Pharmacy Compounding Advisory Committee: Investigational New Drug (IND) Development and Expanded Access (EA)
October 29, 2024

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Disclosure

- **This speaker has no conflicts of interest to disclose**

Objectives

- **Explain pathways under which investigational drugs can be studied and used for treatment based on questions raised in previous PCAC discussions**
- **Provide a brief overview of an Investigational New Drug (IND) submission**
- **Explain the primary purpose of Expanded Access (EA) and how it differs from clinical trials to study investigational products**
- **Discuss the three categories of Expanded Access available**
- **Identify useful resources for determining if Expanded Access is appropriate and preparing requests**

Access to Drug Products Under an IND

- **Clinical Trials Under an IND**
  - **Provide necessary data to determine safety and effectiveness**
  - **Most efficient path to market and broad availability**
  - **Goal is research about the drug potentially leading to approval**
- **Expanded Access**
  - **Presents opportunity to access an investigational medical product for patients with a serious or immediately life-threatening disease or condition who have no comparable or satisfactory alternative therapies**
  - **Goal is access for treatment use**
- **Pathways distinct from 503A and 503B compounding**
  - **Availability of an IND is not a consideration in determining whether a nominated bulk drug substance is appropriate for inclusion on the 503A bulks list**

Some Key Content for IND Submissions

- FDA Forms for IND
  - Form FDA 1571 – Investigational New Drug Application/Form FDA 1572 – Statement of Investigator
  - Form FDA 3926 – Individual Patient Expanded Access Investigational New Drug Application
- Investigator Qualifications (CV)
  - Includes sub-investigators
- Drug substance and drug product information (all manufacturing sites) or Letter of Authorization (LOA) for
  - Identity, Purity, strength, and quality
  - Stability
  - Distribution

Some Key Content for IND Submissions (Continued)

- Safety
  - Evidence that the drug is reasonably safe at the dose and duration proposed
  - Nonclinical/Clinical
- Efficacy
  - Rationale for the intended use of the drug
- Protocol
  - Description of disease or condition
  - Proposed method of administration, dose, and duration
  - Eligibility criteria
  - Clinical procedures and monitoring to evaluate effects and minimize risk
- Informed consent form and Institutional Review Board (IRB) approval

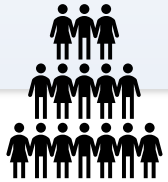
What is Expanded Access (EA)?

- **Expanded Access is the use of an investigational drug or biological product to treat a patient with a serious or immediately life-threatening disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition**
  - **Intent is clearly treatment**
- **Contrasts with investigational drug in a clinical trial where the primary intent is research**
  - **Systematic collection of data with the intent to analyze and learn about the drug**

Three General Categories of Expanded Access and Their Common Requirements

Individual patient
(includes non-emergency and emergency use)

