Ibutamoren mesylate: Summary Report

Summary Report

Ibutamoren mesylate

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GH	Growth hormone
GHD	Growth hormone deficiency
GHRP	Growth hormone-releasing peptide
IGF-1	Insulin-like growth factor-1
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of ibutamoren mesylate (also known as MK-0677 or MK-677) (UNII code: GJ0EGN38UL) which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how ibutamoren mesylate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how ibutamoren mesylate has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of ibutamoren mesylate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Ibutamoren mesylate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA).

Ibutamoren mesylate was nominated for growth hormone deficiency (GHD, including adult onset) and catabolic conditions via an oral capsule up to 25 mg/mL in strength.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of ibutamoren mesylate.[6-10]

Reasons provided for nomination to the 503B Bulks List included:

- There are no FDA-approved products containing ibutamoren mesylate.
- Compounded products may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ibutamoren mesylate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK,

Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for ibutamoren mesylate; name variations of ibutamoren mesylate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing ibutamoren mesylate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: ibutamoren mesylate; and oral administration or therapeutic use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on December 3, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 7, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 7, 2019 for clinical practice guidelines that recommended the use of ibutamoren mesylate and provided sufficient dosing and administration instructions.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which ibutamoren mesylate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if ibutamoren mesylate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which ibutamoren mesylate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of ibutamoren mesylate; setting; total number of patients; number of patients who received ibutamoren mesylate; patient population; indication for use of ibutamoren mesylate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ibutamoren mesylate in a combination product; use and formulation of ibutamoren mesylate in a compounded product; use of ibutamoren mesylate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances ibutamoren mesylate was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use ibutamoren mesylate: endocrinology, naturopathy, oncology, pediatrics, primary care and internal medicine, and urology. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of ibutamoren mesylate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Ibutamoren mesylate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Ibutamoren mesylate is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for ibutamoren mesylate.
- Ibutamoren mesylate is not available in the nominated dosage form and ROA in any of the foreign registries searched.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 377 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 330 titles and abstracts were screened. After screening, the full text of 55 articles was reviewed. Finally, 17 studies were included. Thirty-eight studies were excluded for the following reasons: wrong study design (35 studies); ibutamoren mesylate not used clinically (3).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 17 included studies were published between 1996 and 2018. There were 16 experimental studies, 1 observational study, 0 descriptive studies, and 0 clinical practice guidelines. The 17 studies were conducted in the following countries: Belgium, Canada, Chile, Denmark, Germany, Israel, Norway, Russia, Spain, Sweden, Switzerland, UK, and US.

A total of 1664 patients participated in the 17 included studies. The number of patients in each study ranged from 8 to 563.

Outcome measures differed among the included studies and included: body weight; urinary creatinine and N-telopeptide cross-links; 24-hour urinary urea and ammonia nitrogen; daily nitrogen balance; insulin-like growth factor-1 (IGF-1); insulin growth factor binding protein (IGFBP)-2, IGFBP-3, IGFBP-4, IGFBP-5; growth hormone (GH) concentrations; cortisol; prolactin; thyroid function (thyrotropin, T3, T4); urinary free cortisol; glucose; insulin assays; sleep period; sleep latency; sleep efficiency; sleep maintenance; amounts of wake, stage I, II, III, IV, rapid eye movement (REM), and REM latency; free fatty acids; glycerol; beta-hydroxybutyrate; oral glucose tolerance test; basal metabolic rate; total body fate and fat-free mass; visceral fat mass; total abdominal visceral fat

volume, subcutaneous fat, midthigh skeletal muscle; total body water and extracellular body water; interleukin (IL)-6, IL-1B, IL-6sR; total body mineral content (BMC); bone mineral density (BMD) of the femoral neck, hip, lumbar spine, and total body; leptin; total testosterone; sex hormone-binding globulin (SHBG); osteocalcin and bone-specific alkaline phosphatase (BSAP); lipoprotein(a); total cholesterol; triglycerides; high-density lipoprotein-cholesterol (HDL-C); low-density lipoprotein-cholesterol (LDL-C); LDL particle diameter; serum apolipoprotein A-I and E; lipoprotein lipase activity; objective physical function measures; quality of life and general well-being; Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus); the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); Clinical Dementia Rating Scale sum of boxes (CDR-sob); and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL).

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of ibutamoren mesylate

Three hundred ten patients received ibutamoren mesylate as an experimental treatment for bone formation and resorption, administered orally in doses ranging from 5 mg to 50 mg. Duration of treatment ranged from 14 days to 18 months.

Two hundred eighty-two patients received ibutamoren mesylate as an experimental treatment for Alzheimer's disease, administered orally at a dose of 25 mg. Duration of treatment was 12 months.

One hundred forty-six patients received ibutamoren mesylate as an experimental treatment for post-hip fracture surgery, administered orally at a dose of 25 mg. Duration of treatment was 6 months.

Sixty-two patients received ibutamoren mesylate as an experimental treatment to prevent the decline in fat-free mass and to decrease abdominal visceral fat, administered orally at a dose of 25 mg. Duration of treatment ranged from 1 to 2 years.

