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.

Ibutamoren Mesylate

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FDA Evaluation of Ibutamoren Mesylate

U.S. FOOD & DRUG ADMINISTRATION

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Ibutamoren Mesylate for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Ibutamoren mesylate was nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1,2] Ibutamoren mesylate was evaluated for the following uses: treatment of growth hormone deficiency (GHD), osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease (AD).[3,4,5]

This evaluation pertains to ibutamoren mesylate, also known as MK-677, MK-0677, MK0677, and LUM-201; these terms will be used interchangeably throughout this evaluation consistent with the term used in each reference.

Ibutamoren mesylate products proposed in the nominations are capsules or tablets for oral administration in 10 mg and 25 mg dosage strengths (for purposes of this evaluation, the route of administration of ibutamoren mesylate is oral unless otherwise noted).

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for ibutamoren mesylate,[6] and ibutamoren mesylate is not a component of an FDA-approved drug.[7]

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[1] Nominations evaluated in this memo include: Nomination from Wells Pharmacy Network (Wells) (Document ID: FDA-2015-N-3534-0299) can be accessed at https://www.regulations.gov/document/FDA-2015-N-3534-0299, and Nomination from LDT Health Solutions, Inc. (LDT) on behalf of International Peptide Society (IPS) (Document ID: FDA-2018-N-2973-0002) can be accessed at https://www.regulations.gov/document/FDA-2018-N-2973-0002. In response to FDA's letter requesting clarification regarding uses proposed in the nomination, Wells provided clarification and amended its nominated uses. The updated nomination from Wells (Document ID FDA-2015-N-3534-0307) can be accessed at https://www.regulations.gov/document/FDA-2015-N-3534-0307.

[2] Of note, the LDT nomination page is labeled "Ibutamorelin." In addition, the nomination lists the unique ingredient identifier (UNII) code GJ0EGN38UL, which corresponds to "ibutamoren" (See: FDA's Global Substance Registration System, accessed 10/03/2023, https://precision.fda.gov/uniisearch/srs/unii/GJ0EGN38UL.) However, the nominated ingredient name and certificate of analysis (COA) state "ibutamoren mesylate." Therefore, we consider ibutamoren mesylate as the bulk drug substance nominated. All conclusions that are drawn in this evaluation pertain to the substance ibutamoren mesylate. FDA sent a letter to LDT to clarify whether the proposed use "growth hormone deficiency" was the only medical condition the nominator proposed to treat with ibutamoren mesylate; however, no response was received from the nominator.

[3] Ibutamoren mesylate was nominated for the uses "Increased GH [growth hormone] in deficient adults" (Wells original nomination) and "Growth Hormone Deficiency" (LDT). The updated nomination from Wells included the proposed uses "Treatment of conditions such as hip fracture, sarcopenia, osteoporosis, Alzheimer's disease, obesity, and fibromyalgia as a result of GH deficiency in healthy adults." LDT did not respond to a letter sent by FDA to clarify the uses in its nomination.

[4] Ibutamoren mesylate was also nominated by Wells for use in the treatment of fibromyalgia. However, FDA did not evaluate this proposed use because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for this use in compounded drug products. The nomination cited a study protocol from ClinicalTrials.gov which had no results posted (no safety or efficacy data available), and FDA did not identify safety or effectiveness data of ibutamoren mesylate for use in the treatment of fibromyalgia as a result of GH deficiency in a search of the medical literature. See 80 FR 65765 for information necessary to fully evaluate a substance.

[5] We have explained that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance, though we acknowledge that inclusion of a substance on the 503A Bulks List may not be limited to a specific use. See 84 FR 4696, 4701.

[6] USP-NF website, accessed 10/03/2023, https://www.uspnf.com/ (subscription required).

[7] FDA Orange Book, accessed 10/03/2023, https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

We have evaluated publicly available data on the physicochemical characteristics, historical use, effectiveness, and safety in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing ibutamoren mesylate 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).

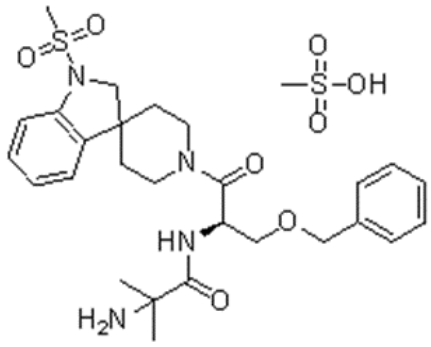
II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically?[8]

We reviewed physical and chemical characterization related information provided by the nominators. Databases including SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP/NF were also searched for information on ibutamoren mesylate. The information below summarizes what FDA found in these databases.

Ibutamoren mesylate is a small chiral molecule containing serine and a non-proteinogenic amino acid, 2-aminoisobutyric acid (Aib), as a substructure. The molecular formula of ibutamoren mesylate is $C_{27}H_{36}N_4O_5S.CH_4O_3S$ and its molecular weight is 624.769 Dalton. The chemical structure of ibutamoren mesylate is shown below. Ibutamoren mesylate is commercially available.[9]

Figure 1. Chemical Structure of Ibutamoren Mesylate[10].



[8] 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).

[9] See, e.g., https://www.caymanchem.com/product/18003/ibutamoren-(mesylate). Accessed February 12, 2024; https://www.tocris.com/products/mk-0677_5272. Accessed February 12, 2024.

[10] https://pubchem.ncbi.nlm.nih.gov/compound/Ibutamoren-Mesylate. Accessed April 26, 2024.

The certificate(s) of analysis (CoAs) provided by both nominators include ID tests (^{1}HNMR and LC-MS per standard) and a purity test by HPLC with the purity limit ≥ 99.00% (testing results of 99.36% and 99.60, respectively). However, neither CoA included tests for chiral purity (% enantiomeric excess), drug substance related impurities, or residual solvents, which normally included quality attributes for this compound. As discussed below, this information can be used to determine whether any impurities related to the synthesis of ibutamoren mesylate are present in the final product.

1. *Stability of the active pharmaceutical ingredient (API) and likely dosage forms*

The CoAs provided by the nominators state that ibutamoren mesylate should be stored either at room temperature (Wells) or at 2-8°C (LDT). However, neither CoA mentioned how long ibutamoren mesylate can be stable under the respective storage conditions. We conducted a literature search but could not find stability data or degradation related information for ibutamoren mesylate when stored at room temperature or at 2-8°C. Therefore, we provide the following information retrieved in our search of the literature on the stability with shelf-life data for ibutamoren mesylate.

It is recommended that ibutamoren mesylate be stored in a tightly closed container in a dry and well-ventilated place.[11] It is stable at -20°C for 4 years in powder form.[12]

2. *Probable routes of API synthesis*

Merck Research Laboratories reported the synthesis of ibutamoren mesylate as described below (Maligres et al. 1997).

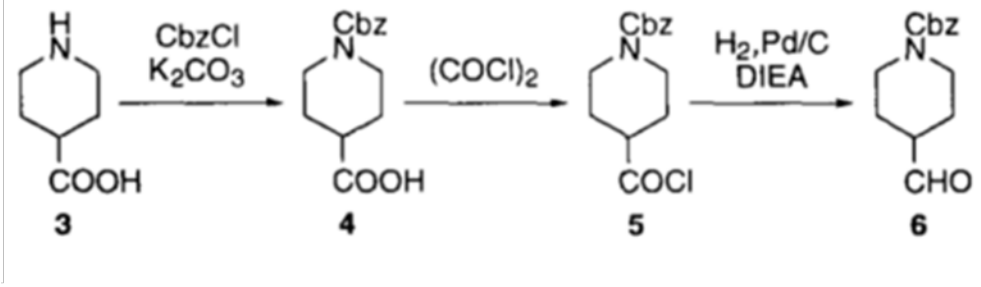
Scheme 1 demonstrates how to obtain aldehyde-6 from commercially available isonipecotic acid 3 by N-protection, conversion of the acid 4 to the acid chloride 5 and Rosenmund type reduction of 5 to 6.

Through the optimized Fischer indole process as shown in scheme 2, spiroindoline-9 can be obtained from aldehyde-6 with 93% overall yield. Then, sulfonamidation of 9 gives sulfonamide-10, which after hydrogenolysis produces deprotected piperidine-11 in 93% yield. Deprotected spiroindoline-11 followed by the treatment with methyl sulfonic acid (MsOH) in ethanol (EtOH) gives 13 in 92% yield. The second coupling with 16 was followed by Boc-deprotection to give MK-677 in 82% yield. Crystallization of crude MK-677 as the MsOH salt from ethyl acetate-EtOH gives the pure drug substance in 74% overall yield from 10. The structure of MK-677 was elucidated via ^{1}HNMR, ^{13}CNMR, FTIR, HRMS, and elemental analyses.

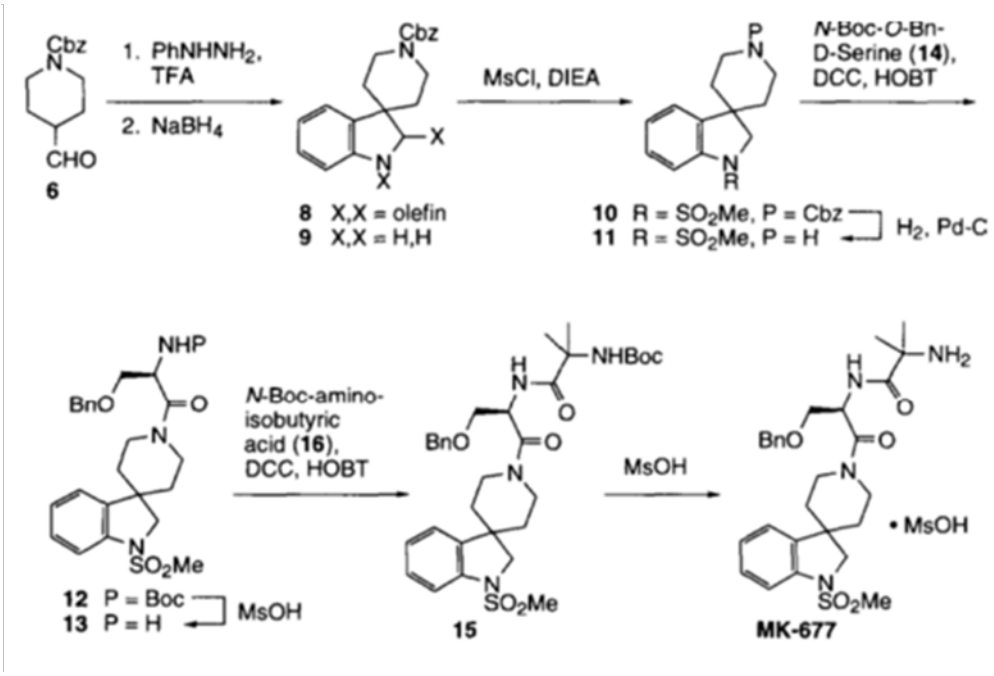
[11] See https://www.apexbt.com/downloader/document/A3481/MSDS.pdf. Accessed February 12, 2024.
[12] See https://cdn.caymanchem.com/cdn/insert/18003.pdf . Accessed July 03, 2024.

Figure 2. The Synthetic Route of Ibutamoren Mesylate (Maligres et al. 1997).

Scheme 1.



Scheme 2.



3. Likely impurities[13]

The likely impurity profile of ibutamoren mesylate would be specific to and determined by the synthetic route used, which means that different synthetic routes used to produce ibutamoren mesylate would result in different impurity profiles. The most likely impurities from the above-mentioned synthetic route (Fig. 2) would be the unreacted starting materials, intermediates, as

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

well as reagents or residual solvents, especially methanesulfonate related impurities, such as ethyl methanesulfonate (a chemical mutagen), which may be formed from methanesulfonic acid used in the final synthetic step.

Because none of the CoAs include any tests, limits, or results for impurities, it is impossible to know the nature and level of individual and total impurities in the nominated bulk drug substance.

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

Ibutamoren mesylate is a white to off-white powder. Its melting point is 158-160°C. The solubility of ibutamoren mesylate in water (H_2O) and ethanol (EtOH) is 92 mg/mL.[14] Because the API is soluble in H_2O and EtOH, particle size and polymorphism are not considered critical quality attributes that affect performance for the proposed dosage forms (tablet and capsule).

5. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

FDA did not identify additional relevant information regarding the physical and chemical characterization of ibutamoren mesylate.

Conclusions: In summary, ibutamoren mesylate is a small chiral molecule containing serine and 2-aminoisobutyric acid (non-proteinogenic amino acid) as a substructure. As reported in the literature, it is stable at -20°C for 3 years in powder form.

In the CoAs provided by both nominators, there is no information about the chiral purity (% enantiomeric excess), drug substance related impurities, or residual solvents, which are considered critical quality attributes for the quality control of ibutamoren mesylate, which is a chiral molecule. Ibutamoren mesylate is not well characterized from a physical and chemical perspective because certain critical characterization data relating to identity, purity, and impurity profiles, specific to the bulk drug substance were neither found in the publicly available scientific literature nor were they provided in the CoAs or USP.

B. Has the substance been used historically in compounding?

This evaluation focuses on ibutamoren mesylate for the oral route of administration and its use in GHD, osteoporosis, hip fracture, sarcopenia, obesity, and AD; however, FDA searched generally for information on the historical use of ibutamoren mesylate in compounding. Databases searched for information on ibutamoren mesylate for this evaluation included PubMed, Embase,

[14] See https://www.mybiosource.com/inhibitor/ibutamoren-mesylate-mk-677/385144 . Accessed July 03, 2024.

Google, Natural Medicines Database, and the Outsourcing Facility Product Reporting Database.[15]

FDA also considered the report provided by the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI).[16]

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

The nominators stated that ibutamoren mesylate has been used to compound drug products but did not provide any additional information regarding the historical use of ibutamoren mesylate in compounding.

Literature shows that, the extent to which ibutamoren mesylate has been used in compounding is unclear. Ibutamoren mesylate was first synthesized in 1995 by researchers at Merck in an attempt to identify an orally active growth hormone secretagogue (GHS) (Patchett et al. 1995). Ibutamoren mesylate was selected for further research (Patchett et al. 1995; Sorbera et al. 2006); however, development was discontinued in 1999 (M-CERSI 2021; Carpino 1999).

The systematic literature review section of the M-CERSI report included several studies dating back to 1996 describing the use of ibutamoren mesylate; however, none of the products used were compounded drug products.[17] Since the publication of the M-CERSI report, six additional studies were identified that discussed the use of ibutamoren mesylate; however, none of the products used were compounded drug products.[18]

Based on information in the Outsourcing Facility Product Report database, one outsourcing facility reported compounding ibutamoren mesylate as a 25 mg capsule in 2019 and 2020.[19, 20]

2. *The medical conditions it has been used to treat*

Due to the potential effect on growth hormone (GH), ibutamoren mesylate has been studied for use in several conditions; however, none of the studies appear to have utilized a compounded formulation.

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[15] Available at https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm.
[16] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 6/5/2023.
[17] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 6/5/2023.
[18] Bright et al. 2021; Bright and Thorner 2022; Cardaci et al. 2022; Cassorla et al. 2023; Svensson et al. 2003; Tatem et al. 2019.
[19] Available at https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm. Accessed 6/8/2023.
[20] 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.

