤ 20.0%	12.6%
Peptide Purity (HPLC)	≥ 95.0%	99.72%
Assay (anhydrous , acetic acid free substance)	95.0 - 105.0%	99.6%
Conclusion: The product is a synthetic peptide and meets the specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a fridge or freezer. Distributed by Danmerica.		

99.6% x 98% x 87.4%
= 85.31% ∴ 10/6/20

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

	Name	Title	Signature	Date
Prepared by	Seka Nadima	Quality Assistant	Seka Nadima	08/25/2020
Released by	Sai Rasane	Quality Assistant		08/26/2020