Twenty-two patients received ibutamoren mesylate as an experimental treatment to improve nutritional status in end-stage renal disease (ESRD), administered orally at a dose of 25 mg. Duration of treatment was 3 months.

Twenty-two patients received ibutamoren mesylate as an experimental treatment for use in older adults, administered orally in doses ranging from 2 mg to 25 mg. Duration of treatment was 42 days.

An unknown number of hypogonadal men on testosterone therapy received ibutamoren mesylate for reduction of body fat mass and increase in skeletal muscle mass at an unknown dose and duration of treatment.

Eighteen patients received ibutamoren mesylate as an experimental treatment in children with GHD, administered orally in doses ranging from 0.2 mg/kg/day to 0.8 mg/kg/day. Duration of treatment was 15 days.

Fifteen patients received ibutamoren mesylate as an experimental treatment to improve sleep quality, administered orally at a dose ranging from 2 mg to 25 mg. Duration of treatment ranged from 21 days to 28 days.

Twelve patients received ibutamoren mesylate as an experimental treatment for use in obese patients, administered orally at a dose of 25 mg. Duration of treatment was 8 weeks.

Eight patients received ibutamoren mesylate as an experimental treatment to reverse the catabolic response to dietary energy restriction, administered orally at a dose of 25 mg. Duration of treatment was 28 days.

Five patients received ibutamoren mesylate as an experimental treatment in adults with GH deficiency, administered orally in doses ranging from 10 mg to 50 mg. Duration of treatment was 8 days.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Ibutamoren was not used as a compounded product, nor was it used in a combination product.

In 12 studies, the authors' concluded that further studies were necessary for the use of ibutamoren mesylate in the treatment of GHD of childhood onset, to increase bone mass and reduce risk of fractures, to improve nutritional status in patients with ESRD, to promote a reduction in body fat in obese patients, to decrease LDL-C concentrations, in the treatment of conditions associated with GHD in older adults, to prevent the decline in fat-free mass and to decrease abdominal visceral fat, in the rehabilitation of patients post-hip fracture, in the treatment of catabolic patients secondary to acute or chronic disease states, and to improve sleep quality. In 3 studies, the authors' concluding statement did not provide a recommendation regarding use of ibutamoren mesylate to promote bone formation and resorption and to modify body composition and total body fat. In 2 studies, the authors' concluding statement did not recommend the use of ibutamoren mesylate to improve overall physical functional performance in patients post-hip fracture surgery and to slow the rate of progression of Alzheimer's disease.

Pharmacology and historical use

Several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ibutamoren mesylate.

Growth hormone (GH), also known as somatotropin, is a protein that is produced by the somatotroph cells found in the anterior lobe of the pituitary gland. GH receptors are found throughout the body and are responsible for many metabolic functions including promoting growth in children, increasing lipolysis, stimulating protein synthesis, and antagonizing insulin.[9] GH is regulated by 3 hypothalamic hormones: growth hormone releasing hormone (GHRH), somatostatin, and ghrelin.[11] GHRH and ghrelin stimulate GH release while somatostatin inhibits release.[11] GH has a pulsatile secretion with production occurring primarily at night and pulses following exercise, trauma, and sleep.[9] GH production rises in childhood with the peak occurring at puberty and then declines with age. As GH declines with age, exogenous administration has many proposed benefits including increasing lean muscle mass, decreasing fat mass, increasing exercise tolerance, and increasing muscle strength.[9] However, due to potential safety concerns associated with supratherapeutic GH levels resulting from the bypass of the normal, regulatory feedback, there has been an interest in the use of GH secretagogues.[9,12]

GH secretagogues include GH releasing peptides (GHRPs), like GHRP2 and GHRP6, and GHRH analogs, like sermorelin. GH secretagogues stimulate the endogenous secretion of GH, GHRPs increase the number of somatotrophs releasing GH and GHRH analogs increase the amount of GH secreted, which maintains levels within normal physiologic levels.[9,13] The action of GHRPs is independent of GHRH so as a result, when a GHRH analog and a GHRP are used together they have a synergistic effect stimulating the release of GH.[9,12]