Ibutamoren mesylate has been studied in adults with childhood onset idiopathic GHD (Chapman et al. 1997) and in children with GHD (Codner et al. 2001; Bright et al. 2021; Bright and Thorner 2022; Cassorla et al. 2023). Ibutamoren mesylate has also been studied in healthy adults to determine the drug's impact on GH and insulin-like growth factor 1 (IGF-1) and whether it would prevent the age-related decline in fat-free mass, and decrease abdominal visceral fat (Nass et al. 2008); to determine its impact on body composition in men (McBride et al. 2018; Cardaci et al. 2022); to determine whether it could reverse the catabolic response to dietary energy restriction (Murphy et al. 1998); and to assess its effect on sleep quality (Copinschi et al. 1997). Ibutamoren mesylate has also been studied in obese males to determine its impact on serum lipoproteins, serum leptin, thyroid hormones, testosterone, and body composition (Svensson et al. 1998b; Svensson et al. 1999a; Svensson et al. 1999b) and in patients who had recently undergone a unilateral hip fracture with non-complicated surgical repair to determine the change in objective functional performance measurements (Adunsky et al. 2011; Bach et al. 2005). Additionally, ibutamoren mesylate has been studied in healthy elderly subjects, obese subjects, elderly patients who met objective criteria for musculoskeletal impairment, and in women with postmenopausal osteoporosis to determine the drug's effect on bone formation, bone resorption, and bone mineral density (BMD) (Murphy et al. 1999; Murphy et al. 2001; Svensson et al. 1998a). Finally, ibutamoren mesylate has been studied in patients with mild to moderate AD to determine the impact on slowing the rate of progression of AD-related symptoms (Sevigny et al. 2008), and in patients with end-stage renal disease to determine the impact on IGF-1 levels (Campbell et al. 2018).

Ibutamoren mesylate is currently being studied for the treatment of pediatric GHD and non-alcoholic fatty liver disease.[21]

According to one subject matter expert (SME) interviewed by M-CERSI, GHSs are often elective "patient demand-based medicine" for use as "lifestyle medications" to improve the appearance of their skin, hair, or body.[22] The SME stated that GHSs can be used alone but that they are often used with other hormone replacement therapies, typically testosterone. Another SME interviewed by M-CERSI stated that children with mild GHD "grow equally well on ibutamoren as they do on [recombinant human] growth hormone" and ibutamoren mesylate has the added advantage of being an oral tablet instead of an injection.[23] The SMEs interviewed by M-CERSI differed in their views on whether ibutamoren mesylate was currently available in compounded drugs.[24]

Ibutamoren mesylate is also marketed online to reverse the aging process and as a selective androgen receptor modulator (SARM) for use as a supplement in bodybuilding and

[21] See https://lumos-pharma.com/our-pipeline/. Accessed 6/5/2023.
[22] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 6/5/2023.
[23] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 6/5/2023.
[24] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 6/5/2023.

weightlifting.[25] Potential benefits listed in this marketing include increasing and strengthening muscle mass, reducing body fat, increasing bone density, preventing muscle loss/wasting, sports performance stimulation (e.g., increasing physical endurance and strength, increasing energy reserves and improving training performance), enhancement of body volume, reversal of nitrogen waste, improving skin health, enhancing cognitive function, improving sleep quality, treating GHD, helping wounds and injuries heal faster, repairing nerve damage, increasing metabolism, and increasing libido.[26]

3. *How widespread its use has been*

Through a Google search, several websites were found that market ibutamoren mesylate products, including 10, 12.5, 20, and 25 mg capsules; 20 mg tablets; 64 mg/mL injection; 1 g powder; and 17, 25, 33, and 67 mg/mL liquid.[27] Some websites advertise that they obtain ibutamoren mesylate from a compounding pharmacy; however, it is not clear whether compounded ibutamoren mesylate products are currently being sold.[28] Some websites that market ibutamoren mesylate state that the product is intended for research purposes only.[29]

One outsourcing facility reported compounding ibutamoren mesylate as a 25 mg capsule in 2019 and 2020.[30]

As discussed previously, ibutamoren mesylate is marketed online to reverse the aging process and as a supplement for use in bodybuilding and weightlifting, and several websites were identified where ibutamoren mesylate could be purchased. Ibutamoren mesylate has also been identified in products sold online that are marketed as SARMs (Van Wagoner et al. 2017; Kim et al. 2022). While ibutamoren mesylate is not a SARM, several online websites incorrectly classify ibutamoren mesylate as a SARM. SARMs have gained popularity for use as performance-

[25] It should be noted that ibutamoren mesylate is a GHS, not a SARM. SARMs are a class of therapeutic compounds that selectively bind androgen receptors in certain tissues and may have similar anabolic properties to anabolic steroids (See: Selective Androgen Receptor Modulators (SARMs) – What Athletes Need to Know. U.S. Anti-Doping Agency (USADA) website, accessed 10/30/2023, https://www.usada.org/spirit-of-sport/education/selective-androgen-receptor-modulators-sarms-prohibited-class-anabolic-agents/).

[26] See, e.g., https://www.ndtv.com/partner-content/health-supplements/ibutamoren-mk-677-review-2023-know-side-effects-risks-dosage-and-more-3918929, https://www.mensjournal.com/health-fitness/mk-677-ibutamoren-results-i-tried-it-for-6-weeks-does-it-work, and https://www.outlookindia.com/outlook-spotlight/ibutamoren-mk-677-sarm-risks-side-effects-results-alternatives-news-215682. Accessed 6/8/2023.

[27] See, e.g., , https://sportstechnologylabs.com/product/mk-677-ibutamoren-25mg-ml/, https://purerawz.co/product/ibutamoren-mk-677/, , https://rwacenter.com/product/mk-677-ibutamoren/, https://mobilecarehealth.shop/product/product-100/, https://telewellnessmd.com/product-search/product/74, and https://www.chemyo.com/mk677/. Administration instructions were not provided. Accessed 4/24/2024.

[28] See, e.g., https://telewellnessmd.com/product-search/product/74, https://rhsupplements.com/mk677, https://evolvetelemed.com/growth-hormones/ibutamoren-mk-677/, https://www.hormonetreatmentcenters.com/growth-hormone-mk-677/, and https://mobilecarehealth.shop/product/product-100/. Accessed 4/24/2024.

[29] See, e.g., https://www.peptidesciences.com/mk-677-ibutamoren-60-capsules, https://sportstechnologylabs.com/product/mk-677-ibutamoren-25mg-ml/, https://www.chemyo.com/mk677/, and https://purerawz.co/product/ibutamoren-mk-677/. Accessed 4/24/2024.

[30] Available at https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm. Accessed 6/8/2023.

enhancing substances (Van Wagoner et al. 2017; Kim et al. 2022) and there are also reports of ibutamoren mesylate use by professional athletes.[31, 32]

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

Ibutamoren mesylate is not recognized in either the European or Japanese Pharmacopeias. According to the M-CERSI report, there are no approved products containing ibutamoren mesylate in Canada, the United Kingdom, Ireland, Belgium, Latvia, Australia,[33] New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, or Namibia.[34] Additionally, there are no products containing ibutamoren mesylate that have been authorized for use in the European Union by the European Medicines Agency.[35] Ibutamoren mesylate was granted orphan designation in June 2017 by the European Commission for the treatment of GHD.[36]

Conclusions: The extent to which ibutamoren mesylate has been historically used in compounding is unclear. FDA identified websites that advertise that they obtain ibutamoren mesylate from a compounding pharmacy, but it is unclear if any compounding pharmacies are actively selling such compounded products. FDA also identified websites that sell products containing ibutamoren mesylate, but it is unclear if these are compounded products. No outsourcing facility has reported compounding products containing ibutamoren mesylate since 2020. At the time of this evaluation, currently available data and published literature is too limited to inform the historical use of ibutamoren mesylate for compounding drug products under section 503A of the FD&C Act.

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, ClinicalTrials.gov, DailyMed, Drugs@FDA, relevant professional healthcare organization websites, and various online clinical references and websites, such as information from National

[31] See, e.g., https://www.sportsintegrityinitiative.com/footballer-banned-from-sport-for-4-months-for-doping-violation/ and https://www.businessinsider.com/tristan-thompson-suspended-ibutamoren-lgd-4033-sarm-2024-1.
[32] Because of its potential to enhance performance, ibutamoren mesylate is on the list of prohibited substances under section S.2.4 of the World Anti-Doping Agency. World Anti-Doping Agency Prohibited List available at https://www.wada-ama.org/sites/default/files/2023-09/2024list_en_final_22_september_2023.pdf. Accessed 1/10/2024.
[33] In 2018 ibutamoren was added to Schedule 4, Prescription only medicines and prescription animal remedies, and Appendix D Part 5, Poisons for which possession without authority is illegal, of the Australian Poisons Standard. Available at https://www.tga.gov.au/resources/publication/scheduling-decisions-final/final-decisions-amending-or-not-amending-current-poisons-standard-april-2018/14-ibutamoren. Accessed 5/13/2024. 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 5/17/2024.
[34] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 5/8/2023.
[35] M-CERSI Summary Report on ibutamoren mesylate. Available at https://archive.hshsl.umaryland.edu/handle/10713/14872. Accessed 5/8/2023.
[36] See https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171882. Accessed 5/8/2023.

Institutes of Health (NIH) and National Organization for Rare Disorders (NORD). In addition to a comprehensive review of pertinent information from these databases, this section provides a discussion of the proposed uses of ibutamoren mesylate.

As noted earlier, ibutamoren mesylate is also known as MK-677, MK-0677, MK0677, and LUM-201; the name listed in the reference will be used in its corresponding description below.

1. Growth Hormone Deficiency

GHD is a disorder characterized by inadequate secretion of GH from the anterior pituitary gland. GH stimulates linear growth (increased height) during childhood, helps maintain body structure in adults, and plays a role in metabolism in both children and adults.[37]

GHD onset can be from birth (congenital) or during childhood or adulthood (acquired). Acquired GHD may develop after any process that damages 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.[38] 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.[39]

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.[40,41] A random GH level is not useful to diagnose GHD because GH levels fluctuate throughout the day.[42] IGF-1 levels are helpful in GHD screening;[43] however, IGF-1 alone is not reliable for the diagnosis of

[37] Human Growth Hormone (HGH). Cleveland Clinic website. https://my.clevelandclinic.org/health/articles/23309-human-growth-hormone-hgh. Accessed Nov 29, 2023.
[38] Growth Hormone Deficiency. Endocrine Society website, accessed 11/04/2023, https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency.
[39] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) website, accessed 11/04/2023, https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main.
[40] 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).
[41] Growth Hormone Deficiency. Endocrine Society website, accessed 11/04/2023, https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) website, accessed 11/04/2023, https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main.
[42] Human Growth Hormone (HGH), Cleveland Clinic website, accessed 11/29/2023, https://my.clevelandclinic.org/health/articles/23309-human-growth-hormone-hgh.
[43] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) website, accessed 11/04/2023, https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main.

GHD (Ibba et al. 2020).[44] Imaging and additional laboratory tests may also be utilized for GHD screening and diagnosis.

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 children and adults with GHD, such as once-daily somatropins 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/or 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 according to clinical response, side effects, and IGF-1 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.[45]

There are no FDA-approved drug products containing ibutamoren mesylate as the active ingredient. Merck, which was previously developing MK-0677, discontinued development in 1999. Lumos Pharma, Inc (Lumos) acquired the license for MK-0677 and renamed it LUM-201; Lumos is developing LUM-201 as an alternative treatment for pediatric GHD. There is an active multi-national, phase 2 study of LUM-201 in pediatric patients with GHD (the OraGrowtH210 Trial) (M-CERSI 2021).[46,47]

Ibutamoren mesylate acts as a GHS, 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 ibutamoren mesylate activates ghrelin receptors on pituitary somatotrophs and in the hypothalamus to stimulate GH release (see Section II.C.1), some residual endogenous GH

[44] 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 patients with evidence of panhypopituitarism (e.g., three or more other pituitary hormone deficiencies) may make provocative testing optional (Molitch et al. 2011).
[45] See Section II.C.2.d regarding availability of alternative therapies for GHD.
[46] See: LUM-201. Lumos website, accessed 10/13/2023, https://lumos-pharma.com/our-pipeline/lum-201/.
[47] Phase 2 Study of LUM-201 in Children With Growth Hormone Deficiency (OraGrowtH210 Trial). NIH ClinicalTrials.gov, accessed 10/13/2023, https://www.clinicaltrials.gov/study/NCT04614337.

secretion must be preserved (i.e., partial and not complete GHD); ibutamoren mesylate would not be expected to increase circulating GH in individuals with absent pituitaries or severely damaged somatotrophs (Chapman et al. 1997).

Ibutamoren mesylate is not mentioned for GHD diagnosis or treatment in professional society guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology (Yuen et al. 2019), Pediatric Endocrine Society (Grimberg et al. 2016), or Endocrine Society Clinical Practice Guideline on the evaluation and treatment of adult GHD (Molitch et al. 2011). A Growth Hormone Research Society guideline on diagnosis, genetics, and therapy of short stature in children mentions that oral ghrelin analogues such as MK-677/LUM-201 are unlikely to be useful in children with severe pituitary forms of GHD but may have potential in children with hypothalamic GHD or milder degrees of pituitary dysfunction; they may also be effective in non-GHD children with low BMI (Collett-Solberg et al. 2019).

In addition, GH secretion declines with physiological aging, primarily in the amplitude of the secretory episodes, although interpulse levels also decline. A reduction of IGF-1 levels occurs in parallel with the decline in average GH secretion in aging. Decreased output by the GH/IGF-1 axis is correlated with increased percentage of total body and visceral fat, decreased muscle mass, decreased physical fitness, decreased immune function, and physiological declines in estrogen and androgen concentrations; whether this decline in GH secretion is causative or only correlative is controversial (Cappola et al. 2023).

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

The nominations cited one reference evaluating the effect of ibutamoren mesylate on the GH/IGF-1 axis in healthy older adults (Chapman et al. 1996), one reference evaluating efficacy of ibutamoren mesylate for GHD (Chapman et al. 1997), and a literature review on GHSs that discussed ibutamoren mesylate for GHD (Sigalos and Pastuszak 2018). Our search of published medical literature retrieved two additional studies on ibutamoren mesylate for treatment of GHD (Codner et al. 2001; Bright et al. 2021).

- Chapman et al. 1996 evaluated stimulation of the GH/IGF-1 axis by daily MK-677 in a randomized (R), double-blind (DB), placebo-controlled (PC) trial. Healthy subjects ages 64 to 81 years received placebo (n=10), MK-677 10 mg (n=12), or MK-677 2 mg then 25 mg (n=10) for two 14-day study periods (separated by a 14- to 21-day washout) with an additional 2-week extension after the second period for collection of IGF-1 and safety data. Authors reported that mean 24-hour GH concentrations increased with MK-677 in a dose-dependent manner by enhancing pulsatile GH secretion, with increases in both the height of the GH pulses and nadir GH concentrations between pulses. In the MK-677 25 mg group, mean serum IGF-1 levels increased from 141 ± 21 mcg/L (mean ± SE) at baseline, to 219 ± 21 mcg/L at 2 weeks, and 265 ± 29 mcg/L at 4 weeks. The authors concluded that at a dose of 25 mg/day, MK-677 restored IGF-1 concentrations in most older subjects to levels seen in

young adults.[48] Study limitations include study population (conducted in healthy older subjects and not subjects with GHD), short duration of treatment, and lack of endpoints such as lean body mass and fat mass; it is unclear whether an increase in IGF-1 levels would correspond to clinically meaningful outcomes.

