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)?	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?	Chemical structure is: H-Aib-His-D-2Nal-D-Phe-Lys-NH2 x.CH3COOH[1]
What is the common name of the substance?	Ipamorelin acetate
Does the substance have a UNII Code?	Not available
What is the chemical grade of the substance?	Mass Spectrometry and UV purity > 99%[2]
What is the strength, quality, stability and purity of the substance?	Certificate of analysis includes mass spectrometry and UV[3]
How is the ingredient supplied?	Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No, but a related substance, Pralmorelin, is approved in Japan.
Has information been submitted about the substance to the USP for consideration of monograph development?	YES per FDA Briefing Document, PCAC Meeting, October 29, 2024, Ipamorelin-related bulk drug substances.
What dosage form(s) will be compounded using the bulk drug substance?	Tablet, capsule, troche, ODT injection
What strength(s) will be compounded from the nominated substance?	Dependent upon prescription but common strengths range from 300mcg to 2mg.
What are the anticipated route(s) of administration of the compounded drug product(s)?	Oral, IM, SQ
Are there safety and efficacy data on compounded drugs using the nominated substance?	YES, see supplemental material listed below. See attachment on number of the number of prescriptions dispensed from 9 compounding pharmacies and the lack of adverse events.
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, Non Alcoholic Fatty Liver Disease, Obesity, Sarcopenia

[1] FDA Briefing Document, PCAC Meeting, October 29, 2024, Ipamorelin-related bulk drug substances.
[2] Id.
[3] Id.

What is the reason for use of a compounded drug product rather than an FDA-approved product?	There is no FDA approved product containing the bulk drug substance
Is there any other relevant information?	YES, see supplemental material listed below.

Supplemental publications on the bulk drug substance:

Preclinical

1) Aagaard, Niels Kristian, et al. Growth hormone and growth hormone secretagogue effects on nitrogen balance and urea synthesis in steroid treated rats. Growth Horm IGF Res. 2009 Oct;19(5):426-31.

> Design: Five groups of rats were included: (1) free-fed controls (2) pair-fed controls (3) prednisolone (delcortol, 4 mg x kg(-1) x day(-1)) (4) prednisolone and GH (1 mg x kg(-1) x day(-1)) (5) prednisolone and Ipamorelin (0.5 mg x kg(-1) x day(-1)). After seven days the hepatic capacity of urea-N synthesis (CUNS) was determined in parallel with measurements of liver mRNA levels of urea cycle enzymes, whole-body N-balance, and N-contents of various organs.
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> Outcome: Accelerated nitrogen wasting in the liver and other organs caused by prednisolone treatment was counteracted by treatment with either GH or its secretagogue Ipamorelin

2) Pietra, Claudio et al. Preclinical Pharmacological Profile of Ipamorelin a Novel Gastroprokinetic for Intestinal Dysmotility. May 2011 Gastroenterology 140(5).

> Outcome: The preclinical data demonstrate that IPA is a potent ghrelin agonist with efficacy in a pivotal experimental model of POI. The pharmacological profile of IPA supports the current evaluation of the compound in the clinical development for POI.

3) Raun, Kirsten et al. Ipamorelin, the first selective growth hormone secretagogue. Eur J Endocrinol. 1998 Nov;139(5):552-61

> Authors report on Ipamorelin in several different animals and conclude that ipamorelin is the first GHRP-receptor agonist with a selectivity for GH release similar to that displayed by GHRH. The specificity of ipamorelin makes this compound a very interesting candidate for future clinical development.

4) Jiménez-Reina, L et al. Influence of chronic treatment with the growth hormone secretagogue Ipamorelin, in young female rats: somatotroph response in vitro. Histol Histopathol. 2002;17(3):707-14.

> In order to determine the effects of chronic treatment with the GHS Ipamorelin on the composition of the somatotroph cell population and on somatotroph GH content, an in vitro analysis was performed of the percentage of somatotroph cells (% of total), the ratio of different GH cell types (strongly/weakly-staining) and individual GH content, in pituitary cell cultures obtained from young female rats receiving Ipamorelin over 21 days (Ipamorelin group) and the effects were compared with those of GHRH (GHRH group) or saline (saline group). Outcome: These data suggest that, at least in the young female rat, the GHS Ipamorelin is able to exert a dynamic control effect on the somatotroph population and on GH hormone content.