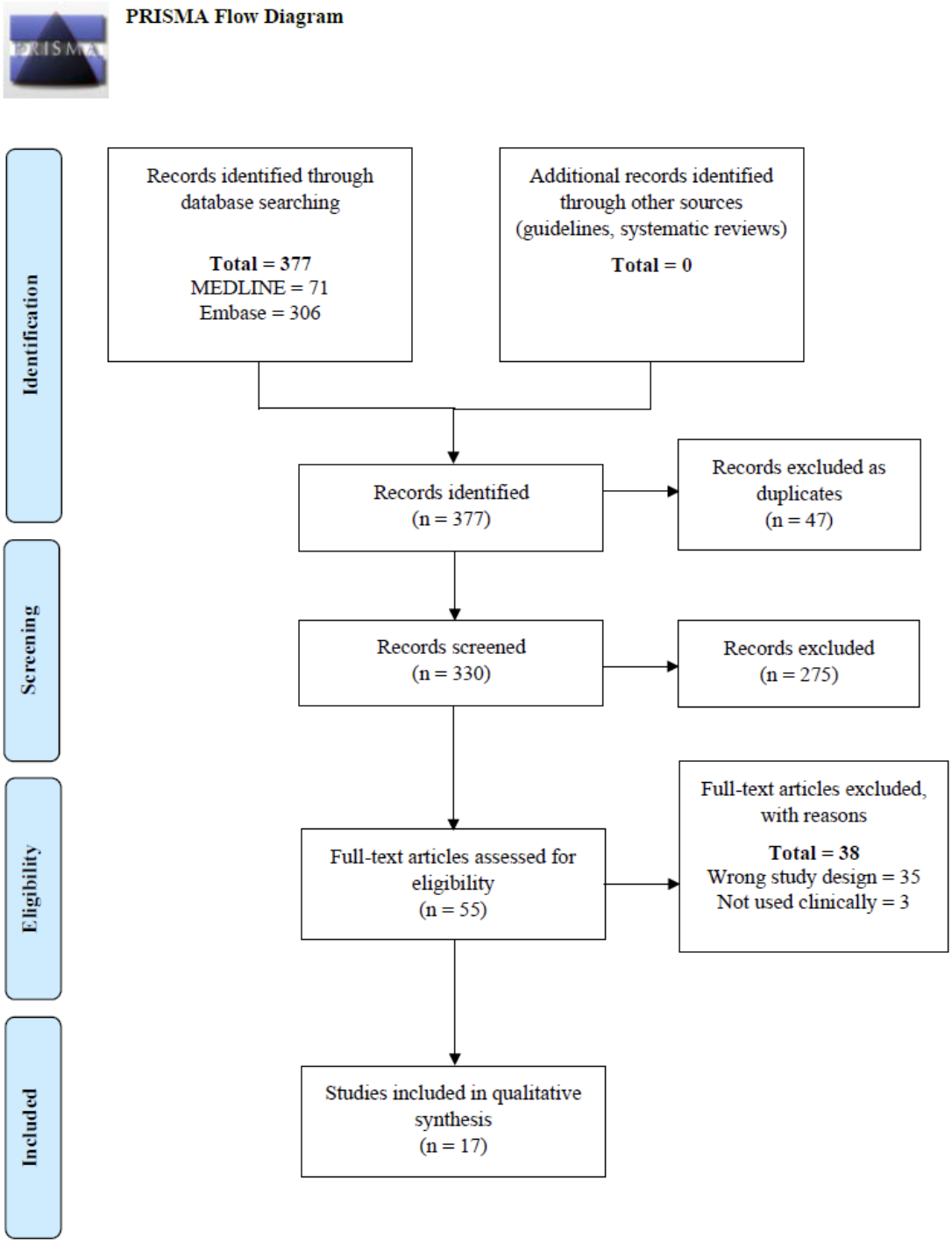
GHRPs were first synthesized in 1977 and GHRP6 was the first that was found to have significant in vivo activity; however, due to its poor oral bioavailability and short half-life, it had to be administered frequently and as an injection.[9] Additionally, "as a peptide it did not lend itself to the optimization of pharmacokinetic properties".[14] Due to these challenges, using GHRP6 as a model structure, Merck began searching for a nonpeptide mimetic that had a high oral bioavailability and pharmacokinetics that would allow for once daily oral administration.[14] A breakthrough occurred when L-692,429 was discovered as it showed that it was possible to design a small molecule peptidomimetic agonist for GHRP6.[14] While this molecule had an improved oral bioavailability, the pharmacokinetic properties did not allow for a once daily oral administration.[14] Continued modifications led to the development of L-163,191 which was shown to have "excellent potency, selectivity, and oral bioavailability, as well as appropriate pharmacokinetics suitable for once daily oral dosing" and with continued research found "to have an excellent safety profile."[14] This led to the clinical development of L-163,191 as MK-0677, or ibutamoren mesylate.[9,14]

Ibutamoren mesylate binds to the ghrelin receptor and was found to not only enhance the pulsatile release of GH but also act as an antagonist to somatostatin allowing for GH levels to remain elevated for up to 360 minutes after a single oral dose.[13,15] In 1996, Chapman et al studied the effects of 2 mg, 10 mg, and 25 mg of MK-677 administered orally once daily compared to placebo in 32 healthy adults between the ages of 64-81 years.[16] Patients were randomized to receive either MK-677 or placebo; GH and IGF-1, a surrogate blood marker for GH, levels were measured. After 2 weeks, GH and IGF-1 levels in the 10 mg and 25 mg MK-677 groups were significantly increased compared at baseline in a dose-dependent manner; participants that received 25 mg of MK-677 had IGF-1 levels restored to normal levels seen in young adults. Additionally, it was found that the GH increase was due to enhanced pulsatile GH secretion and not an increase in the number of pulses. This was the first study to show that daily administration of a GH secretagogue could increase GH and IGF-1 levels in older adults.[16]