- Chapman et al. 1997 evaluated the effect of MK-677 on the GH/IGF-1 axis in nine adults with severe GHD[49] who received MK-677 or placebo for two 4-day periods in a R, DB, PC study. There were two study groups: Group 1 (n=4) received placebo and MK-677 10 mg daily in a cross-over fashion in periods 1 and 2, and Group 2 (n=5) received MK-677 10 mg in period 1 then MK-677 50 mg in period 2. Serum IGF-1 and 24-hour mean GH concentrations increased in all subjects who received MK-677 as compared to baseline, although 24-hour mean GH remained below the age-adjusted normal range in all subjects, and IGF-1 increased into the age-adjusted normal range in two subjects treated with MK-677 50 mg; placebo treatment had no effect on these parameters:
  - MK-677 10 mg: 24-hour mean GH concentration increased by 79 ± 19% (mean ± SE) from baseline (0.14 to 0.26 mcg/L); IGF-1 increased by 52 ± 20% (65 to 99 mcg/L)
  - MK-677 50 mg: 24-hour mean GH concentration increased by 82 ± 29% from baseline (0.21 to 0.39 mcg/L); IGF-1 increased by 79 ± 9% (84 to 150 mcg/L)

  The GH response to MK-677 was greater in subjects who were the least GH/IGF-1 deficient at baseline. Insulin-like growth factor-binding protein-3 (IGFBP-3)[50] also increased. The authors concluded that daily MK-677 administration for 4 days to selected men with GHD was associated with increased levels of GH, IGF-1, and IGFBP-3, and that there may be a therapeutic role in the treatment of some patients with GHD. The authors added that further studies are needed to determine the effects of MK-677 in other populations, such as women and children with idiopathic GHD, as well as its long-term safety and efficacy. Study limitations include short study duration (two 4-day treatment periods), small sample size, and endpoints that did not evaluate therapeutic effect.[51]

[48] IGF-1 levels vary with age and sex. For example, the reference interval for men ages 31 to 35 is 95-290 ng/mL, while the reference interval for men ages 71 to 75 is 53-222 ng/mL. See: Insulin-like Growth Factor 1 (IGF-1). Labcorp website, accessed 11/04/2023, https://www.labcorp.com/tests/010363/insulin-like-growth-factor-1-igf-1.
[49] Authors noted that because MK-677 acts on somatotropic cells in the anterior pituitary, MK-677 would not be expected to increase circulating GH in individuals with absent pituitaries or severely damaged somatotropic cells. Therefore, authors studied young adults who had been diagnosed with GHD during childhood and had not had pituitary or hypothalamic tumor, surgery, or radiotherapy, noting that GHD in such subjects is often idiopathic. Subjects had been treated with GH during childhood but had not been treated with GH or any GHS for at least 6 months prior to the study.
[50] IGFBP-3 is a biomarker with a similar secretion pattern to IGF-1. Low IGFBP-3 is observed with GHD, similar to low IGF-1 levels. See: Insulin-Like Growth Factor-Binding Protein 3, Serum. Mayo Clinic Laboratories, accessed 10/19/2023, https://endocrinology.testcatalog.org/show/IGFB3.
[51] Example efficacy measures in clinical trials to support FDA approval of rhGH for adults with GHD were body composition (lean body mass and fat mass) and lipid parameters. See for example label for Humatrope (somatropin), BLA 019640/S-105. Drugs@FDA, accessed 12/05/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019640.

- Codner et al. 2001 evaluated the effects of ibutamoren mesylate on the GH/IGF-1 axis in 18 children with idiopathic GHD[52] in a R, partially DB, PC, multicenter study.
  - Group 1 (n=2) received ibutamoren mesylate 0.2 mg/kg/day on days 1-7 and placebo on days 8-14
  - Group 2 (n=4) received placebo on days 1-7 and ibutamoren mesylate 0.2 mg/kg/day on days 8-14
  - Group 3 (n=12) received placebo on days 1-7 and ibutamoren mesylate 0.8 mg/kg/day on days 8-14

  On day 15 all subjects received a single dose of ibutamoren mesylate 0.8 mg/kg. After administration of ibutamoren mesylate 0.8 mg/kg for 8 days (Group 3), the median increases (on day 15) from baseline were as follows:
  - Peak GH concentration (mcg/L): 3.8 (range, 0 to 34.3)
  - GH area under the concentration-time curve from time zero to 8 hours (AUC_{0-8}) (mcg·h/L): 4.3 (range, 1.3 to 35.6)
  - IGF-1 (mcg/L): 12 (range, -4 to 116)
  - IGFBP-3 (mcg/L): 0.4 (range, -0.9 to 1.5)

  A measurable increase in GH and IGF-1 were observed in two subjects in Group 2 and seven subjects in Group 3; the authors observed that subjects with baseline IGF-1 > 50 mcg/L[53] had a greater response to ibutamoren mesylate. There was no change in triiodothyronine (T_3), thyroxine (T_4), or thyroid-stimulating hormone (TSH) with ibutamoren mesylate 0.8 mg/kg/day. The authors concluded that short-term administration of ibutamoren mesylate can increase GH, IGF-1, and IGFBP-3 levels in some children with GHD and noted that subsequent studies would be required to address whether prolonged treatment can selectively induce sustained increases in GH, IGF-1, and IGFBP-3 and increase growth velocity. Study limitations include small sample size, short study duration, and lack of evaluation of clinically meaningful endpoints.

- Bright et al. 2021 evaluated data from an earlier completed R, DB, PC trial of daily LUM-201 in 68 prepubertal children with GHD.[54] After measurement of peak GH response to a single dose of LUM-201 0.8 mg/kg, subjects received LUM-201 0.4 mg/kg/day (n=22), LUM 0.8 mg/kg/day (n=24), or placebo (n=22) for 6 months. After 6 months, 20 subjects receiving placebo were switched to subcutaneous injections of rhGH 0.3 mg/kg/week. The mean annualized height velocity for the LUM-201 groups (6.0 cm/year in the LUM-201 0.4 mg/kg/day group and 6.9 cm/year in the LUM-201 0.8 mg/kg/day group) was higher than the

[52] Children were prepubertal (Tanner stage 1) with an average chronologic age of 10.6 years. GHD was defined as GH responses below 10 mcg/L to at least two standard provocative tests associated with a growth velocity below the 10th percentile or < 4 cm over the preceding 12 months. Of note, some institutions use > 10 ng/mL as a cut-off for normal GH response with stimulation testing (See: Growth Hormone Stimulation. Labcorp website, accessed 10/17/2023, https://www.labcorp.com/resource/growth-hormone-stimulation); however, based on newer assays and standards, levels > 7 ng/mL have been suggested as a threshold (Collett-Solberg et al. 2019).

[53] Reference intervals for IGF-1 levels vary by age and sex. See: Insulin-like Growth Factor 1. Labcorp website, accessed 10/17/2023, https://www.labcorp.com/tests/010363/insulin-like-growth-factor-1-igf-1.

[54] Children had short stature (height standard deviation score [HT-SDS] < -2), slow height velocity (< 10th percentile for age and gender) and a bone age delay of at least 1 year. Bone age was ≤ 8 years for girls and ≤ 9 years for boys. Subjects were treatment-naïve. Maximal GH responses to two standard GH stimulation tests of < 10 ng/ mL and an absence of other growth-limiting conditions were required. Based on prior observations that the children with more severe GHD might not respond to GHS, subjects with pretreatment peak GH responses of <1.9 ng/mL to a single dose of LUM-201 were not randomized to receive treatment.

placebo group (4.5 cm/year) but lower than subjects treated with rhGH (11.1 cm/year). Peak GH ≥ 5 ng/mL with a single dose of LUM-201 and a baseline IGF-1 concentration > 30 ng/mL were found to be positive predictive enrichment markers for increased height velocity (HV) on LUM-201 treatment. Conversely, a peak GH < 5 ng/mL and a baseline IGF-1 concentration ≤ 30 ng/mL enriched HV response to rhGH. Authors suggested that LUM-201 might be reserved for pediatric subjects with more moderate GHD, whereas children with more severe GHD would be better served with rhGH. Limitations include retrospective analysis of data collected from 1996-1998; e.g., authors note contemporary differences in assays and rhGH dosing, and lack of data available on covariates such as mid-parental height.

Sigalos and Pastuszak 2018 described safety and efficacy of GHSs, including studies that evaluated effects of ibutamoren mesylate in GHD, hip fracture, obesity, sleep, nitrogen wasting in a catabolic state, bone turnover, and changes in body composition in elderly subjects. Studies (Chapman et al. 1996; Murphy et al. 1998; Svensson et al. 1998b; Murphy et al. 1999; Codner et al. 2001; Murphy et al. 2001; Bach et al. 2004; Nass et al. 2008; Sevigny et al. 2008; Adunsky et al. 2011) in this literature review that provided relevant efficacy information on ibutamoren mesylate are individually described under each proposed use.

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 with 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.[55,56]

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

There are multiple FDA-approved drug products that treat the same medical condition as that proposed for the ibutamoren mesylate compounded drug products.[57] The following are FDA-approved drug products and examples for each:

- Somatropin (e.g., Humatrope[58], Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton for SC injection): a daily rhGH, indicated for replacement of endogenous GH in adults with

[55] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) website, accessed 11/04/2023, https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main.
[56] See: Growth Hormone Deficiency. Endocrine Society website, accessed 11/04/2023, https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency.
[57] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[58] See, e.g., label for Humatrope (somatropin), BLA 019640/S-105. Drugs@FDA, accessed 12/05/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019640. Additional indications include pediatric patients with short stature associated with Turner syndrome; Idiopathic Short Stature (ISS), height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range; short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency; short stature born small for gestational age (SGA) with no catch-up growth by 2 years to 4 years of age.

GHD, and for pediatric patients with growth failure due to inadequate secretion of endogenous GH

- Lonapegsomatropin-tcgd (Skytrofa SC injection[59]): a weekly human GH prodrug indicated for pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous GH
- Somapacitan-beco (Sogroya SC injection[60]): a weekly human GH analog indicated for replacement of endogenous GH in adults with GHD and treatment of pediatric patients aged 2.5 years and older who have growth failure due to inadequate secretion of endogenous GH
- Somatrogon-ghla (Ngenla SC injection[61]): a weekly human GH analog indicated for treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous GH

d. Conclusion

Based on available clinical information, there is insufficient data to establish effectiveness of ibutamoren mesylate for use in treating GHD, a serious condition. Available clinical data are limited by small sample sizes, short study durations, and lack of assessment of endpoints that could demonstrate therapeutic effect, such as body composition in adult subjects with GHD, or height velocity and final adult height in pediatric subjects with GHD. Results from clinical trials conducted in children with GHD that did measure height velocity suggest inferior efficacy compared to approved therapies for GHD, and further study is needed to identify whether a subset of pediatric patients with GHD may see comparable benefit. In addition, there are currently FDA-approved drugs with established efficacy for the treatment of adults with GHD and growth failure due to GHD in children.

2. Osteoporosis

Osteoporosis is a bone disease that develops when BMD and bone mass decrease or when the structure and strength of bone changes; this can lead to a decrease in bone strength that, in turn, can increase the risk of fractures. Osteoporosis is typically asymptomatic until fractures occur. Diagnosis of osteoporosis involves assessment of clinical history, signs and symptoms, and tests that measure BMD, such as dual-energy X-ray absorptiometry (DXA). Treatment of osteoporosis aims to prevent fractures and may include nutrition, exercise, and medications such as bisphosphonates, calcitonin, estrogen agonists/antagonists, estrogen and combined estrogen and progestin, parathyroid hormone (PTH) analog sand PTH-related peptide (PTHrP) analogs, receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors, and sclerostin inhibitors.[62]

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[59] See label for Skytrofa (lonapegsomatropin-tcgd), BLA 761177/S-1. Drugs@FDA, accessed 12/05/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761177.
[60] See label for SOGROYA (somapacitan-beco), BLA 761156/S-5. Drugs@FDA, accessed 12/05/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761156.
[61] See label for Ngenla (somatrogon-ghla), BLA 761184. Drugs@FDA, accessed 12/13/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761184.
[62] See: Osteoporosis. NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases, accessed 10/04/2023, https://www.niams.nih.gov/health-topics/osteoporosis.

GH and IGF-1 are important regulators of bone homeostasis throughout life (Giustina et al. 2008). Aging is associated with declining serum concentrations of GH and IGF-1; this reduction may contribute to the decrease in bone mass that accompanies normal aging (Murphy et al. 2001). Adult GHD causes low bone turnover osteoporosis, leading to increased fracture risk, and the low bone mass can be partially reversed with GH replacement (Giustina et al. 2008). GHSs, such as ibutamoren mesylate, have been evaluated in osteoporosis due to their anabolic effects (Murphy et al. 2001).

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

The nominations for ibutamoren mesylate made reference to one publication evaluating efficacy of ibutamoren mesylate for osteoporosis (Murphy et al. 2001) and a literature review on GHSs (Sigalos and Pastuszak 2018). Our search did not retrieve additional relevant studies.

- Murphy et al. 2001 evaluated the effects of alendronate (bisphosphonate that increases bone mass) and MK-677, individually and in combination, on markers of bone turnover in subjects with osteoporosis in a multicenter, R, DB, PC 6-month study with planned extensions from 6-12 and 12-18 months. Postmenopausal women with osteoporosis[63] ages 64 to 85 years received one of four treatments for 12 months:
  - Group I: MK-677 25 mg plus alendronate 10 mg (MK-677/alendronate) (n=111)
  - Group II: Alendronate 10 mg plus MK-677 placebo (n=109)
  - Group III: MK-677 25 mg plus alendronate placebo (n=36)
  - Group IV: MK-677 placebo plus alendronate placebo (n=36)

  Subjects who received MK-677 or placebo through month 12 received MK-677/alendronate from months 12 to 18 while the other groups continued their assigned therapy. Subjects also received oral calcium carbonate 500 mg daily. Authors hypothesized that combining administration of an anabolic GHS with alendronate, a bisphosphonate that decreases bone resorption and formation, may result in less suppression of bone formation and improve the BMD response to alendronate. The percent change from baseline in serum osteocalcin (a marker of bone formation) and urinary N-telopeptide cross-links (NTx) (a marker of bone resorption) were the primary and secondary endpoints, respectively. Percent change from baseline of the femoral neck BMD was the prespecified key BMD endpoint.

  Osteocalcin increased by approximately 22% and urinary NTx by 41% from baseline in the MK-677 alone group. Osteocalcin and NTx decreased with alendronate as authors expected; the reduction in bone formation and resorption was mitigated with MK-677/alendronate compared with alendronate alone based on mean relative changes in osteocalcin and NTx. BMD increased at the femoral neck with MK-677/alendronate (4.2%) more than alendronate alone at 18 months (2.5%); however, similar enhancement was not seen in BMD of the lumbar spine, total hip, or total body as compared with alendronate alone. MK-677 alone for 12 months did not increase BMD at any site significantly compared with placebo; the authors stated that the group receiving MK-677 alone may have experienced a trend toward a net decrease, relative to placebo, in total BMD over 12 months.

[63] Subjects had a femoral neck BMD at least 2.0 standard deviations (SD) below the mean peak value for healthy young women but no more than 3.0 SD below the age-specific mean.

Increased IGF-1 levels from baseline by approximately 40% were observed with MK-677, with or without alendronate, supporting a persistent GH secretory response per authors. The authors concluded that the anabolic effect of MK-677 attenuated the indirect suppressive effect of alendronate on bone formation, but it did not translate into significant increases in BMD at sites other than the femoral neck. The authors noted that although the femoral neck is an important site for fracture prevention, the lack of enhancement in bone mass at other sites compared with alendronate alone is a concern when weighed against the potential side effects of enhanced GH secretion (safety outcomes discussed in Section II.C.2).