Intermediate-size population



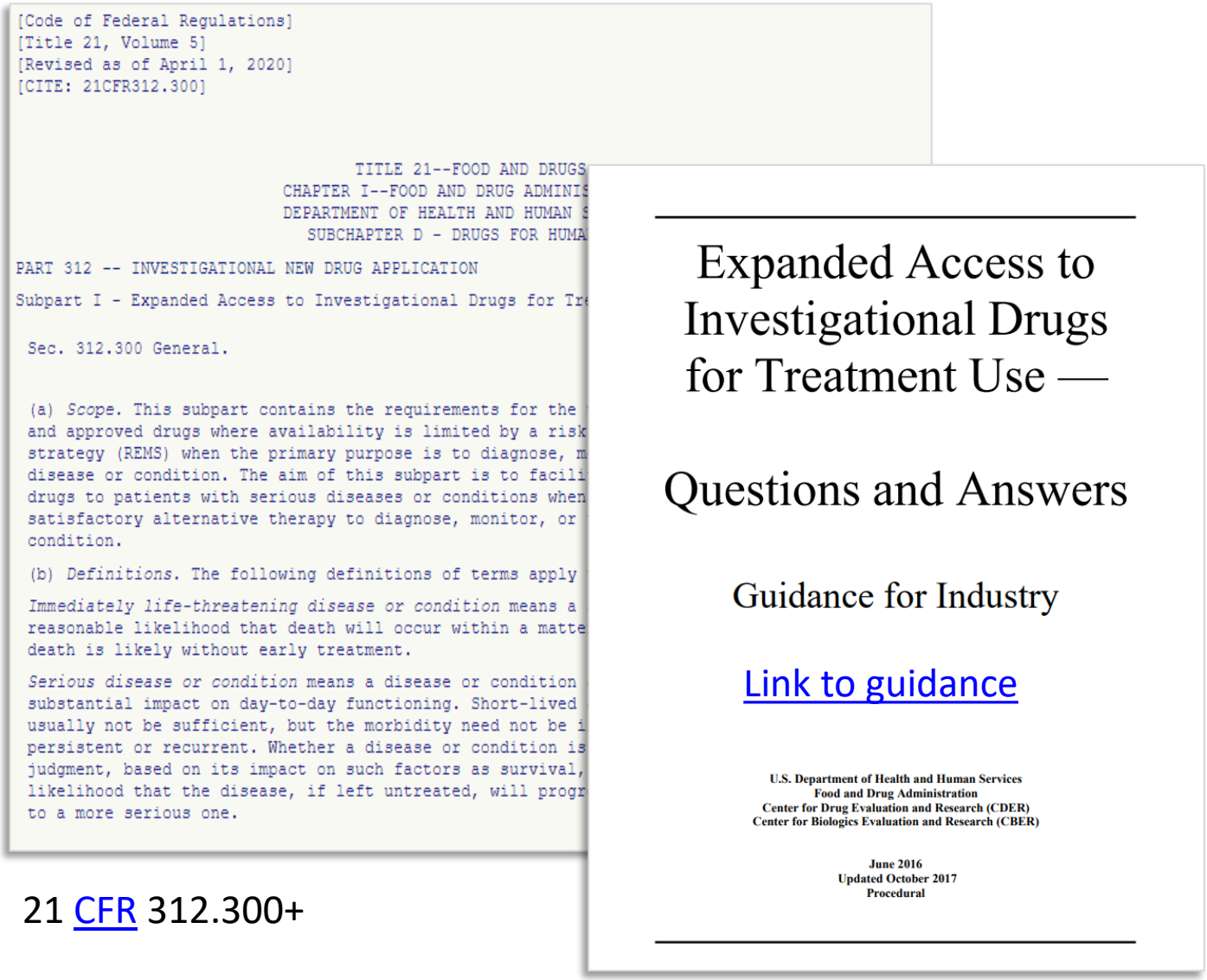
Treatment Investigational New Drug (IND) or Treatment Protocol

Common Requirements:*

1. Patients have serious or immediately life-threatening disease or condition
2. No comparable or satisfactory alternative therapy
3. Patient is unable to participate in a clinical trial for the investigational product
4. Potential benefits must justify the potential risks of the treatment
5. Providing the product under EA must not interfere with or compromise the potential development of the expanded access use

* Under EA, access to an investigational product additionally depends on a sponsor or manufacturer choosing to make the product available to patients.

Expanded Access Regulations and Guidance


[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2020]
[CITE: 21CFR312.300]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINIS
DEPARTMENT OF HEALTH AND HUMAN S
SUBCHAPTER D - DRUGS FOR HUMA

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Subpart I - Expanded Access to Investigational Drugs for Tr

Sec. 312.300 General.

(a) *Scope.* This subpart contains the requirements for the
and approved drugs where availability is limited by a risk
strategy (REMS) when the primary purpose is to diagnose, m
disease or condition. The aim of this subpart is to facili
drugs to patients with serious diseases or conditions when
satisfactory alternative therapy to diagnose, monitor, or
condition.

(b) *Definitions.* The following definitions of terms apply

Immediately life-threatening disease or condition means a
reasonable likelihood that death will occur within a matte
death is likely without early treatment.

Serious disease or condition means a disease or condition
substantial impact on day-to-day functioning. Short-lived
usually not be sufficient, but the morbidity need not be i
persistent or recurrent. Whether a disease or condition is
judgment, based on its impact on such factors as survival,
likelihood that the disease, if left untreated, will progr
to a more serious one.

Expanded Access to Investigational Drugs for Treatment Use —

Questions and Answers

Guidance for Industry

Link to guidance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2016
Updated October 2017
Procedural

21 CFR 312.300+

- **Describe the general criteria applicable to all categories of expanded access, and additional criteria that must be met for each expanded access category**
- **Describe the requirements for submission**
- **Describe the safeguards applicable to EA programs, such as informed consent, IRB review, and reporting requirements**

Human Subject Protections Apply to All EA Categories

- **Drugs in EA are *investigational drugs*, and they are subject to the following requirements from 21 CFR:**
  - Part 50 – **Protection of Human Subjects** (including informed consent)
  - Part 56 – **Institutional Review Board**
  - Part 312 – **IND Application** (including clinical holds based on safety, and reporting requirements (e.g., adverse event reports, annual reports))