Copinschi et al evaluated the use of 5 mg and 25 mg of MK-677 compared to placebo in 9 healthy males between the ages of 18-30 years to evaluate the effect on pulsatile GH secretion, IGF-1 levels, and adrenocortical function.[17] Additionally, the medication was taken at night to determine whether it would enhance the physiological release of GH that occurs at night.[17] The study found that the amount of GH secreted was similar in all 3 groups; however, in the MK-677 groups the number of GH pulses was increased. IGF-1 levels were also increased, in a dose-dependent manner, in the MK-677 groups compared to placebo. This study concluded that the use of "MK-677 for the treatment of relative somatotrophic deficiency, particular in older adults compromised by such deficiency, deserves further investigation."[17]

Several studies were conducted evaluating the use of ibutamoren mesylate in various disease states and Merck was developing the drug for FDA approval for use in GH deficient children, recovery of hip fractures, and to treat the frail elderly; however, Merck discontinued its development in 1999.[18] After Merck discontinued development, Ammonett Pharma LLC continued to develop MK-0677 for treatment of GHDin children and in 2017 received a designated orphan status from FDA for treatment of GHD.[19] In 2018, Lumos Pharma, Inc acquired the license for MK-0677 from Ammonett Pharma LLC, renamed it LUM-201, and is currently developing it for treatment of pediatric GHD, Turner Syndrome, and children born small for gestational age (SGA).[20] Lumos Pharma, Inc is currently recruiting participants for a multi-national, phase 2 study of LUM-201 in pediatric GHD (the OraGrowtH210 Trial) with expected results in mid-2022.[20,21]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Observational[22]	1
Experimental[6-8,10,15,16,23-32]	16
Clinical practice guideline	0

Table 4. Number of studies by country

Country	**Number of Studies**
Belgium[30]	1
Sweden[10,26-28]	4
United States (US)[6,8,16,22,24,25,29,31,32]	9
Multiple Countries • Chile, Russia, Sweden, US[7] • Belgium, Canada, Denmark, Sweden, Switzerland, UK, US[23] • Denmark, Germany, Israel, Norway, Spain, Sweden, UK, US[15]	3
	Total US[a]: 12 Total Non-US Countries[a]: 8

[a]Studies 7, 15, 23 counted in both US and non-US total.