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

Osteoporosis is associated with an increased risk of potentially serious fractures which can generate a heavy burden of morbidity and an increased risk of mortality (Leboime et al. 2010).

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

There are FDA-approved products that treat the same medical condition as that proposed for the ibutamoren mesylate compounded drug products.[64] The following are pharmacotherapies by drug class with examples for each:[65]

- Bisphosphonate (e.g., alendronate sodium oral tablet[66], alendronate sodium oral solution[67], ibandronate sodium IV injection[68])
- Calcitonin receptor agonist (e.g., calcitonin salmon nasal spray[69], calcitonin salmon intramuscular or SC injection[70])
- Estrogen agonist/antagonist (e.g., raloxifene hydrochloride oral tablet[71])

[64] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[65] See: Osteoporosis. NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases, accessed 10/14/2023, https://www.niams.nih.gov/health-topics/osteoporosis.
[66] See label for alendronate sodium, ANDA 090124. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=815a87c4-e489-4eb9-9a2e-fb7a16642f01.
[67] See label for alendronate sodium, ANDA 214512. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=81589178-10c9-4806-91eb-54e638d35b8d.
[68] See label for ibandronate sodium, ANDA 204222. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=9fad4982-95af-d711-f50a-867311835143.
[69] See label for calcitonin salmon, ANDA 076396. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c82eb602-12e1-692b-d660-f8d5b5736b54.
[70] See label for calcitonin salmon, ANDA 212416. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7d4507aa-8e10-44a6-bc6e-3176aa8b23cc.
[71] See label for raloxifene hydrochloride, ANDA 090842. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8fef5bfd-a786-4442-b09b-f3b81812cdac.

- Estrogen and combined estrogen and progestin (e.g., conjugated estrogens [Premarin oral tablet[72]], conjugated estrogens/medroxyprogesterone acetate [Prempro oral tablet[73]], estradiol [Dotti transdermal system[74]])
- Parathyroid hormone (PTH) analog and PTH-related peptide (PTHrP) analog (teriparatide [Forteo SC injection[75]], abaloparatide [Tymlos SC injection[76]])
- Receptor activator of nuclear factor kappa-B ligand (RANK ligand/RANKL) inhibitor (e.g., denosumab [Prolia SC injection[77]])
- Sclerostin inhibitor (romosozumab-aqqg [Evenity SC injection[78]])

d. Conclusion

Based on available clinical information, there are insufficient data to establish the effectiveness of ibutamoren mesylate for treatment of osteoporosis. Clinical trials observed changes in markers of bone turnover with ibutamoren mesylate but did not observe increases in BMD as compared to an FDA-approved drug product; fractures were not a specified endpoint. In addition, there are currently FDA-approved therapies with established efficacy for osteoporosis, which is a serious disease.

3. Hip Fracture

Hip fractures, which occur in the upper portion of the femur, often occur in patients 65 years and older as the result of falls. Symptoms are typically acute pain at the fracture site, and patients are often not able to stand or bear weight. Hip fractures are diagnosed on imaging studies such as X-rays.[79]

According to information from the American Academy of Orthopaedic Surgeons, most hip fractures require surgical treatment within 1 to 2 days of injury. Only a very small group of nondisplaced fractures in healthy patients can be treated without surgery, while a separate group of patients may be too sick to safely undergo surgery. Surgical treatment is required to relieve

[72] See label for Premarin (conjugated estrogens), NDA 004782/S-176. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=004782.
[73] See label for Prempro (conjugated estrogens/medroxyprogesterone tablets), NDA 020527/S-65. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=020527.
[74] See label for Dotti (estradiol transdermal), ANDA 211293. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b119df4a-c514-4804-b1a8-b09c6058e80d.
[75] See label for Forteo (teriparatide), NDA 021318/S-56. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=021318.
[76] See label for Tymlos (abaloparatide), NDA 208743/S-13. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208743.
[77] See label for Prolia (denosumab), BLA 125320/S-211. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=125320.
[78] See label for Evenity (romosozumab-aqqg), BLA 761062/S-2. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761062.
[79] See: Hip Fractures. OrthoInfo from the American Academy of Orthopaedic Surgeons (AAOS), accessed 10/12/2023, https://orthoinfo.aaos.org/en/diseases--conditions/hip-fractures/.

the acute pain of the fracture and to allow the patient to get out of bed. Having surgery as soon as possible can lessen the risk of complications.[80]

Treatment for hip fracture usually involves a combination of prompt surgical repair, rehabilitation (physical therapy and occupational therapy), and medication to manage pain and to prevent blood clots and infection.[81] Physical therapy often focuses on range-of-motion and strengthening exercises.[82] Recommendations for postoperative rehabilitation often include early mobilization and physical therapy in the acute phase after surgery and after discharge (Lee et al. 2011); however, successful long-term management of elderly patients with hip fractures has proved challenging, with poor outcomes commonly reported (Bach et al. 2004). Immobilization following an acute event such as hip fracture causes rapid muscle loss that may impact effective rehabilitation and functional recovery, potentially resulting in permanent disability and loss of independent living. Ensuing muscle atrophy may be superimposed on sarcopenic age-related changes in skeletal muscle. Stimulation of the GH/IGF-1 axis to improve functional recovery after hip fracture has been investigated (Adunsky et al. 2011).

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

The nominations for ibutamoren mesylate made reference to one publication evaluating efficacy of ibutamoren mesylate for hip fracture (Adunsky et al. 2011) and a literature review that discussed studies performed in subjects with hip fracture (Sigalos and Pastuszak 2018). Our search retrieved an additional study on ibutamoren mesylate for hip fracture (Bach et al. 2004).

- Bach et al. 2004 evaluated the effect of MK-0677 on functional recovery in subjects recovering from hip fracture in a R, DB, PC trial. Subjects ≥ 65 years with recent hip fractures were randomized to receive MK-0677 25 mg (n=84) or placebo (n=77) daily for 6 months. Investigators measured the change in objective functional performance measures (FPMs) that included tasks such as stair climb, repeated weight lift, and stand balance. Investigators also assessed IGF-1 levels, health-related quality of life using the Sickness Impact Profile for Nursing Homes (SIP-NH), and ability to live independently.

  Both MK-0677 and placebo groups showed improvement over time with no differences in overall change in FPMs or in the overall SIP-NH score. The MK-0677 group showed trends in greater improvement relative to placebo in three of four lower extremity FPMs, in the physical domain of the SIP-NH, and in the ability to live independently. IGF-1 levels increased by 84% in the MK-0677 group compared with 17% in placebo. The authors concluded that although MK-0677 treatment increased IGF-1, it was uncertain whether clinically significant effects on physical function were achieved. The authors noted that measuring function in clinical trials in patients with hip fracture is difficult because of the lack of validated outcome measures, high variability, and the lack of baseline assessment. Present FPMs may not be sufficiently responsive for use as the primary endpoint of small

[80] Ibid.
[81] See: Hip Fracture. MayoClinic.org, accessed 11/04/2023, https://www.mayoclinic.org/diseases-conditions/hip-fracture/diagnosis-treatment/drc-20373472.
[82] Ibid.

intervention studies; alternatively, stimulation of GH may not result in significant functional improvement. Authors noted that limitations of FPMs include unknown clinical relevance of measured changes, measure of functional status at discrete time points, and lack of assessment of pre-fracture status.

- Adunsky et al. 2011 evaluated MK-0677 in patients recovering from hip fracture in a R, DB, PC multicenter study. Patients ≥ 60 years with a recent unilateral hip fracture were randomized to MK-0677 25 mg (n=62) or placebo (n=61) daily for 24 weeks. Primary outcomes were a rank analysis of change in objective FPMs and IGF-1 levels. At 24 weeks, mean stair climbing power (assessing lower extremity power) increased by 12.5 watts in the MK-0677 group (95% confidence interval (CI) = -10.95-35.88; P = 0.292) compared with placebo. Gait speed (assessing a component of physical function performance) increased by 0.1 m/s as compared with placebo in change from baseline.[83] There was no improvement in MK-0677-treated patients in several other FPMs. The MK-0677 group experienced fewer falls during the study than placebo. IGF-1 levels in patients receiving MK-0677 increased by 51.4 ng/ml compared to placebo; however, the authors noted that in patients treated with MK-0677 25 mg/day, the increase in IGF-1 was not paralleled by improvement in most FPMs.

  The trial was terminated early due to a safety signal of CHF in subjects (four patients [6.5%] in the MK-0677 group versus one [1.7%] in placebo; safety information discussed in Section II.C.2). The authors noted that this phase 2 study has a number of limitations and that the results should be considered in the context of the following: small sample size and absence of a single primary endpoint; the study population was almost entirely white so that inference from the data may not be applicable to other ethnicities; the study included selected rather than consecutive hip fracture patients and excluded a great number of non-eligible patients that may have affected the results; and the heterogeneity of rehabilitation settings may introduce bias and interfere with interpretation of results. The authors concluded that although MK-0677 might be associated with some improvement in lower extremity function which might have explained the trend toward a decrease in falls, "the AEs associated with MK-677 in a relatively small patient population makes it likely that the risk benefit of this drug for this indication is not acceptable."

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

Hip fractures substantially increase the risk of major morbidity and death in older patients.[84]

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

[83] Per authors, a change in 0.1 m/s in gait speed has been established as clinically meaningful in hip fracture patients.
[84] See: Hip fracture in adults: Epidemiology and medical management. UptoDate, accessed 10/12/2023, www.uptodate.com.

There are no FDA-approved drug products indicated for the treatment of hip fracture.[85] Treatment for hip fracture usually involves a combination of prompt surgical repair, rehabilitation, and medication to manage pain.[86] Unless contraindicated, bisphosphonates are used to reduce the risk of another hip fracture. Calcium and vitamin D supplements are usually combined with bisphosphonate therapy (LeBlanc et al. 2014).

d. Conclusion

Based on available clinical information, there are insufficient data to establish effectiveness of ibutamoren mesylate for the treatment of hip fracture. Clinical trials concluded that it was uncertain whether clinically significant effects on physical function were achieved, and that an increase in IGF-1 levels was not paralleled by improvement in most functional performance measures. There are no FDA-approved drug products indicated for the treatment of hip fracture, a serious condition; however, there exist a number of other treatment methods, including a combination of prompt surgical repair, rehabilitation, and medications to manage pain and to prevent blood clots and infection.

4. Sarcopenia

Sarcopenia is defined as an age-associated loss of skeletal muscle function and muscle mass (Dent al. 2018). Sarcopenia is described as a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality (Cruz-Jentoft et al. 2019). The etiology of sarcopenia is likely multifactorial, with causes such as declines in activity and nutritional intake, disease triggers, inflammatory pathway activation, and hormonal changes all potentially contributing. Symptoms may include strength and functional declines that can contribute to adverse health outcomes such as loss of function, disability, and frailty (Walston 2012). Sarcopenia shares many characteristics with other disease states typically associated with risk of fall and fracture, including osteoporosis, frailty, and obesity (Marty et al. 2017). Sarcopenia is diagnosed based on low muscle strength and low muscle quantity or quality (Cruz-Jentoft et al. 2019).

There are no FDA-approved drugs indicated for sarcopenia. Current treatment interventions focus on increasing activity and providing adequate nutrition, although many different therapeutic targets have been studied in related populations evaluating effects on muscle mass, muscle strength, and physical performance (Marty et al. 2017). Sarcopenia is associated with a decline in GH secretion and IGF-1 levels; some therapeutic interventions have focused on stimulation of the GH/IGF-1 axis (Adunsky et al. 2011).

[85] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[86] See: Hip Fracture. MayoClinic.org, accessed 11/04/2023, https://www.mayoclinic.org/diseases-conditions/hip-fracture/diagnosis-treatment/drc-20373472.

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

References submitted by the nominator did not include studies specifically evaluating ibutamoren mesylate for subjects with sarcopenia; rather, the references investigated ibutamoren mesylate in healthy older adults (Nass et al. 2008), older adults with strength deficits (Plotkin et al. 1997), and younger adults with diet-induced catabolism (Murphy et al. 1998).

- Plotkin et al. 1997 (abstract only) evaluated the effect of MK-677 on GH and IGF-1 in a R, DB, PC pilot study. Men and women ages 65 to 94 years (N=104) with known strength deficits[87] received daily placebo or MK-677 5 mg, 10 mg, or 25 mg for 2 weeks; subsequently, all MK-677 groups received MK-677 25 mg for 7 additional weeks. IGF-1 levels at baseline were 93 ± 4 ng/mL (mean ± SE) and increased in a dose-dependent manner by 40-65% after 2 weeks (reference does not specify differences between groups or placebo). Mean 24-hour serum GH levels increased 250 ± 170% with MK-677 (dose unspecified) compared to baseline. The authors discussed that the GHS can increase pulsatile GH secretion, warranting further evaluation of clinical benefit in this population. We note that the study is limited by the lack of available information in the abstract and the lack of clinically meaningful endpoints.

- Murphy et al. 1998 investigated whether MK-677 can reverse diet-induced protein catabolism in a R, DB, PC, two-period crossover study. Eight healthy male subjects ages 24 to 39 years were calorically restricted (18 kcal/kg/day) for two 14-day periods (14 to 21-day washout periods). During the last 7 days of each diet period, subjects received MK-677 25 mg or placebo daily. During the first week of caloric restriction (i.e., diet alone), daily nitrogen losses were similar for both treatment groups. During the second week of the study (diet and study drug), mean daily nitrogen balance in the MK-677 group was 0.31 g/day (positive) versus -1.48 g/d with placebo. Authors also reported that area under the curve (AUC) day 8-14 nitrogen balance response was +2.69 g/d in the MK-677 group versus -8.97 g/day in the placebo group. During the study treatment week (days 8-14), there was less weight loss in the MK-677 group than placebo. Peak GH was increased after a single dose and after a week of dosing with MK-677 as compared to placebo. IGF-1 declined in each group following initial caloric restriction; subsequently, mean IGF-1 increased significantly with MK-677 to 264 ng/mL (mean for the last 5 days of treatment) compared with 188 ng/mL with placebo. Authors concluded that MK-677 reverses diet-induced nitrogen wasting, suggesting that it may be useful in treating catabolic conditions if the short-term anabolic effects are maintained. The authors noted that future studies should attempt to determine whether the anabolic effects of MK-677 will persist with prolonged treatment, and whether they will be associated with clinical benefits. Study limitations include the short study duration and a very small sample size. The subjects evaluated were healthy adults with diet-induced protein catabolism, so applicability of the results to patients with sarcopenia is unclear.

[87] Strength deficits are not described in the abstract; it is unclear whether these subjects were diagnosed with sarcopenia.

- Nass et al. 2008 is a proof-of concept study that evaluated the effects of MK-677 on body composition in a 2-year, R, DB, PC, modified-crossover clinical trial. Healthy adults ages 60 to 81 years received MK-677 25 mg (n=47) or placebo (n=24) once daily for 1 year. After 1 year, placebo-treated subjects were crossed over to MK-677 (n=20), and MK-677-treated subjects were randomized to continue MK-677 (n=20) or change to placebo (n=19). The two primary endpoints were fat-free mass (FFM) and abdominal visceral fat (AVF).