5) Venkova, Kalina et al. Efficacy of ipamorelin, a novel ghrelin mimetic, in a rodent model of postoperative ileus. J Pharmacol Exp Ther. 2009 Jun;329(3):1110-6.

> The present study investigates whether ipamorelin, a selective growth hormone secretagogue and agonist of the ghrelin receptor, would accelerate gastrointestinal transit and ameliorate the symptoms in a rodent model of postoperative ileus (POI).
>
> Conclusion: In conclusion, our study suggests that post-operative treatment with ipamorelin administered via multiple i.v. bolus infusions over a period of 48 h may be useful in the clinic to overcome the symptoms and accelerate the recovery in patients with POI.

Clinical

6) Beck, David E. 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. 2014 Dec;29(12):1527-34.

> This proof-of-concept, phase 2, randomized study evaluated the safety and efficacy of the ghrelin-receptor agonist ipamorelin in the treatment of postoperative ileus following abdominal surgery (ClinicalTrials.gov NCT00672074). The design was a multicenter, double-blind, placebo-controlled, clinical trial of hospitalized patients.
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> Outcome: Overall incidence of any treatment-emergent adverse events was 87.5 % in the ipamorelin group and 94.8 % in placebo group. Median time to first tolerated meal was 25.3 and 32.6 h in the ipamorelin and placebo groups, respectively (p=0.15). Limitations: This proof of concept study was small and enrolled patients with a broad range of underlying conditions. Conclusions: Ipamorelin 0.03-mg/kg twice daily for up to 7 days was well tolerated. There were no significant differences between ipamorelin and placebo in the key and secondary efficacy analyses.

7) Gobburu, Jogarao et al. Pharmacokinetic-Pharmacodynamic Modeling of Ipamorelin, a Growth Hormone Releasing Peptide, in Human Volunteers. Pharm Res. 1999 Sep;16(9):1412-6. doi: 10

> Purpose: To examine the pharmacokinetics (PK) and pharmacodynamics (PD) of ipamorelin, a growth hormone (GH) releasing peptide, in healthy volunteers.
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> Methods: A trial was conducted with a dose escalation design comprising 5 different infusion rates (4.21, 14.02, 42.13, 84.27 and 140.45 nmol/kg over 15 minutes) with eight healthy male subjects at each dose level. Concentrations of ipamorelin and growth hormone were measured.
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> Outcome: The proposed PK/PD model provides a useful characterization of ipamorelin disposition and GH responses across a range of doses.

Reviews

8) Ankerson, Michael et al. Growth hormone secretagogues: recent advances and applications. Drug Discov Today. 1999 Nov;4(11):497-506

The discovery of a new class of compounds that stimulate the release of growth hormone (GH) in a manner distinctly different from growth hormone-releasing hormone (GHRH) is advancing the understanding of the mechanisms that control GH secretion.

Conclusion: Several potential indications have been explored clinically and, as some of these compounds are orally active, they could offer attractive alternatives to recombinant human growth hormone (hGH) in treating GH disorders such as growth hormone deficiency (GHD),age-related conditions, obesity and catabolic conditions.

9) Dieguez, Carlos et al. Ghrelin: a step forward in the understanding of somatotroph cell function and growth regulation. Eur J Endocrinol. 2000 May;142(5):413-7.

Conclusion: In summary, the isolation of ghrelin can be considered a landmark in the GH field which opens up the possibility of gaining a greater insight into our understanding of the mechanisms involved in the regulation of GH secretion and somatic growth. The challenge now is to use the greater insight in knowledge that this discovery brings to improve the diagnosis and treatment of different disease states associated with altered GH secretion.

10) Khatib, Nazli et al. Ghrelin: Ghrelin as a Regulatory Peptide in Growth Hormone Secretion. J Clin Diagn Res. 2014 Aug;8(8):MC13-7

Background: Ghrelin is a type of growth hormone (GH) secretagogue that stimulates the release of GH. It is a first hormone linking gastrointestinal-pituitary axis.