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Bone formation and resorption					
Murphy *et al*., 1999, US[24]	Study 1: Randomized, double-blind, placebo-controlled, parallel-group study Study 2: Double-blind, randomized, parallel-group study Study 3: Double-blind, multicenter, parallel-group, pilot study	Study 1: 32 Healthy elderly adults (53%, range 65-81 y) Study 2: 50 Healthy elderly adults (64%, range 65-85 y) Study 3: 105 Elderly patients with functional impairment (66%, range 65-94 y)	Study 1: • 10 mg (12) • 25 mg (10) • Placebo (10) Study 2: • 25/50 mg (30) • Placebo (20) Study 3: • 5/10/25 mg (63) • Placebo (28)	Study 1: serum IGF-1 concentrations Study 2: serum IGF-1, serum osteocalcin Study 3: serum osteocalcin and BSAP, IGF-1	Based on elevations in biochemical markers of bone resorption and formation (osteocalcin and BSAP), once daily dosing of MK-677 stimulates bone turnover in elderly adults.
Murphy, *et al*., 2001, US[31]	Multi-center, randomized, double-blind, placebo-controlled, parallel group study	292 Postmenopausal women with osteoporosis (0%, range 64-85 y)	Months 0-12 • MK-677 25 mg + alendronate 10 mg (111) • Placebo + alendronate 10 mg (109) • MK-677 25 mg + placebo (36) • Placebo + placebo (36) Months 12-18 • MK-677 25 mg + alendronate 10 mg (111) • Placebo + alendronate 10 mg (109) • MK-677 25 mg + alendronate 10 mg (36) • MK-677 25 mg + alendronate 10 mg (35)	Urine chemistry values, hormones, bone mineral density of the femoral neck, hip, lumbar spine, and total body	MK-677 did not lead to significant changes in BMD at sites other than the femoral neck. The lack of enhancement in bone mass at other sites compared with that seen with alendronate is a concern when the potential side effects of increased GH secretion is taken into account.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Svensson, *et al*., 1998, Sweden[28]	Randomized, double-blind, parallel and placebo-controlled trial	24 Obese patients (100%, range 19-49 y)	• 25 mg (12) • Placebo (12)	IGF-1, IGFBP-3, IGFBP-4, IGFBP-5, IL-6, IL-1B, IL-6sR, markers of bone formation and resorption, GH, cortisol, total body BMC, BMD, total spine BMD	Short-term treatment with MK-677 led to increases in markers of bone resorption and formation. Future long-term studies are needed to determine if long-term treatment can increase bone mass.
Indication 2: Obese males					
Svensson, *et al*., 1999, Sweden[26]	Randomized, double-blind, parallel and placebo-controlled trial	24 Obese patients (100%, range 19-49 y)	• 25 mg (12) • Placebo (12)	Leptin, thyroid hormones, total testosterone, SHBG	"MK-677 treatment is able to affect circulating factors of importance for adipose tissue and fuel metabolism.
Svensson, *et al*., 1999, Sweden[27]	Randomized, double-blind, parallel and placebo-controlled trial	24 Obese patients (100%, range 19-49 y)	• 25 mg (12) • Placebo (12)	Lipoprotein(a), total cholesterol, triglycerides, HDL-C, LDL-C, LDL particle diameter, serum apolipoprotein A-I and E, lipoprotein lipase activity	Treatment did not significantly change lipoprotein(a) levels. There were transient changes in other lipoprotein concentrations and a decrease in the LDL-C/HDL-C ratio.
Svensson, *et al*., 1998, Sweden[10]	Randomized, double-blind, parallel and placebo-controlled trial	24 Obese patients (100%, range 19-49 y)	• 25 mg (12) • Placebo (12)	GH, IGF-1, IGFBP-3, free fatty acids, glycerol, b-hydroxybutyrate, prolactin, cortisol, oral glucose tolerance test, basal metabolic rate, total body nitrogen, total body fat and fat-free mass, visceral fat mass, total abdominal visceral fat volume	Treatment with MK-677 led to an increase in GH, IGF-1, and IGFBP-3. Further studies are needed to evaluate wither MK-677 can promote a reduction in body fat.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Physical functional performance post-hip fracture surgery					
Adunsky, *et al*., 2011, multi-country[15]	Randomized, double-blind, placebo-controlled, multicenter study	123 Ambulatory patients post-hip fracture surgery (26.8%, range 64-95 y)	• 25 mg (62) • Placebo (61)	Change in objective physical function measures, IGF-1 levels	The increase in IGF-1 levels seen was not paralleled to an improvement in most functional performance measures. The trial was stopped early; MK-677 has an unfavorable safety profile in this patient population.
Bach, *et al*., 2005, multi-country[23]	Multi-center, randomized, double-blind, placebo-controlled, parallel group, controlled trial	161 Adults post-hip fracture surgery (21.7%, mean 79.2 y)	• 25 mg (84) • Placebo (77)	Change in objection functional performance measures, IGF-1, change in health-related quality of life	MK-677 increased IGF-1 levels, however, it is uncertain whether clinically significant benefits were seen regarding physical function.
Indication 4: Adults with growth hormone deficiency					
Chapman, *et al*., 1997, US[6]	Randomized, double-blind, placebo-controlled study	9 Patients with idiopathic GH deficiency of childhood onset (100%, range 17-34 y)	Group 1 • 10 mg (2) • Placebo for 4 days than 10 mg for 4 days (2) Group 2 • 10 mg for 4 days than 50 mg for 4 days (5)	GH concentrations, cortisol, PRL, IGF-1, IGFBP-3, thyroid function, urine free cortisol, glucose, insulin assays	"Oral administration of GHRP-mimetic compounds may have a role in the treatment of GH deficiency of childhood onset."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 5: Alzheimer's Disease					
Sevigny, *et al*., 2008, US[32]	Randomized, double-blind, placebo-controlled trial	563 Patients with Alzheimer's Disease (42%, mean 75.9 ± 8.9 y)	• 25 mg (282) • Placebo (281)	Change from baseline to 12 months on the CIBIC-plus, ADAS-Cog, CDR-sob, and ADCS-ADL	MK-677 was ineffective at slowing the rate of progression of Alzheimer's Disease.
Indication 6: Anthropomorphic parameters					
McBride, *et al*., 2018, US[22]	Cohort	145 Hypogonadal men on testosterone therapy (100%, mean 37.3 ± 8.3 y)	–	Exercise intensity, InBody impedance-based body composition analysis	Ibutamoren was the only GH secretagogue to show significantly positive effects on LBM, BFM, and SMM.
Indication 7: Growth hormone deficiency in children					
Codner, *et al*., 2001, multi-country[7]	Multi-center, partially double-blind, randomized study	18 Pre-pubertal Tanner stage I children with idiopathic GH deficiency (83%, mean 10.6 ± 0.8 y)	Group I (2) • 0.2 mg/kg/day days 1-7, placebo days 8-14 Group II (4) • Placebo days 1-7, 0.2 mg/kg/day days 8-14 Group III (12) • Placebo days 1-7, 0.8 mg/kg/day days 8-14 All patients received 0.8 mg/kg once on day 15	GH, IGF-1, IGFBP-3, prolactin, cortisol, thyrotropin, T3, T4, glucose, insulin, urinary free cortisol	Ibutamoren mesylate can increase GH, IGF-1, and IGFBP-3 levels. "Thus this compound is applicable for testing its effect on growth velocity."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 8: Improve nutritional status in patients with end-stage renal disease					
Campbell, et al., 2018, US[29]	Randomized crossover double-blind study	22 Patients with ESRD (72.7%, range 47.7-71.5 y)	• 25 mg (22) • Placebo (22)	IGF-1 level	MK-677 increased IGF-1 levels. Further studies are needed to evaluate whether MK-677 can improve PEW, LBM, physical strength, and quality of life in ESRD patients.
Indication 9: Older adults					
Chapman, *et al*., 1996, US[16]	Randomized, double-blind, placebo-controlled trial	32 Healthy older patients (53%, range 64-81 y)	Panel A • 2 mg for 14 days, washout, 25 mg for 28 days (10) • Placebo (6) Panel B • 10 mg in the AM for 14 days, washout, 10 mg in the PM for 28 days (6) • 10 mg in the PM for 14 days, washout, 10 mg in the AM for 28 days (6) • Placebo (4)	GH concentrations, cortisol, PRL, IGF-1	"This is the first study to demonstrate that serum GH and IGF-1 concentrations can be increased in older adults by chronic administration of an oral GH secretagogue."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 10: Prevent decline in fat-free mass and decrease abdominal visceral fat					
Nass, *et al*., 2008, US[25]	Randomized, double-blind, modified crossover trial	65 Healthy older adults (35%, range 60.2-80.7 y)	Year 1 • 25 mg (43) • Placebo (22) Year 2 • Group 1: 25 mg (17) • Group 2: Placebo (17) • Group 3: 25 mg (19)	Serum GH and IGF-1 levels; 24-hour mean GH and endogenous GH secretory dynamics; fat-free mass and total body fat; BMD of the femoral neck, spine, and hip; abdominal visceral and subcutaneous fat and midthigh skeletal muscle; total body water and extracellular body water; concentric force flexion and extension of the knee and shoulder; function tests; 4 questionnaires to assess quality of life and general well-being; cholesterol, cortisol, and insulin sensitivity	"Daily MK-677 significantly increased GH and IGF-1 levels to those of healthy young adults without serious adverse effects. Long-term functional studies are indicated."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 11: Reverse catabolic response to dietary energy restriction					
Murphy, *et al*., 1998, US[8]	Double-blind, placebo-controlled, randomized, two-period, cross-over study	8 Healthy adults (100%, range 24-39 y)	• 25 mg (8) • Placebo (8)	Body weight, urinary creatinine, 24-hour urinary urea and ammonia nitrogen, daily nitrogen balance, IGF-1, IGFBP-2, IGFBP-3, GH concentrations	"MK-677 reverses diet-induced nitrogen wasting, suggesting that if these short-term anabolic effects are maintained in patients who are catabolic because of certain acute or chronic disease states, it may be useful in treating catabolic conditions."
Indication 12: Sleep quality					
Copinschi, *et al*., 1997, Belgium[30]	Study 1: Double-blind, placebo-controlled, three-period, crossover study Study 2: placebo-controlled, randomized study	Study 1: 9 Healthy adults (100%, range 18-30 y) Study 2: 6 Older adults (67%, range 65-71 y)	Study 1 (9) • 5 mg, 25 mg, or placebo for 7 days, 14-day washout, then repeated until all patients were in all 3 groups Study 2 (6) • 2 mg for 14 days, 14-day washout, 25 mg for 14 days	Sleep period; sleep latency; sleep efficiency; sleep maintenance; amounts of wake, stage I, II, III IV, stage REM; and REM latency	"MK-677 may simultaneously improve sleep quality and correct the relative hyposomatotropism of senescence."