  After 12 months, 24-hour mean GH increased 1.8-fold and IGF-1 levels increased by 1.5-fold from baseline in the MK-677 group. Mean FFM decreased -0.5 kg in the placebo group and increased 1.1 kg in the MK-677 group. There were no differences in AVF or total fat mass. However, the average increase in limb fat in the MK-677 group (1.1 kg) was greater than with placebo (0.24 kg). Body weight increased 0.8 kg in the placebo and 2.7 kg in the MK-677 group. Femoral neck BMD declined at 12 months with MK-677, consistent with increased bone remodeling per authors. Increased FFM did not result in changes in strength or function. Two-year exploratory analyses confirmed the 1-year results. The authors concluded that MK-677 enhanced pulsatile GH secretion and increased FFM over 12 months. While subjects with sarcopenia were not studied, the authors noted that MK-677 counteracted important factors that contribute to the development of sarcopenia: reduced secretion of GH, loss of FFM, and inadequate food intake. Study limitations include small sample size, and that the subjects evaluated were healthy older adults and not subjects with sarcopenia, so applicability of the results to patients with sarcopenia is unclear.

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

Sarcopenia is associated with a risk of falls, fractures, functional decline, hospitalization, and increased mortality (Dent et al. 2018).

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

There are no FDA-approved products indicated for sarcopenia.[88]

d. Conclusion

Based on available clinical information, there are insufficient data to establish effectiveness of ibutamoren mesylate for treatment of sarcopenia, a potentially serious condition. Clinical trials were not conducted in subjects diagnosed with sarcopenia. Clinical meaningfulness of increasing GH and IGF-1 in patients with sarcopenia has not been established. There are no FDA-approved drug products indicated for the treatment of sarcopenia; current treatment interventions focus on increasing activity and providing adequate nutrition.

5. Obesity

[88] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

Obesity is defined by the increase in size and amount of fat cells in the body. Obesity is a chronic health condition that increases the risk for heart disease and is linked to other health problems, such as type 2 diabetes and cancer. Risk factors for obesity include lack of physical activity, unhealthy eating behaviors, insufficient good-quality sleep, stress, chronic health conditions, genetics, certain medications, and one's environment. Diagnosis may be based on medical history and high BMI. For adults, obesity is defined as BMI ≥ 30 kg/m^2.[89]

Treatment options may involve dietary or nutritional counselling, behavioral weight-loss programs, medicines, or surgery. Products approved for treatment of obesity target various parts of the body, such as the brain and gastrointestinal tract.[90] Obesity has been associated with blunted GH secretion with a decrease in the amount of GH secreted per burst (Svensson et al. 1998b).

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

The nominations for ibutamoren mesylate made reference to two publications evaluating efficacy of ibutamoren mesylate for the treatment of obesity (Svensson et al. 1998b; Svensson et al. 1999b) and to a literature review on GHSs (Sigalos and Pastuszak 2018). Our search of published medical literature retrieved one additional study (Svensson et al. 1999a).

- Svensson et al. 1998b investigated the effects of MK-677 on GH secretion and body composition in 24 otherwise healthy obese males in a R, DB, PC, parallel trial. Subjects with obesity ages 18 to 50 years were treated with MK-677 25 mg (n=12) or placebo (n=12) daily for 8 weeks. Primary endpoints were GH secretion, body composition, energy expenditure, and glucose homeostasis. Peak serum GH increased after the initial dose of MK-677 and through the study period (65.4 ± 13.1 [mean ± SEM] mIU/L at treatment initiation, 17.0 ± 3.3 at 2 weeks, and 14.3 ± 3.9 at 8 weeks) compared to placebo (2.0 ± 0.8, 1.5 ± 0.8, and 0.9 ± 0.4 mIU/L at the same points). Serum IGF-1 increased approximately 40% with MK-677 treatment compared to placebo. Serum IGFBP-3 also increased. FFM increased in the MK-677 group when determined with DXA or using a four-compartment model.[91] Total body fat and visceral fat were not changed. The basal metabolic rate (BMR) increased at 2 weeks but not 8 weeks in the MK-677 group. Authors concluded that MK-677 in healthy obese males caused a sustained increase in GH, IGF-1, and IGFBP-3 levels, and that changes in body composition and energy expenditure were of an anabolic nature with a sustained increase in FFM and a transient increase in BMR. The authors noted that further studies are needed to evaluate whether a higher dose of MK-677 or a more prolonged treatment period can promote a reduction in body fat. Study limitations include the small sample size, short study duration, and study population (investigation was only in adult males ≤ 50 years).

[89] See: Overweight and Obesity. NIH National Heart, Lung, and Blood Institute, accessed 10/12/2023, https://www.nhlbi.nih.gov/health/overweight-and-obesity.
[90] Ibid.
[91] A four-compartment model may include water, protein, mineral, and fat in analysis of body composition, as compared to a traditional two-compartment model in which body weight is partitioned into fat and FFM (Heymsfield et al. 1990a).

- Svensson et al. 1999a and 1999b reported additional biomarker data from Svensson et al. 1998b. Svensson et al. 1999a evaluated the effects of MK-677 on serum leptin levels.[92] Authors reported a transient increase in leptin and leptin/body fat ratio after MK-677 treatment for 2 weeks, but no change was observed at 8 weeks. Svensson et al. 1999b evaluated the effect of MK-677 on serum lipoproteins. Lipoprotein(a) did not change from baseline, while serum triglycerides, HDL cholesterol, apolipoprotein A-I, and apolipoprotein E transiently increased at 2 weeks of MK-677 treatment but not at 8 weeks. Serum total cholesterol tended to increase after 2 weeks of MK-677 but was unchanged from baseline at 8 weeks. LDL cholesterol was unchanged compared with placebo throughout the study. LDL/HDL cholesterol ratio was reduced after 8 weeks of MK-677 treatment. Mean LDL particle diameter decreased with MK-677 treatment at 2 weeks, but not at 8 weeks.

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

Obesity increases the risk for many serious diseases and health conditions such as type 2 diabetes, heart disease, stroke, and certain types of cancers.[93]

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

There are FDA-approved drug products that treat the medical condition proposed for the ibutamoren mesylate compounded drug products.[94] There are drug products that are FDA-approved as adjunctive therapy for weight loss or weight management. Examples include the following drugs or drug classes:

- Glucagon-like peptide-1 (GLP-1) receptor agonist (e.g., liraglutide [Saxenda SC injection[95]], semaglutide [Ozempic, Wegovy SC injection[96]])
- Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (tirzepatide [Zepbound SC injection[97]])
- Naltrexone HCl and bupropion HCl (Contrave[98] extended-release oral tablets): an opioid antagonist (naltrexone) and an aminoketone antidepressant (bupropion)

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[92] Authors note that leptin is secreted by adipocytes and has been found to reflect the amount of total body fat.
[93] See: Health Effects of Overweight and Obesity. CDC website, accessed 11/09/2023, https://www.cdc.gov/healthy-weight-growth/food-activity/overweight-obesity-impacts-health.html?CDC_AAref_Val=https://www.cdc.gov/healthyweight/effects/index.html.
[94] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[95] See, e.g., label for Saxenda (liraglutide), NDA 206321/S-16. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=206321.
[96] See, e.g., label for Wegovy (semaglutide), NDA 215256/S-7. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=215256.
[97] See label for Zepbound (tirzepatide), NDA 217806. Drugs@FDA, accessed 11/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217806.
[98] See label for Contrave (naltrexone hydrochloride and bupropion hydrochloride), NDA 200063/S-21. Drugs@FDA, accessed 12/05/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=200063.

- Orlistat (Xenical oral capsules[99]): an inhibitor of gastrointestinal lipases
- Phentermine and topiramate (Qsymia oral capsules[100]): a sympathomimetic amine anorectic (phentermine) with a sulfamate-substituted monosaccharide (topiramate)

d. Conclusion

Based on available clinical information, there are insufficient data to establish effectiveness of ibutamoren mesylate for treatment of obesity, which increases the risk for many serious diseases and health conditions. Studies are limited by their small size and short duration. In addition, there are currently FDA-approved therapies with established efficacy for the proposed use.

6. Alzheimer's Disease

Alzheimer's disease (AD) is a progressive disease that affects memory, thinking, and behavior. AD is the most common cause of dementia among older adults and is the seventh leading cause of death in the United States. Changes in the brain, including amyloid plaques and neurofibrillary tangles, may precede clinical symptoms. Symptoms may include memory loss and mild cognitive impairment, progressing to behavior changes and inability to communicate. Various terms and definitions are used to describe the stages of AD based on symptoms, with a general progression of stages from mild cognitive impairment to severe dementia.

Specific causes of AD are not fully understood but likely include a combination of age-related changes in the brain and genetic, environmental, and lifestyle factors.[101] Diagnosis is typically made by a detailed clinical assessment.[102] Treatment of AD depends in part on the AD stage; there are FDA-approved medications for early AD (e.g., lecanemab-irmb), mild to moderate AD (e.g., cholinesterase inhibitors), and moderate to severe AD (e.g., memantine, donepezil, rivastigmine patch). There are also medications approved to treat symptoms associated with AD (e.g., brexipiprazole).[103] There are currently no known interventions that will cure AD. Activation of the GH/IGF-1 axis has been considered as a clinical therapeutic target. Patients with AD have been observed to have lower levels of circulating IGF-1 compared to age-matched controls (Sevigny et al. 2008).

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

The nominations for ibutamoren mesylate made reference to one publication evaluating efficacy of ibutamoren mesylate for AD (Sevigny et al. 2008) and a literature review that discussed the

[99] See label for Xenical (orlistat), NDA 020766/S-38. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=020766.
[100] See label for Qsymia (phentermine and topiramate), NDA 022580/S-23. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022580.
[101] See: Alzheimer's Disease Fact Sheet. NIH National Institute on Aging, accessed 10/12/2023, https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet.
[102] See: Clinical features and diagnosis of Alzheimer disease. UpToDate, accessed 10/12/2023, www.uptodate.com.
[103] See: How is Alzheimer's Disease Treated? NIH National Institute on Aging, accessed 10/12/2023, https://www.nia.nih.gov/health/how-alzheimers-disease-treated.

study by Sevigny et al. 2008 (Sigalos and Pastuszak 2018). Our search of published medical literature did not retrieve additional studies.

Sevigny et al. 2008 evaluated the effect of MK-677 on disease progression in AD in a R, DB, PC multi-center trial in 563 subjects with mild to moderate AD. Authors examined whether MK-677, a potent inducer of IGF-1 secretion per authors, slows the rate of progression of symptoms in subjects with AD. Subjects were randomized to receive MK-677 25 mg (n=282) or placebo (n=281) daily for 12 months. Subjects were allowed to take marketed cholinesterase inhibitors or memantine if on stable doses. Efficacy measures were mean change from baseline at month 12 on the Clinician's Interview Based Impression of Change with caregiver input (CIBIC-plus), the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and the Clinical Dementia Rating-sum of boxes (CDR-sob).

Administration of MK-677 25 mg resulted in a 60.1% increase in serum IGF-1 levels at 6 weeks and a 72.9% increase at 12 months. In mixed-effects models that included treatment, time, randomization strata, and interaction of treatment-by-time, there were no significant differences between the treatment groups on the CIBIC-plus or the mean change from baseline scores on the ADAS-Cog, ADCS-ADL, or CDR-sob scores over 12 months. The authors concluded that despite noting a robust increase in IGF-1, MK-677 was ineffective at slowing the rate of progression of AD.

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

AD is a serious condition and a leading cause of death in the United States.[104]

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 ibutamoren mesylate compounded drug products.[105] There are several FDA-approved drug products to either treat or manage symptoms of AD at different stages of disease.[106] Examples include the following drugs or drug classes:

- Cholinesterase inhibitors (e.g., donepezil hydrochloride oral tablet[107], galantamine hydrobromide oral solution[108], Adlarity [donepezil] transdermal patch system[109])

[104] See: Alzheimer's Disease and Related Dementias. Centers for Disease Control and Prevention (CDC) website, accessed 10/04/2023, https://www.cdc.gov/aging/aginginfo/alzheimers.htm.
[105] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.
[106] See: How is Alzheimer's Disease Treated? NIH National Institute on Aging, accessed 10/14/2023, https://www.nia.nih.gov/health/how-alzheimers-disease-treated.
[107] See label for donepezil hydrochloride tablet, ANDA 078662. NIH DailyMed, accessed 12/05/2023, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=297e86e8-d248-4cc9-9d9c-2ef9efb4414d.
[108] See label for galantamine, ANDA 078185. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d5b0e225-e94d-4324-afb2-b6e51c949dd0.
[109] See label for Adlarity (donepezil), NDA 212304. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=212304.

- Memantine hydrochloride (e.g., oral tablet[110], oral capsule[111], oral solution[112]): an N-methyl-D-aspartate (NMDA) receptor antagonist
- Lecanemab-irmb (Leqembi IV injection[113]): targets protein beta-amyloid to help reduce amyloid plaques
- Aducanumab-avwa (Aduhelm IV injection[114]): targets beta-amyloid
- Brexipiprazole (Rexulti oral tablet[115]): atypical antipsychotic for treatment of agitation associated with dementia due to AD

d. Conclusion

Available clinical information suggests that ibutamoren mesylate lacks effectiveness in treating AD. This is especially concerning given the serious nature of AD. Additionally, there are currently FDA-approved therapies with established efficacy for the proposed use.

Overall Conclusions: We conclude that there is insufficient information to support the effectiveness of ibutamoren mesylate for the treatment of GHD, osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease. Most of the available clinical data have limitations such as lack of demonstration of clinically meaningful therapeutic effects, small study sizes, and short study durations. Clinical trials did not evaluate, or did not demonstrate, that ibutamoren mesylate provides clinically meaningful improvement for the proposed uses GHD, osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease. In addition, there are currently FDA-approved drugs with established efficacy for GHD, osteoporosis, obesity, and Alzheimer's disease, and alternative treatment methods for hip fracture and sarcopenia.

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

1. Nonclinical Assessment

The nominators submitted nonclinical information with the nominations. Specifically, the nominators provided articles that report the pharmacological properties of ibutamoren mesylate (Bailey et al. 1999; Holst et al. 2009; Muller et al. 2002). The articles do not include nonclinical toxicity data on ibutamoren mesylate.

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[110] See label for memantine hydrochloride, ANDA 090048. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a71e2482-5266-d03e-8b36-862afe78c9a4.
[111] See label for memantine hydrochloride, ANDA 205825. NIH DailyMed, accessed 12/05/2023, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f2b7538d-8ca1-4ac7-a172-d268e2fa9a52.
[112] See label for memantine hydrochloride, ANDA 204033. NIH DailyMed, accessed 10/14/2023, https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e4be161c-3bca-4e7e-b80c-c3f6dde3addf.
[113] See label for Leqembi® (lecanemab-irmb, BLA 761269/S-1. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761269.
[114] This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). See label for Aduhelm (aducanumab-avwa) injection, BLA 761178/S-11. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761178.
[115] See label for Rexulti (brexipiprazole) tablets, NDA 205422/S-9. Drugs@FDA, accessed 10/14/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=205422.

The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemical Agency, Google, Generally Recognized as Safe Notice Inventory, LactMed, LiverTox, National Toxicology Program website, PubChem, PubMed, Pharmapendium, USP, and Web of Science.

a. General pharmacology of the drug substance

Ibutamoren mesylate is the mesylate salt of a non-peptide small molecule that binds to and activates ghrelin receptors (Holst et al. 2009). Acting as a ghrelin receptor agonist, ibutamoren (the active moiety of the salt) can induce GH release from the anterior pituitary gland in vitro and in vivo (reviewed in Muller et al. 2002; Patchett et al. 1995).