Objective: This review highlights the interaction of ghrelin with GHRH and somatostatin to regulate the secretion of GH and intends to explore the possible physiological role of the ghrelin-pituitary-GH axis linkage system.

Conclusion: Studies suggests that ghrelin is a powerful pharmacological agent that exerts a potent, time-dependent stimulation of pulsatile secretion of GH.

11) Moulin, Aline, et al. Recent Developments in Ghrelin Receptor Ligands. ChemMedChem. 2007 Sep;2(9):1242-59.

The 28-amino acid peptide ghrelin is a neuroendocrine hormone synthesized primarily in the stomach. It stimulates growth hormone secretion and appetite, thus promoting food intake and body-weight gain. The pharmacological properties of this peptide are mediated by the growth hormone secretagogue receptor type 1a (GHS-R1a).

Conclusion: The discovery of new agents that either mimic or modulate the actions of ghrelin via GHS-R1a has attracted considerable interest in recent years. Because endogenous ghrelin appears to play an important role in the long-term regulation of energy balance, GHS-R1a antagonists may be useful in the prevention of weight gain.

12) Sinha, Deepankar, et al. Beyond the androgen receptor: the role of growth hormone secretagogues in the modern management of body composition in hypogonadal males. Transl Androl Urol. 2020 Mar;9(Suppl 2):S149-S159.

Although testosterone remains the gold standard for hypogonadism management, its benefits are not always conserved across different populations, especially with regards to changes in body composition. Partially in response to this, growth hormone secretagogues (GHS) have emerged as a potential novel adjunctive therapy for some of the symptoms of hypogonadism, although current data on their clinical efficacy largely remain lacking. The present review examines the existing literature on the use of GHS and explores their potential complementary role in the management of hypogonadal and eugonadal males with metabolic syndrome or subclinical hypogonadism (SH).

Conclusion: The above literature therefore draws attention to ipamorelin as a potent and selective stimulator of GH that can significantly influence the GI system, body composition, and adiposity. Adverse effects associated with treatment were rare and similar to those reported with sermorelin.

13) Ma, Ingrid et al. Growth hormone and nonalcoholic fatty liver disease. Immunometabolism (Cobham). 2023 Jul 27;5(3).

Nonalcoholic fatty liver disease (NAFLD) is a prevalent cause of liver disease and metabolic comorbidities. Obesity is strongly associated with NAFLD and is also a state of relative deficiency of growth hormone (GH). Evidence supports a role of reduced GH and insulin-like growth factor-1 (IGF-1) in NAFLD pathogenesis.

Conclusion: Taken together, evidence supports an important role for perturbations in the GH/IGF-1 axis as one of the pathogenic mechanisms of NAFLD and suggests that further study is needed to assess whether augmentation of GH and/or IGF-1 may be a safe and effective therapeutic strategy for NAFLD.

14) Ishida, Junichi et al. Growth hormone secretagogues: history, mechanism of action, and clinical development. CSM Rapid Communications 2020; 3: 25–37

Growth hormone secretagogues (GHSs) are a generic term to describe compounds that increase growth hormone (GH) release. GHSs include agonists of the growth hormone secretagogue receptor (GHS-R), whose natural ligand is ghrelin, and agonists of the growth hormone-releasing hormone (GHRH) receptor, to which the GHRH binds as a native ligand. Several GHSs have been developed with a view to treating or diagnosing of GH deficiency, which causes growth retardation, gastrointestinal dysfunction, and altered body composition, in parallel with extensive research to identify GHRH, GHS-R, and ghrelin. This review focuses on the research history and the pharmacology of each GHS, which reached randomized clinical trials. Furthermore, authors highlight the publicly disclosed clinical trials regarding GHSs.

15) Pennisi, Patricia et al. Role of Growth Hormone in Liver Regeneration. Endocrinology. 2004 Oct;145(10):4748-55.

Liver regeneration is a fundamental mechanism by which the liver responds to injury. This process is regulated by endogenous growth factors and cytokines, and it involves proliferation of all mature cells that exist within the intact organ.

Conclusion: These results suggest that GH plays a critical role in liver regeneration, although whether it acts directly or indirectly remains to be determined.