Abbreviations: "–", not mentioned; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; BFM, body fat mass; BMC, bone mineral content; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; CDR-sob, Clinical Dementia Rating Scale sum of boxes; CIBC-plus, Clinician's Interview-Based Impression of Change plus Caregiver Input; ESRD, end-stage renal disease; GH, growth hormone; GHRP, growth hormone releasing peptide; HDL-C; high-density lipoprotein-cholesterol; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor binding protein; IL, interleukin; LBM, lean body mass; LDL-C, low-density lipoprotein-cholesterol; MK-677, ibutamoren mesylate; PRL, prolactin; PEW, protein-energy wasting; SHBG, sex hormone-binding globulin; SMM, skeletal muscle mass.

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Bone formation and resorption[8,31]	5-50 mg/day	–	–	Oral	14 days – 18 months
Physical functional performance post-hip fracture surgery[15,23]	25 mg	–	–	Oral	6 months
Adults with growth hormone deficiency[6]	10-50 mg/day	–	–	Oral	8 days
Alzheimer's disease[32]	25 mg/day	–	–	Oral	12 months
Anthropomorphic parameters[22]	–	–	–	–	–
Children with growth hormone deficiency[7]	0.2-0.8 mg/kg/day	2 mg/mL	Liquid	Oral	15 days
Improve nutritional status in patients with end-stage renal disease[29]	25 mg/day	–	–	Oral	3 months
Healthy older adults[16]	2-25mg/day	–	–	Oral	42 days
Reverse catabolic response to dietary energy restriction[8]	25 mg/day	–	–	Oral	28 days
Prevent decline in fat-free mass and decrease abdominal visceral fat[25]	25 mg/day	–	Tablet	Oral	2 years

Abbreviations: "–", not mentioned

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Obese males[10,26,27]	25 mg/day	–	–	Oral	8 weeks
Bone formation and resorption[28]	25 mg/day	–	–	Oral	8 weeks
Improve sleep quality[30]	2-25 mg/day	–	–	Oral	21-28 days

Abbreviations: "–", not mentioned

Table 8. Number of studies by combinations

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Four SMEs discussed ibutamoren mesylate. The 4 SMEs were medical doctors. The SMEs specialized and/or were board-certified in endocrinology, oncology, and urology, working in academic medical centers or retired. The SMEs had been in practice for 8 to 40 years.