Ghrelin receptors are G-protein coupled receptors that signal primarily via $G_{\alpha 11/q}$-mediated phospholipase activation (Howard et al. 1996; Root and Root 2002). In addition to binding to and activating ghrelin receptors on pituitary somatotrophs to directly stimulate GH release from these cells, ibutamoren (the active moiety of the salt) can bind to and activate ghrelin receptors on growth hormone releasing hormone (GHRH)-positive neurons in the hypothalamus to trigger release of GHRH that, in turn, can stimulate GH release from the somatotrophs (Bailey et al. 1999; Patchett et al. 1995).

A single intravenous (IV) or oral dose of ibutamoren mesylate increases serum GH levels in different animal species, including dogs and rats (Lee et al. 2018). However, continuous treatment has been reported to abolish the GHS activity of ibutamoren mesylate. For instance, serum GH concentrations in rats treated daily with ibutamoren mesylate for 6 weeks (4 mg/kg/day; oral gavage) are comparable to those in untreated rats (Jacks et al. 1996; Lee et al. 2018). It has been proposed that the loss of the GHS activity may be due to: (i) ibutamoren mesylate-induced increased expression of hypothalamic somatostatin, a hormone that suppresses GH release from the pituitary (Lee et al. 2018), and/or (ii) agonist-induced ghrelin receptor internalization and desensitization.

Although ghrelin receptors are highly expressed in the heart, an in-vitro study reported that ibutamoren mesylate (1000 nM) had no effect on the hemodynamics of isolated heart preparations from rats (Frascarelli et al. 2003). The nonclinical finding that in-vivo treatments of in rats with ibutamoren mesylate and other ghrelin receptor agonists induce hypotension (Sales da Silva et al. 2020) suggests that a compensatory increase in cardiac output may develop following in-vivo treatment with ghrelin receptor agonists.

Ghrelin receptors are also 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 also reported that, in rats, ghrelin: (i) stimulates dopamine release in the VTA, a response typically evoked by drugs of abuse (Edvardsson et al. 2021), and (ii) increases heroin consumption and seeking behavior (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 rewarding brain regions, ibutamoren mesylate, 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 lacking to demonstrate whether ibutamoren mesylate has reinforcing and/or addictive properties.

b. Pharmacokinetics/Toxicokinetics (TK)

The oral bioavailability of ibutamoren mesylate in dogs is reported to be >60% (Patchett et al. 1995).

An in-vitro study carried out in equine liver microsomes revealed that ibutamoren is metabolized via CYP450-catalyzed phase I reactions, primarily oxidation, and phase II reactions, primarily glucuronidation (Philip et al. 2021). An in-vivo study conducted with two thoroughbred horses (one gelding and one mare) treated orally with ibutamoren mesylate (125 mg, once a day for 3 days) confirmed the in-vitro findings (Cutler et al. 2022).

c. Acute toxicity[116]

At the time of this evaluation, FDA did not identify nonclinical acute toxicity studies with ibutamoren mesylate in the publicly available scientific literature.

d. Repeat-dose toxicity[117]

At the time of this evaluation, FDA did not identify nonclinical repeat-dose toxicity studies with ibutamoren mesylate in the publicly available scientific literature.

e. Genotoxicity[118]

At the time of this evaluation, FDA did not identify nonclinical genotoxicity studies with ibutamoren mesylate in the publicly available scientific literature.

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[116] 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.

[117] 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.

[118] 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

f. Developmental and reproductive toxicity[119]

At the time of this evaluation, FDA did not identify nonclinical developmental and reproductive toxicity studies with ibutamoren mesylate in the publicly available scientific literature. 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-growth hormone releasing peptide-6, hereafter referred to as D-Lys^3-GHRP-6) can have 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 ibutamoren is an example.

In the study by Luque and collaborators, treatments consisted of subcutaneous (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).

- 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) and 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 both ghrelin and the antagonist, delayed embryo development. In experimental group 3, ghrelin (4 nmol/day) and 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-Lys3-

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.

[119] 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.

GHRP6) or a ghrelin receptor agonist (ghrelin) negatively affected fertilization and embryofetal development.

It remains to be determined whether ibutamoren mesylate, a substance that like ghrelin acts as a ghrelin receptor agonist, can negatively impact fertilization and embryofetal development as ghrelin did in the studies discussed above.

g. Carcinogenicity[120]

At the time of this evaluation, FDA did not identify nonclinical carcinogenicity studies with ibutamoren mesylate in the publicly available literature.

Conclusions: According to nonclinical pharmacological studies, the desired clinical response of increased GH secretion is likely to be lost during continuous oral treatment with ibutamoren mesylate. In addition, ibutamoren mesylate can induce hypotension in rats. As with other ghrelin receptor agonists, ibutamoren mesylate may have behavioral reinforcing properties that could contribute to development of addiction. From the nonclinical toxicological perspective, the publicly available finding that developmental toxicity can be induced by gestational exposures to a substance that, like ibutamoren, acts as a ghrelin receptor agonist raises additional safety concerns.

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), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), ClinicalTrials.gov, relevant professional healthcare organization websites, and various online clinical references and websites, such as information from the NIH.

As noted earlier, ibutamoren mesylate is also known as MK-677, MK-0677, MK0677, and LUM-201; the name listed in the reference will be used in its corresponding description below.

a. Pharmacokinetic data

References submitted by the nominators briefly discuss human pharmacokinetic (PK) information:

- Chapman et al. 1996 mentioned MK-677's "high oral bioavailability and its long duration of action," but further details on the PK profile were not provided.

[120] 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.

- Thorner 1997 stated that "[a] single dose of MK-677 is long-acting (24 hours) and is orally active;" further details on PK profile were not provided.

We did not identify additional PK data for ibutamoren mesylate in our search of the medical literature.

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

FAERS

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for ibutamoren mesylate (search strategy also included "ibutamoren") through October 1, 2023. The search retrieved three applicable reports which are summarized below (none of the cases specify use of a compounded product):[121]

- One report describes vomiting and upper abdominal pain after taking MK677. FDA's ability to interpret this report is limited by insufficient case details and unspecified time between MK677 intake and reported AEs.

- One report describes a 41-year-old male who was "very sick" and could not "feel one of his fingers." Per report, he took "Ibuta-677" (salt was not specified) for 5 days. FDA's ability to interpret this report is limited by insufficient case details and unspecified time between drug intake and reported AEs. There is an unclear temporal relationship between ibutamoren intake and hypoesthesia of the fingers.

- One report describes a 68-year-old male with a history of pulmonary embolism and cardiac stent taking ibutamoren (salt was not specified) for weight loss who sustained permanent secondary deficits from a "large intracranial infarct." Concomitant medications included "Affinity mood, Affinity Sleep, Affinity Health," metoprolol, omeprazole, testosterone, and tamoxifen. Interpretation of the role of ibutamoren is limited by concomitant medications.

CAERS

CFSAN collects reports of AEs involving food, cosmetics, and dietary supplements in the CAERS database.[122] A search of CAERS was conducted on August 17, 2023, for AEs associated with ibutamoren mesylate. Three cases associated with the use of ibutamoren were reported from December 2015 through March 2022, two of which are summarized below (one of the cases, a

[121] 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 ibutamoren mesylate based on FAERS data alone.

[122] Ibutamoren is listed in the NIH Dietary Supplement Label Database. See: NIH Office of Dietary Supplements, Dietary Supplement Label Database, accessed 10/14/2023, https://dsld.od.nih.gov/search/ibutamoren%20mesylate/bWFya2V0X3N0YXR1cz1hbGwvZW50cnlfZGF0ZT0yMDE1LDIwMjIvc29ydD1tYXRjaC9wYWdlX3NpemU9MjAv.

report of a 68-year-old man who experienced a stroke while taking ibutamoren, is already summarized above in the FAERS section):[123]

- A 30-year-old male was taking "DNA Pharma SARM Ibutamoren MK-677" (ibutamoren 25 mg)[124] and experienced weight loss, diarrhea, headache, and abdominal discomfort. No further information was provided (i.e., duration of use, concomitant medications, or temporal relationship to product) which limits interpretation of this AE report.

- A male (age not specified) consumed "DNA Anabolics SARM MK 677" (ibutamoren)[125] capsules (dosage strength not specified) as a "strength enhancing supplement." After taking the product for "several weeks," he noticed that the product label stated, "Not for Human Consumption, For Laboratory Use Only." He reported decreased activity and mood alteration with the use of this product (duration unspecified), which subsided after he stopped taking the product. The temporal relation suggests a potential association, but information is too limited to establish causality.

Published Case Reports

We found three case reports in published medical literature that reported AEs associated with ibutamoren use; however, interpretation of causality is limited by use of concomitant medications, specifically SARMs, in all cases.

- Flores et al. 2019 reported on the case of a 24-year-old man who developed hepatomegaly and elevated bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT). He reported recently using "gym supplements" with active components LGD-4033 and MK-2866 (both SARMs)[126,127] and MK-677 (dosage strengths not reported).

- Cardaci et al. 2022 reported on a 25-year-old male who self-administered oral LGD-4033 10 mg (a SARM)[128] and MK-677 15 mg daily for 5 weeks. Authors observed increased body mass, total lean body mass, and total fat mass; decreased BMD; increased AST and ALT; decreased high-density lipoprotein (HDL) cholesterol; and increased total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol. Authors noted that previous investigations described MK-677-mediated increases in BMD and blood glucose and

[123] Both cases refer to the ingredient name as "ibutamoren" and do not specify the mesylate salt.
[124] It should be noted that MK-677 is a GHS, not a SARM. SARMs are a class of therapeutic compounds that selectively bind androgen receptors in certain tissues and may have similar anabolic properties to anabolic steroids (See: Selective Androgen Receptor Modulators (SARMs) – What Athletes Need to Know. U.S. Anti-Doping Agency (USADA) website, accessed 10/30/2023, https://www.usada.org/spirit-of-sport/education/selective-androgen-receptor-modulators-sarms-prohibited-class-anabolic-agents/).
[125] Ibid.
[126] See: Top 5 Things to Know About LGD-4033. USADA website, accessed 10/30/2023, https://www.usada.org/spirit-of-sport/education/5-things-to-know-about-lgd-4033/.
[127] MK-2866 is also known as ostarine. See: Substance Profile: What Athletes Need to Know about Ostarine. USADA website, accessed 10/30/2023, https://www.usada.org/spirit-of-sport/education/substance-profile-ostarine/.
[128] See: Top 5 Things to Know About LGD-4033. USADA website, accessed 10/30/2023, https://www.usada.org/spirit-of-sport/education/5-things-to-know-about-lgd-4033/.

decreases in LDL cholesterol and suggested that the discrepancy with their findings was likely attributable to coadministration with LGD-4033.

- Sotornik et al. 2022 reported on a 47-year-old male recreational bodybuilder who developed hyperglycemia, elevated glycosylated hemoglobin A1C (HbA1C), and dyslipidemia. He reported recent (3 months) use of performance-enhancing drugs (PEDs) purchased from a fitness center, including two SARMs (RAD140 5 mg twice daily and andarine 25 mg twice daily, 5 days per week)[129] as well as ibutamoren (salt was not specified) 25 mg daily, 5 days per week. He had a family history of obesity and diabetes, and a check-up 3 years earlier showed metabolic syndrome. Authors believed his hyperglycemic crisis and lipolysis were triggered by the addition of PEDs, despite this dysmetabolic status.

c. Clinical studies assessing safety

A summary of relevant safety data on oral administration of ibutamoren mesylate from clinical studies is provided if safety outcomes were reported. We discuss references submitted by the nominators and publications we found in the published medical literature.

Growth Hormone Deficiency

- Chapman et al. 1996 investigated the stimulatory effects on IGF-1 in 32 healthy subjects ages 64 to 81 years who received placebo or MK-677 daily for two separate 14-day study periods with a 14-day extension:
  - MK-677 2 mg (period 1) then MK-677 25 mg (period 2) (n=10)
  - Placebo (period 1 and 2) (n=10) (varied if given in morning or evening)
  - MK-677 10 mg (period 1 and 2) (n=12) (varied if given in morning or evening)

  There were no serious clinical or laboratory AEs. There were five reports of mild appetite increase and three reports of mild abdominal pain in subjects on MK-677 (doses not specified). In subjects on MK-677 25 mg, mean serum cortisol levels did not differ from baseline after 14 days and mean prolactin concentration increased approximately 24% but remained within the normal range.[130] Fasting blood glucose increased above baseline by 25.3 ± 6.6% (mean ± standard error [SE]) at 2 weeks and 26.9 ± 6.8% at 4 weeks in subjects on MK-677 25 mg. The authors discussed that changes in glucose were correlated with body mass index (BMI), suggesting that the GH stimulatory effects of MK-677 may result in impaired glucose tolerance in individuals with predisposing risk factors. The authors noted that it was not known whether these effects on carbohydrate metabolism would persist with longer term administration and stated that further studies were needed to establish the long-term safety of MK-677, particularly its effect on glucose and insulin levels.

[129] See: Selective Androgen Receptor Modulators (SARMs) – What Athletes Need to Know. U.S. Anti-Doping Agency (USADA) website, accessed 10/30/2023, https://www.usada.org/spirit-of-sport/education/selective-androgen-receptor-modulators-sarms-prohibited-class-anabolic-agents/.

[130] Prolactin levels increased from 7 ± 0.5 to 8.6 ± 0.7 mcg/L (mean ± SE). Reference intervals for men and women ages 51 to 80 years are 3.6 to 25.2 ng/mL. See: Prolactin. Labcorp website, accessed 02/12/2024, https://www.labcorp.com/tests/004465/prolactin.

- Chapman et al. 1997 evaluated nine adults with severe GHD[131] who received MK-677 or placebo for two 4-day periods. Group 1 (n=4) received placebo and MK-677 10 mg daily in a cross-over fashion in periods 1 and 2, and Group 2 (n=5) received MK-677 10 mg in period 1 followed by MK-677 50 mg in period 2. Fasting and postprandial insulin and postprandial glucose increased with MK-677; postprandial insulin also increased in the placebo group. Per the authors, there were no "significant changes" from baseline in cortisol or prolactin levels. Reported AEs included:
  - MK-677 10 mg: headache (1 report), diarrhea (1), dry skin (3), increased AST 98 U/L (normal range cited in reference 0–50 U/L) (1); all possibly drug-related per the investigator.
  - MK-677 50 mg: night sweats (1), numbness in ulnar nerve distribution area of right hand that lasted one day (1); not specified if possibly drug-related.

- Codner et al. 2001 evaluated ibutamoren mesylate in 18 children with GHD. Group 1 (n=2) received ibutamoren mesylate 0.2 mg/kg/day on days 1-7 and placebo on days 8-14. Group 2 (n=4) received placebo on days 1-7 and ibutamoren mesylate 0.2 mg/kg/day on days 8-14. Group 3 (n=12) received placebo on days 1-7 and ibutamoren mesylate 0.8 mg/kg/day on days 8-14. Groups 1 and 2 were studied first to assess safety at the low dose prior to proceeding to the higher dose. On day 15 all subjects received a single 0.8 mg/kg dose of ibutamoren mesylate. There was no change in serum prolactin, glucose, peak serum cortisol, insulin, or 24-hour urinary free cortisol with ibutamoren mesylate 0.8 mg/kg/day for 8 days (Group 3). Drug-related AEs included:
  - Ibutamoren mesylate 0.2 mg/kg:
    - Increased creatinine (1 report); values returned to normal after completion of treatment with the study drug (the timeframe was not specified)
    - Increased white blood cell (WBC) count (1); returned to normal after completion of treatment with the study drug (the timeframe was not specified)
  - Ibutamoren mesylate 0.8 mg/kg:
    - Vomiting (2)
    - Headache (1)
    - Increased appetite (1)
    - Asymptomatic increases (1.5-fold to 4-fold) in serum transaminase levels, which declined to within normal range 1 to 4 weeks after the final dose of study drug (3); two subjects had concomitant viral symptoms and medications
    - Increased WBC count (1); returned to normal after completion of treatment with the study drug (the timeframe was not specified)

- Bright et al. 2021 evaluated daily LUM-201 in 68 prepubertal children with GHD. After measurement of peak GH response to a single dose of LUM-201 0.8 mg/kg, subjects received LUM-201 0.4 mg/kg/day (n=22), LUM 0.8 mg/kg/day (n=24), or placebo (n=22) for 6 months. Authors report that LUM-201 was "generally well tolerated." The most frequently reported drug-related AE was "increased appetite," with 2.5- to 3-fold higher incidence rate reported in the LUM-201 group compared to placebo. Authors noted that increased appetite

[131] Authors studied young adults who had been diagnosed with GHD during childhood and had not had pituitary or hypothalamic tumor, surgery, or radiotherapy. Subjects had been treated with GH during childhood but had not been treated with GH or any GHS for at least 6 months prior to the study.

can be concurrent with catch-up growth and therefore may be a consequence of the therapeutic goal.

Osteoporosis

- Murphy et al. 1999 evaluated daily MK-677 on markers of bone turnover in three trials:[132]
  - Healthy subjects aged 65 to 85 years received placebo, MK-677 10 mg, or MK-677 25 mg for 2 weeks (n=10-12 per group).
  - Healthy subjects ages 65 to 85 years were randomized to receive placebo for 4 weeks (n=20), or MK-677 25 mg for 2 weeks followed by MK-677 50 mg for 2 weeks (n=30).
  - Ambulatory subjects ages 65 to 94 years with functional impairment[133] received placebo for 9 weeks (n=28) or MK-677 5, 10, or 25 mg for 2 weeks, followed by MK-677 25 mg for 7 weeks (n=63).

  There were no drug-related serious adverse events (SAEs) reported in those who received MK-677 (no mention of SAEs with placebo). Two subjects discontinued MK-677 due to an AE felt to be drug-related by the investigator: lightheadedness/tiredness and shortness of breath (1 subject) and warm sensation (1). Musculoskeletal complaints were reported by 14% of subjects in the MK-677 and 11% in the placebo group. Fluid retention was reported by 4% in the MK-677 and 5% in the placebo group. One subject receiving MK-677 (dose not specified) reported carpal tunnel syndrome.

  Hyperglycemia was the most common laboratory AE with MK-677. Increased glucose values were noted in the 2- and 4-week studies, but no subject discontinued due to hyperglycemia. In the 4-week study, 7% of subjects (n=2) receiving MK-677 had reversible increases (1.5-2.5 times greater than the upper limit of normal) in serum transaminase values. Transaminase elevations were not noted in the other two studies in subjects receiving MK-677. In the 9-week study, five subjects (6%) reduced the MK-677 dose from 25 mg to 10 mg due to hyperglycemia (fasting glucose >140 mg/dL); three of these subjects were subsequently discontinued due to hyperglycemia despite dose reduction. Also, mean increase from baseline prolactin of 27% was observed, but post-treatment values were within physiologic range.

- Murphy et al. 2001 evaluated alendronate and MK-677, individually and in combination, in 292 subjects with osteoporosis. Postmenopausal women with osteoporosis ages 64 to 85 years received MK-677 25 mg plus alendronate 10 mg (MK-677/alendronate) (n=111); alendronate 10 mg (n=109); MK-677 25 mg (n=36); or placebo (n=36) for 12 months. Subjects who received MK-677 or placebo through month 12 received MK-677/alendronate from months 12-18 while the other groups continued their assigned therapy. Subjects also received oral calcium carbonate 500 mg daily. Of the 292, 25 (8.6%) subjects discontinued due to AEs that were judged to be related to study treatment, listed below per treatment arm:

[132] We note that these trials were not conducted in subjects with osteoporosis but are discussed in this subsection because they evaluated markers of bone turnover. The adult skeleton is continuously remodeled via bone resorption and formation; bone resorption later in life and prolonged bone loss leads to low BMD and eventually osteoporosis. Bone turnover markers have been used for research purposes to better understand the effects of bone-active medications and diseases (Bauer 2019).

[133] Subjects had a strength deficit at extensor or flexor muscles of the knee and met objective criteria for musculoskeletal impairment based on a National Institute of Aging performance-based measure score of 4–11.

- MK-677/alendronate:
  - Hypertension (2 subjects)
  - Bloating/fluid retention (2)
  - Headache, night sweats, pain, hip/leg (1)
  - Heartburn (1)
  - Rash (1)
  - Hyperglycemia (3)
  - Hyperprolactinemia (1)
- Alendronate (1 subject each):
  - Bloating/fluid retention
  - Headache, night sweats, pain, hip/leg
  - Indigestion/abdominal pain
  - Heartburn
  - Esophageal ulcer
- MK-677:
  - Headache, night sweats, pain, hip/leg (1)
  - Indigestion/abdominal pain (1)
  - Hyperprolactinemia (2)
  - Transaminase elevation, >3 times the upper limit of normal (2)
- Placebo (1 subject each):
  - Indigestion/abdominal pain
  - Esophageal ulcer
  - Rash

Per the authors, GH-mediated AEs were noted in groups receiving MK-677:

- Weight gain: MK-677/ alendronate or MK-677 groups (21),
- Edema/swelling: MK-677/ alendronate or MK-677 groups (17),
- Abdominal distension: MK-677/alendronate group (10),
- Carpal tunnel syndrome: MK-677/alendronate group (1), placebo (1),
- Breast tenderness: MK-677 group (1), alendronate group (2)

No deaths or hip fractures occurred. One subject in the MK-677/alendronate group had a vertebral compression fracture of L1 and T12 identified radiographically. Seventeen patients experienced a "clinical syndrome of fracture"[134] reported as AE: MK-677/alendronate (6), alendronate (9), MK-677 (2), and placebo (0).

Hip Fracture

- Bach et al. 2004 evaluated subjects ages ≥ 65 years recovering from hip fracture who were randomized to receive MK-0677 25 mg (n=84) or placebo (n=77) once daily for 6 months. Subjects were followed for an additional 6 months after completion of therapy.

  SAEs were reported in both groups at rates of: MK-0677 24% (20/84) versus placebo 18% (14/77). These SAEs included reports of thrombosis, four in the MK-0677 and none in the placebo group; thromboses were reported as non-drug related but no details were provided. Six deaths were reported, three in the MK-0677 group during active treatment and three in the placebo group during months 7-12; causes of death were varied and were assessed as not

[134] "Clinical syndrome of fracture" definition was not provided in the reference. We were unable to find its definition in the medical literature.

being related to treatment. The MK-0677 group reported increases in serum glucose, insulin, and HbA1c. The mean changes from baseline, MK-0677 versus placebo group, were: glucose 8.0 versus -1.6 mg/dL, insulin 2.0 versus -4 mcU/mL, and HbA1C 0.7% versus 0.3%.

The MK-0677 group reported more drug related AEs (reported by investigator as possibly, probably, or definitely drug related) compared to placebo: 24% (20/84) versus 17% (13/77). There were more discontinuations due to clinical AEs in the MK-0677 group (12% [10/84]) compared to placebo (2.6% [2/77]). These occurred for a variety of reasons; per the authors, there were no evident treatment-related trends in reasons for discontinuation. The most common AE (drug related and non-drug related) reported during the study was falls (MK-0677 18% versus placebo group 22%). The authors noted that there were more reports of edema and fluid overload in the MK-0677 group (n=16) than with placebo (n=10) and more reports of musculoskeletal (pain) in the placebo group (n=56) than MK-0677 (n=35).

- Adunsky et al. 2011 evaluated patients ages ≥ 60 years with a recent unilateral hip fracture assigned to receive MK-0677 25 mg (n=62) or placebo (n=61) daily for 24 weeks. One or more AEs were reported by 48 (77%) patients receiving MK-0677 versus 33 (55%) with placebo. Below is a summary of AEs as described by the authors:
  - SAEs: 15 patients (24%) on MK-0677 and eight (13%) on placebo (authors did not specify the SAEs and whether they were drug-related). One patient taking MK-0677 died during the study due to SAEs of sepsis and pneumonia; these AEs were not considered by the investigator to be related to the study drug.
  - Discontinuations due to AEs: seven patients (11.3%) on MK-0677 and four (6.6%) on placebo (the range of reasons for discontinuation was broad, making it difficult to conclude whether there may be additional safety concerns with MK-0677)
  - AEs which may possibly be mechanism-based included (per authors):
    - Congestive heart failure (CHF): four patients (6.5%) in the MK-0677 group versus one (1.7%) in placebo
    - Systolic and diastolic blood pressure (BP) increased with MK-0677 versus placebo by week 4 and remained elevated throughout the study (mean change from baseline for systolic BP ranged from 11.9 to 16.4 mmHg in the MK-0677 group and from 2.3 to -2.3 mmHg in placebo; the mean change from baseline for the diastolic BP ranged from 4.9 to 7.5 mmHg in the MK-0677 group and from 2.2 to 3.7 mmHg in placebo)
  - Mean body weight increased in the MK-0677 group gradually during the study and decreased with placebo
  - Clinical and laboratory AEs with higher frequency in the MK-0677 group included:
    - Myalgia: MK-0677 4 (6.5%) versus placebo 1 (1.7%),
    - Arthralgia: MK-0677 4 (8.1%) versus placebo 1 (1.7%),
    - Elevated blood glucose: MK-0677 4 (6.5%) versus placebo 1 (1.7%)
    - Increased HbA1C: MK-0677 3 (4.8%) versus placebo 0

The study was terminated early due to a safety signal of CHF (four in the MK-0677 group). The authors concluded that, "the AEs associated with MK-677 in a relatively small patient population makes it likely that the risk benefit of this drug for this indication is not acceptable," and stated, "MK-0677 has an unfavorable safety profile" in hip fracture patients.

Alzheimer's Disease

Sevigny et al. 2008 evaluated patients with mild to moderate AD who were randomized to receive MK-677 25 mg (n=282) or placebo (n=281) daily for 12 months. Patients were allowed to take marketed cholinesterase inhibitors or memantine if on stable doses. AEs were recorded by a blinded investigator as to seriousness, intensity, and drug-relatedness (possible, probably, definite drug-related, or not drug-related). Incidence of AEs, SAEs, and serious drug-related AEs were comparable between groups. Per authors, "drug-related clinical adverse experiences occurred in 100 (35.5%) patients in the MK-677 group and 67 (23.9%) in the placebo group …The imbalance in distribution of these investigator-determined drug-related adverse experiences occurred primarily in the categories of general disorders (fatigue, peripheral edema), nervous system disorders (dizziness, headache, somnolence), and psychiatric disorders (agitation, confusional state)." Further details were not provided on these AEs. Thirty-two (11.3%) patients in the MK-677 group and 29 (10.4%) in placebo discontinued therapy due to AEs. Three patients on MK-677 and seven on placebo died from AEs that began while receiving study drug or within 14 days of the last dose of study drug; none of these were considered to be drug-related. Drug-related laboratory AEs occurred more frequently with MK-677 (22.1%) than placebo (10%), driven almost exclusively by blood glucose and HbA1C; blood glucose increased in 15.4% of patients on MK-677 versus 4.6% with placebo, and 11.1% of patients on MK-677 had an increase in HbA1C versus 1.4% with placebo.

Obesity

Svensson et al. 1998b evaluated 24 subjects with obesity ages 18 to 50 years who received MK-677 25 mg (n=12) or placebo (n=12) daily for 8 weeks. Peak serum prolactin and cortisol increased after MK-677 first administration but were not significantly different than placebo at 2 or 8 weeks. Fasting glucose and insulin were unchanged in MK-677 and placebo groups, whereas an oral glucose tolerance test showed impairment of glucose homeostasis at 2 and 8 weeks in the MK-677 group. Two subjects discontinued after 1-2 weeks (one in the MK-677 group and the other unspecified); one subject was diagnosed with hypothyroidism based on pre-study testing, and one subject experienced a 3-fold increase in ALT and AST which decreased spontaneously after discontinuation of MK-677 (of note, this subject violated study protocol by ingesting alcohol around the time of ALT/AST elevation). Five subjects on MK-677 had mild AEs that were considered to be drug-related:

- Transient gastritis at 4 weeks and transient mild sweating at 6 weeks (1 subject)
- Glucose concentration of 10 mmol/L at 6 weeks (spontaneously decreased 1 week later) (1)
- Asymptomatic transient increases in ALT and/or AST (specific values not reported) (3)

Sarcopenia

- Plotkin et al. 1997 (abstract only) is a pilot study that evaluated MK-677 in men and women ages 65 to 94 (N=104) with known strength deficits.[135] Subjects received daily placebo or MK-677 5 mg, 10 mg, or 25 mg for 2 weeks; subsequently, all MK-677 groups received MK-677 25 mg for 7 additional weeks. In subjects on MK-677, there was no detectable change in mean 24-hour cortisol level, and serum prolactin levels increased by 17% but remained within normal range. An approximate 8% increase in mean fasting blood sugar (5.3 ± 0.1 to 5.7 ± 1.7 mmol/L) was observed at week 9.

[135] Strength deficits were not described in the abstract.

- Murphy et al. 1998 evaluated MK-677 for diet-induced protein catabolism in eight healthy male subjects ages 24 to 39 years. Subjects were calorically restricted for two 14-day periods; during the last 7 days of each diet period, subjects received MK-677 25 mg or placebo once daily. AEs included "short-lived" reports of stomachache and dizziness (n=1, MK-677), diarrhea (n=1, placebo), and headache (n=2, placebo). An elevated fasting blood glucose (142 mg/dL) was noted on day 14 in one subject on MK-677.

- Nass et al. 2008 evaluated healthy adults ages 60 to 81 years who were randomized to receive MK-677 25 mg (n=47) or placebo (n=24) once daily for 1 year. After 1 year, placebo-treated subjects were crossed over to MK-677 (n=20), and MK-677-treated subjects were randomized to continue MK-677 (n=20) or change to placebo (n=19). The most frequent AEs were:
  - Mild transient lower extremity edema (MK-677 = 19/43, placebo = 6/22 subjects)
  - Transient muscle pain (MK-677 = 14/43, placebo = 2/22)
  - Increased appetite (MK-677 = 29/43, placebo = 8/22)

  Fasting blood glucose increased on average 5 mg/dL on MK-677 and insulin sensitivity declined. Cortisol decreased in placebo and increased in the MK-677 group. HbA1c increased 0.2% on MK-677. In four subjects, MK-677 dose was down-titrated to 10 mg because of:
  - Increased fasting glucose after crossover from placebo to MK-677 in year 2
  - Increased fasting glucose on MK-677 (1 subject, withdrew after 3 months)
  - Increased joint pain on MK-677 (2 subjects, withdrew after 12 months)

  Additional AEs were reported in the following groups with no causality assessment provided:
  - MK-677: adenocarcinoma of the tongue diagnosed at 12 months (1 subject); myocardial infarction 7 days after starting treatment (1 subject)
  - Placebo: renal cell carcinoma at 6 months (1 subject)
  - MK-677 then placebo: colon cancer at the end of year 2 (on MK-677 in year 1 and placebo on year 2) (1 subject)

In addition, a literature review by Sigalos and Pastuszak 2018 was cited by one of the nominators. This reference described safety and efficacy of GHSs,[136] including studies that evaluated effects of ibutamoren mesylate in GHD, hip fracture, obesity, sleep, nitrogen wasting in a catabolic state, bone turnover, and changes in body composition in elderly subjects. Relevant safety information on ibutamoren mesylate from studies (Chapman et al. 1996; Murphy et al. 1998; Svensson et al. 1998b; Murphy et al. 1999; Codner et al. 2001; Murphy et al. 2001; Bach et al. 2004; Nass et al. 2008; Sevigny et al. 2008; Adunsky et al. 2011) discussed in this literature review are individually described above.