GH is commercially available as an FDA approved product, however, it has very narrow indications and is tightly regulated. When GH is administered exogenously as an injection, the natural secretion of GH is inhibited. It was well known that morphine stimulates GH release and in the 1970s there was interest in the synthesis of opiate-like peptides and their potential ability to stimulate the release of GH. This led to the development of GHRP that was shown to "stimulate growth hormone without any analgesic effect and was not addictive." In developing GHRP, researchers discovered that it worked on a secretagogue receptor separate from GHRH, which works on a GHRH receptor.

Merck became very interested in GHRP because it was a small peptide and they wanted to develop a mimetic of GHRP. The result was ibutamoren mesylate (MK-677), the first peptidomimetic drug ever developed and, as one SME stated, "it was a real breakthrough for pharmacology and therapeutics." Merck continued to study the drug and in a two-year study the use of a daily ibutamoren mesylate tablet was evaluated in people over the age of 65 and, as one SME stated, they found that "it could restore growth hormone secretion to that seen in 20-30 year-olds." The SME added that this study also found that "in the patients who were treated with placebo they lost half a kilo [kilogram] of lean body mass or skeletal muscle, while those on the drug [ibutamoren] gained 1-2 kilos [kilograms]. This is 20% of the loss of muscle mass between the ages of 20 and 70 restored within a year." The SME stated that ibutamoren mesylate was also studied for use in Alzheimer's disease, hip fractures, children with GHD, fibromyalgia, and "just about everything" but unfortunately, after 20 years of research Merck decided to close the program.

However, after recent interest in the product, ibutamoren mesylate is currently being developed for children with GHD. While a Merck study conducted in the 1990s showed that ibutamoren mesylate was not as effective as GH, one SME said that the level of deficiency of the child is important. The SME stated that "the more deficient you are, the more you have to replace." Children with a severe deficiency "grew like weeds when given growth hormone" but "the majority of children today when treated only have mild growth hormone deficiency." These children "grow much more slowly and they grow equally well on ibutamoren as they do on growth hormone." The SME continued stating "that's what it's been developed for and it'll probably be 70% of the growth hormone market." Ibutamoren mesylate also has the benefit of being an oral tablet because, as the SME said, "nobody likes to tell their child 'it's time for your injection.'" Additionally, when a GH secretagogue is administered it stimulates GH release and "the axis can respond to it" which "restores the growth hormone to what it should be and secreted, and that's really important for normal growth."

When administered to children, ibutamoren mesylate is monitored based on the child's growth and the IGF-I levels. One SME said, "the beauty of secretagogues is the feedback mechanisms are still intact, so it's very difficult to overtreat patients." The SME said, "we go by what's normal growth, and we go by the growth charts, that's what we want to restore children to." The SME stated that "most people would be satisfied with a growth velocity of something like 8 cm [centimeters] a year between the ages of 4 and 10."

According to one SME who specializes in urology, GH secretagogues address a limited set of conditions and are more often elective "patient demand-based medicine." In many cases people seek these drugs as "lifestyle medications" to improve the appearance of their skin, hair, or body. GH secretagogues can be used as single agents, but one SME said that most of their patients come in with a hormone deficiency, which is usually testosterone. The patients are started on hormone replacement therapy and have positive results but still have a desire to improve their physical appearance, which may lead to prescribing GH secretagogues as a solution. Some clinicians may measure a patient's IGF-I level initially and periodically to monitor therapy. However, since these medications are often prescribed for patients who want a desired physical outcome and "it takes a while for IGF-1 to actually go up" these levels may not always be used. Compared to other GH secretagogues, one of the benefits of ibutamoren mesylate is that since it was being developed by Merck, there is a lot of initial clinical trial data "showing that it can be very beneficial." The clinical trial data also outlined a clear dosing regimen, once a day, typically at night when the GH pathway is the most active.

Two SMEs had not heard of ibutamoren mesylate, but one stated that regarding catabolic conditions "if it works there would be a need." While GH secretagogues can be used for GHD, they can also be used for muscle wasting or cachexia. One SME stated that ibutamoren mesylate is "a fantastic drug" and hopes that it will be approved in 2-3 years for use in children. However, the SME did not see any way it could be compounded since the API is not available. The SME also stated that "it [GH] is abused by athletes" and while "this drug [ibutamoren] is pretty safe, I think it would be irresponsible to say it should be widely available to be bought off the shelf." In contrast, another SME said that the only way to obtain GH secretagogues is through compounding pharmacies due to the products not being approved for use. The SME continued that "anecdotally over the years…they [GH secretagogues] seem to work as advertised, and they seem to be quite safe, but we don't have the peer review literature to prove that, just yet."