In summary, ibutamoren mesylate has been evaluated in various populations including adults and children with GHD; adults with obesity; and older adults with strength deficits, functional impairment, osteoporosis, hip fracture, and AD. Ibutamoren mesylate was evaluated in fixed single or multiple doses ranging from 2 mg to 50 mg per day or weight-based doses ranging from 0.2 mg/kg/day to 0.8 mg/kg/day with study durations up to 2 years. Serious AEs reported in the

[136] GHSs are 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).

studies included CHF, thrombosis, cancer, and myocardial infarction. AEs leading to discontinuation included hyperglycemia; hyperprolactinemia; increased transaminase levels; hypertension; bloating/fluid retention; headache, night sweats, hip/leg pain; indigestion/abdominal pain; heartburn; rash; lightheadedness/tiredness and shortness of breath; and warm sensation. Common AEs that were reported in multiple studies included hyperglycemia, increased HbA1C, increased insulin, increased transaminase levels, headache, musculoskeletal complaints, fluid retention, and increased appetite.

d. Other safety information

GHSs, such as ibutamoren mesylate, 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) product 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.[137] FDA is concerned that similar potential risks will be associated with the use of ibutamoren mesylate. A number of AEs that are known to be associated with rhGH therapy were reported with ibutamoren mesylate in the clinical studies discussed in Section II.C.2.c (e.g., hyperglycemia and fluid retention). In addition, there is a risk of QT prolongation associated with the use of the approved GHS macimorelin acetate (Macrilen oral solution[138]). There are insufficient data to conclude that ibutamoren mesylate, a GHS that stimulates the GH/IGF-1 axis, would not raise safety concerns similar to those associated with approved products that stimulate GH release.

When compared with younger adults, older individuals with high IGF-1 levels have been observed to be at increased risk for incident disease (such as dementia, vascular disease, and osteoporosis) or death. In addition, higher IGF-1 levels appeared to be associated with cancer risk across ages. (Zhang et al. 2021).[139] We note that the proposed uses of ibutamoren mesylate include conditions that typically affect older adults, such as osteoporosis, hip fracture, sarcopenia, and Alzheimer's disease. There is a lack of safety data on the use of ibutamoren mesylate and its risks associated with higher IGF-1 levels, particularly in the population in which it is proposed to be used.

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

[137] See, e.g., label for Humatrope (somatropin), BLA 019640/S-105. Drugs@FDA, accessed 12/11/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019640.
[138] Macrilen is indicated for the diagnosis of adult GHD. See label for Macrilen (macimorelin acetate), NDA 205598. Drugs@FDA, accessed 12/12/2023, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=205598.
[139] See: IGF-1 Hormone: Good for the Young but Bad for the Old. Albert Einstein College of Medicine website, accessed 02/12/2024, https://www.einsteinmed.edu/research-briefs/2640/igf-1-hormone-good-for-the-young-but-bad-for-the-old/.

There are FDA-approved drug products that treat the same medical conditions as those proposed for the ibutamoren mesylate compounded drug products, as described in Section II.C.[140] There are no FDA-approved drug products for sarcopenia or hip fracture.

Conclusions: Based on available clinical data, there are serious safety concerns related to ibutamoren mesylate use including hyperglycemia, liver enzyme elevations, edema and fluid overload, and CHF in elderly patients recovering from hip fracture. Other AEs reported in clinical trials include musculoskeletal pain, increase in appetite, and hyperprolactinemia. FDA's ability to interpret CAERS and FAERS reports is limited by lack of information in the reports and confounding factors such as concomitant medications. Ibutamoren mesylate stimulates production of endogenous GH which in turn stimulates production of IGF-1. There are known potential risks associated with the use of drug products that increase IGF-1 levels, such as glucose intolerance and fluid retention. In addition, we note that the proposed uses of ibutamoren mesylate include conditions that typically affect older adults, such as osteoporosis, hip fracture, sarcopenia, and Alzheimer's disease. Older individuals with high IGF-1 levels have been observed to be at increased risk for incident disease or death; higher IGF-1 levels also appeared to be associated with cancer risk across ages. There is lack of safety data on the use of ibutamoren mesylate and its risks associated with higher IGF-1 levels particularly for its proposed uses in older adults. In addition, there are currently available FDA-approved therapies for the treatment of adults with GHD and growth failure due to GHD in children, osteoporosis, obesity, and Alzheimer's disease; these drugs have well-characterized safety profiles and have been shown to be safe for their labeled use.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate ibutamoren mesylate for the 503A Bulks List. After considering the information currently available, a balancing of the criteria **weighs against** ibutamoren mesylate being placed on that list based on the following:

1. Ibutamoren mesylate is a small chiral molecule containing serine and a non-proteinogenic amino acid, 2-aminoisobutyric acid (Aib) as a substructure. As reported in the literature, it is stable at -20 °C for 3 years in powder form.

   In the CoAs provided by both nominators, there is no information about the chiral purity (% enantiomeric excess), drug substance related impurities, or residual solvents, which are considered critical quality attributes for the quality control of the nominated bulk drug substance. Ibutamoren mesylate is not well characterized from a physical and chemical perspective because certain critical characterization data relating to identity, purity, and impurity profiles, specific to the bulk drug substance were neither found in the publicly available scientific literature nor were they provided in the CoAs or USP.

[140] 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.

2. The extent to which ibutamoren mesylate has been historically used in compounding is unclear. FDA identified websites that advertise that they obtain ibutamoren mesylate from a compounding pharmacy, but it is unclear if any compounding pharmacies are actively selling such compounded products. FDA also identified websites that sell products containing ibutamoren mesylate, but it is unclear if these are compounded products. No outsourcing facility has reported compounding products containing ibutamoren mesylate since 2020. At the time of this evaluation, currently available data and published literature is too limited to inform the historical use of ibutamoren mesylate for compounding drug products under section 503A of the FD&C Act.

3. We conclude that there is insufficient information to support the effectiveness of ibutamoren mesylate for the treatment of GHD, osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease. Most of the available clinical data have limitations such as lack of demonstration of clinically meaningful therapeutic effects, small study sizes, and short study durations. Clinical trials did not evaluate, or did not demonstrate, that ibutamoren mesylate provides clinically meaningful improvement for the proposed uses GHD, osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease. In addition, there are currently FDA-approved drugs with established efficacy for GHD, osteoporosis, obesity, and Alzheimer's disease, and alternative treatment methods for hip fracture and sarcopenia.

4. Findings from nonclinical pharmacological studies revealed that: (i) the desired response of increased GH secretion can be lost during continuous oral treatment with ibutamoren mesylate, and (ii) ibutamoren mesylate can induce hypotension in rats. Acting as a ghrelin receptor agonist, ibutamoren mesylate may have behavioral reinforcing properties that could contribute to development of addiction. From the nonclinical toxicological perspective, the finding that developmental toxicity can be induced by gestational exposures to ghrelin, a substance that like ibutamoren acts as a ghrelin receptor agonist, raises additional safety concerns.

   Based on available clinical data, there are serious safety concerns related to ibutamoren mesylate use including hyperglycemia, liver enzyme elevations, edema and fluid overload, and CHF in elderly patients recovering from hip fracture. Other AEs reported in clinical trials include musculoskeletal pain, increase in appetite, and hyperprolactinemia. FDA's ability to interpret CAERS and FAERS reports is limited by lack of information in the reports and confounding factors such as concomitant medications. Ibutamoren mesylate stimulates production of endogenous GH which in turn stimulates production of IGF-1. There are known potential risks associated with the use of drug products that increase IGF-1 levels, such as glucose intolerance and fluid retention. In addition, we note that the proposed uses of ibutamoren mesylate include conditions that typically affect older adults, such as osteoporosis, hip fracture, sarcopenia, and Alzheimer's disease. Older individuals with high IGF-1 levels have been observed to be at increased risk for incident disease or death; higher IGF-1 levels also appeared to be associated with cancer risk across ages. There is lack of safety data on the use of ibutamoren mesylate and its risks associated with higher

IGF-1 levels particularly for its proposed uses in older adults. In addition, there are currently available FDA-approved therapies for the treatment of adults with GHD and growth failure due to GHD in children, osteoporosis, obesity, and Alzheimer's disease; these drugs have well-characterized safety profiles and have been shown to be safe for their labeled uses.

On balance, the physiochemical characterization, limited information on historical use, lack of evidence of effectiveness, and the specific safety concerns identified for ibutamoren mesylate weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal regarding this substance is based on the fact that ibutamoren mesylate is not well characterized from a physicochemical perspective, the potential serious safety risks associated with the use of ibutamoren mesylate, the limited evidence of benefit associated with the use of ibutamoren mesylate for the nominated conditions, the seriousness of the conditions for which ibutamoren mesylate was nominated to be used, and the availability of FDA-approved drug products that are indicated to treat many of these uses. Accordingly, we propose not adding ibutamoren mesylate to the 503A Bulks List.

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Ibutamoren Mesylate 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	Ibutamoren Mesylate
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	2-amino-2-methyl-N-[(2R)-1-(1-methylsulfonylspiro[2H-indole-3,4'-piperidine]-1'-yl)-1-oxo-3-phenylmethoxypropan-2-yl]propanamide;methanesulfonic acid
Common Name(s)	Ibutamoren Mesylate, MK-677, MK0677, MK-0677
UNII Code	GJ0EGN38UL
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of AX Pharmacueticals Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	No
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Oral capsules
Compounded Strengths	25 mg
Anticipated Routes of Administration	Oral
Saftey & Efficacy Data	Thorner, Michael O. "Age-Related Decline In Growth Hormone Secretion: Clinical Significance and Potential Reversibility." *Transactions of the American Clinical and Climatological Associations*, vol. 108, 1997, pp. 99–108.
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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

AX Pharmaceutical Corp

CERTIFICATE OF ANALYSIS

Ibutamoren Mesylate (MK-0677)

Lot Number	D183-18F04SH	**MFG Date**	June 04, 2018
Molecular Formula	$C_{27}H_{36}N_4O_5S \cdot CH_4O_3S$	**Retest Date**	June 03, 2020
CAS Number	159752-10-0	**Batch QTY**	1KG
Storage: Store the product at temperature 2 ~ 8°C.			
Tests	**Specifications**		**Results**
Appearance	Off-white powder		Conforms
Identification	1H-NMR, LC-MS: As per standard		Conforms
Melting point	158°C ~ 160°C		159°C ~ 159.5°C
Purity	≥ 99%		99.60%
Conclusion: The product complies with specifications **Original Reference No.:** 20180604			
Transcription: **Date:**	**Issued by:** **Date:**		**Approved by:** **Date:**

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

100 West Beaver Creek Road, Unit 12; Richmond Hill, ON L4B 1H4, Canada
Email: sales@axpharmacetuical.com; Tel: (289)842-3088/(905)886-4994; Fax: (416) 352-1618

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?	Ibutamoren Mesylate
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?	**IUPAC Name:** 2-amino-2-methyl-*N*-[(2*S*)-1-(1-methylsulfonylspiro[2*H*-indole-3,4'-piperidine]-1'-yl)-1-oxo-3-phenylmethoxypropan-2-yl]propanamide;methanesulfonic acid *Ibutamoren Mesylate*
What is the common name of the substance?	Ibutamoren L-163,191 MK-0677 (mesylate salt) AKOS025149517 $C_{28}H_{40}N_4O_8S_2$ CAS# 159752-10-0
Does the substance have a UNII code?	R90JB6QJ2B
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?	Powder, Bulk
Is the substance recognized in foreign pharmacopoeias or registered in other countries?	Unknown
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?	Tablet
What strength(s) will be compounded from the nominated substance?	10mg & 25mg
What is the anticipated route(s) of administration of the compounded drug product(s)?	Oral
Are there safety and efficacy data on compounded drugs using the nominated substance?	**ClinicalTrials.gov Identifier**: NCT00116129 **US Patent# for Use**: US 7.442,706 B2 *METHODS FOR TREATING SARCOPENIA WITH A GROWTH HORMONE SECRETAGOGUE* **Clinical Studies:** (1) Chapman IM, Bach MA, Van Cauter E. Farmer M. Krupa D, Taylor A M et al. *Stimulation of the growth hormone (GH)-insulin-like growth factor axis by daily oral admin* US 7,442,706 B2 19 administration of a GH secretagogue (MK-677) in healthy elderly subjects. J. Clin Endocrinol Metab 1996; 81:4249 4257. (2) Chapman IM, Hartman ML, Straume M. Johnson ML, Veldhuis JD, Thorner MO. *Enhanced sensitivity growth hormone (GH) chemiluminescence assay reveals lower post-glucose nadir GH concentrations in men than women*. J Clin Endocrinol Metab 1994; 78:1312-1319. (3) Johnson ML, Virostko A, Veldhuis J D, Evans W. S. *Deconvolution analysis as a hormone pulse-detection algorithm*. Methods Enzymol 2004; 384:40-54.

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(10) Schoeller DA, van Santen E. Peterson D. W. Dietz W. Jaspan J. Klein PD. Hydrometry. In: Roche AF, Heymsfield SB, Lohman TG, editors. Human Body Composition. Champagne, Ill.: Human Kinetics, 1996: 25-49.

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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?	Increased GH in deficient adults
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Product not available commercially
Is there any other relevant information?	C of A attached

Darmerica
198 Wilshire Boulevard
Casselberry, FL 32707
www.darmerica.com

Certificate of Analysis

Ibutamoren Mesylate

Product Name : Ibutamoren Mesylate
Mfg. Date : Jun 11, 2021
CAS No. : 159752-10-0

Lot No. : DS6115
Exp. Date : Jun 10, 2024
Batch Qty : 22 kg

TESTS	SPECIFICATIONS	RESULTS
Appearance	White to off-white powder	Off-white powder
^{1}HNMR	Conforms to structure	Conforms
LC-MS	[M-Methanesulfonic acid+H]$^+$: (530.1-530.2)	530.1
Purity (By HPLC)	≥ 99.00%	99.36%

Conclusion: The product meets the specifications.
Long Term Storage: Store in a sealed container at room temperature.
CAUTION: Ensure product is sealed properly to avoid oxidation and absorption of moisture.
ID Test was confirmed by FT-IR on-site. Distributed by Darmerica.

Note: Analytical results transcribed from the original COA provided by Shengdu Kechang Fine Chemicals Co.; Ltd.; Lot No. SMM20210611.

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

	Name	Title	Signature	Date
Prepared by	Christina Boykin	Quality Assistant		07/13/2021
Released by	Harun Kapidzic	Quality Assistant		07/14/2021

Ibutamoren Mesylate
Nomination Clarification

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
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	Name	Title	Signature	Date
Prepared by	Christina Boykin	Quality Assistant		07/13/2021
Released by	Harun Kapidzic	Quality Assistant		07/14/2021