Summary of survey results

Zero people responded to the survey distributed via professional medical associations and available on the project website.

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which ibutamoren mesylate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded ibutamoren mesylate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded ibutamoren mesylate

No respondents to survey distributed via professional medical associations

CONCLUSION

Ibutamoren mesylate was nominated for inclusion on the 503B Bulks List as an oral capsule to treat GHD and catabolic conditions. Ibutamoren mesylate is not available in the nominated dosage forms and ROA in any of the national medical registries searched.

From the literature review, ibutamoren mesylate has been studied to treat GHD as well as use in various conditions associated with declining GH levels, including post-hip fracture surgery to facilitate the rehabilitation process, to improve anthropomorphic parameters, to improve the nutritional status in patients with ESRD, to promote bone formation and resorption, Alzheimer's disease, to improve sleep quality, to reverse the catabolic response to dietary energy restrictions, and use in obese patients. All of the studies utilized ibutamoren mesylate as a once daily product with doses ranging from 2 mg to 50 mg. None of the authors' recommended the routine use of ibutamoren mesylate, however several studies reported positive preliminary results concluding that additional studies are warranted. Ibutamoren mesylate has a designated orphan drug status for treatment of GHD and is currently being developed by Lumos Pharma, Inc under then name LUM-201. Lumos Pharma, Inc is currently recruiting participants for a multi-national, phase 2 study of LUM-201 in pediatric GHD (the OraGrowtH210 Trial) with expected results in mid-2022.

From the interviews conducted, only 2 SMEs were familiar with ibutamoren mesylate. However, a third SME stated that there would be a need for it in catabolic conditions if it worked. Ibutamoren was being developed by Merck, but after 20 years of research they decided to close the program. Recent interest has led to ibutamoren being developed for use in children with GHD and one SME hoped that it will be approved for use in children in the next 2-3 years. Ibutamoren mesylate is also used as a "lifestyle medication" for patients that want to "feel better" and "try to mitigate muscle loss." Since it was being developed by Merck, there is a lot of initial clinical trial data "showing that it can be very beneficial" and outline a clear dosing regimen. The 2 SMEs that were familiar with ibutamoren mesylated differed in their opinions on compounding ibutamoren. One SME stated that while it is a "fantastic drug" and is "pretty safe," since the API is not available did not see any way that it could be compounded. The other SME said that since GH secretagogues, including ibutamoren mesylate, are not currently approved for use the only way to obtain them is through a compounding pharmacy.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to November 27, 2019
- Date last searched: December 3, 2019
- Limits: Humans (search hedge); English language
- Number of results: 71
- Notes: Included investigational drug numbers due to small number of results.

1	ibutamoren$.tw.	8
2	(l163191 or l 163191 or mk0677 or "mk 0677" or mk677 or mk 677).tw.	92
3	or/1-2	97
4	exp animals/ not humans/	4646734
5	3 not 4	71
6	limit 5 to english language	71

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 3, 2019
- Limits: Humans (search hedge); English language
- Number of results: 306
- Notes: Included investigational drug numbers due to small number of results.

1	ibutamoren'/de	553
2	ibutamoren':ti,ab,tn	13
3	l 163191':ti,ab,tn	15
4	l163191':ti,ab,tn	0
5	mk 0677':ti,ab,tn	149
6	mk 677':ti,ab,tn	108
7	mk677':ti,ab,tn	1
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	567
9	enteral drug administration'/de	270
10	oral drug administration'/de	403470
11	drug administration':lnk	1687505
12	oral*':ti,ab	928371
13	drug therapy'/de	681571
14	add on therapy'/de	18175
15	hormonal therapy'/de	44137
16	drug comparison':lnk	588616
17	drug therapy':lnk	3774607
18	therap*':ti,ab	3963810
19	treat*':ti,ab	7642433
20	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	12071606
21	#8 AND #20	361
22	[animals]/lim NOT [humans]/lim	5958409

23	#21 NOT #22	315
24	#21 NOT #22 AND [english]/lim	306

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded ibutamoren mesylate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer ibutamoren mesylate to your patients?

   - o Yes
   - o No

3. I prescribe or administer ibutamoren mesylate for the following conditions or diseases: (check all that apply)

   - o Catabolic conditions
   - o Growth hormone deficiency
   - o Other (please describe) _____

4. I use ibutamoren mesylate with my patients as the following: (check all that apply)

   - o FDA-approved drug product
   - o Compounded drugs product
   - o Over-the-counter drug product
   - o Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
   - o Other (please describe) _____

5. I use compounded ibutamoren mesylate because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing ibutamoren mesylate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded ibutamoren mesylate at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded ibutamoren mesylate from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.