EA Program Initiatives (Drugs and Biological Products)

- Creation of Form FDA 3926 for Individual Patient Expanded Access Investigational New Drug Application (IND) (2016)
- Updated guidances and website (2016, 2017, updated draft in 2022)
- Collaboration with the Reagan-Udall Foundation (RUF)
  - Expanded Access Navigator (2017)
  - Expanded Access eRequest mobile app (2020)
- Oncology Center of Excellence “Project Facilitate” (2019)
- Continual outreach efforts through publications, meetings, and webinars
- FDA EA Coordinating Committee (EACC)

User-friendly FDA Webpages for EA

Expanded Access

- Information for Patients
- Information for Physicians
- Information for Industry
- Information for Institutional Review Boards (IRBs)
- How to Submit a Request (Forms)
- Keywords, Definitions, and Resources
- Submission Data
- Contact Information

Español

Sometimes called “compassionate use”, expanded access is a potential pathway for a patient with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Expanded access may be appropriate when all the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product’s development or marketing approval for the treatment indication.

Key Contact Information

1. During Normal Business Hours (8 a.m. - 4:30 p.m. ET, weekdays)

For **specific questions** during normal business hours:

- **Investigational drugs:** 301-796-3400 or druginfo@fda.hhs.gov [CDER's Division of Drug Information], or contact the appropriate review division, if known
  - **Oncology drugs:** 240-402-0004 or ONCProjectFacilitate@fda.hhs.gov
- **Investigational medical devices:** 301-796-7100 or DICE@fda.hhs.gov [CDRH's Division of Industry and Consumer Education]
- **Investigational biologics:** 240-402-8020 or 800-835-4709 or industry.biologics@fda.hhs.gov [CBER's Office of Communication, Outreach and Development]

For **general questions**, or if you are unsure of who to contact, contact the Patient Affairs Staff at 301-796-8460 or patientaffairs@fda.hhs.gov.

2. After 4:30 p.m. ET weekdays and all day on weekends

For **emergency requests** for all medical products (drugs, biologics, and medical devices) contact **FDA's Emergency Call Center** at 866-300-4374.

https://www.fda.gov/news-events/public-health-focus/expanded-access

Series of Informational Videos

Questions/Contact Us

- **CDER Division of Drug Information**
  druginfo@fda.hhs.gov
- **FDA's EA contact info**
  https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information

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References

21 CFR part 312: Investigational New Drug Application. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

21 CFR 312.300 on Expanded Access to Investigational Drugs for Treatment Use. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.300.

Guidance for industry *Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers* (2017). Available at https://www.fda.gov/media/85675/download.

Guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* (2017). Available at https://www.fda.gov/media/91160/download.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

L-theanine

Pharmacy Compounding Advisory Committee Meeting

October 29, 2024

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Office of New Drugs (OND)
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Special Thanks to: **Office of New Drugs - Division of Psychiatry**

Nomination

- L-theanine was nominated for inclusion on the list of bulk drug substances (BDS) that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- L-theanine was evaluated for the following uses:
  - Sleep disorders
  - Anxiety disorders
- L-theanine products proposed in the nominations are:
  - Sublingual (SL) 2.5 mg tablet
  - Topical 10% cream
  - Subcutaneous (SC)/intramuscular (IM) injection 75 mg vial (10 mg/mL) solution
  - Oral 50 mg, 100 mg, and 200 mg capsules

Evaluation Criteria

- Physical and chemical characterization
- Historical use in compounding
- Safety
- Available evidence of effectiveness or lack of effectiveness

Physical and Chemical Characterization (1)

- L-theanine (γ-glutamylethylamide or N-ethyl-L-glutamine) is a non-proteinogenic amino acid present in the tea plant (*Camellia sinensis*)
- Molecular formula: $C_7H_{14}N_2O_3$, Molecular weight: 174.200 g/mol
- White to off-white, odorless, crystalline powder
- Soluble in water up to 20 mg/mL
- L-theanine powder is reportedly stable for 2 years at 2-8°C
- Solutions in distilled water reportedly may be stored at -20°C for up to 2 months

Physical and Chemical Characterization (2)

- There is no USP monograph for L-theanine
- There is limited or no information for BDS characterization including:
  - Any tests, limits, or results for impurities, which would allow FDA to assess the nature and level of individual impurities or total impurities in the nominated BDS
  - Endotoxin control is critical for injectable dosage forms (SC and IM)

Conclusion:

- The nominated BDS, L-theanine, is not well characterized from the physical and chemical characterization perspective due to lack of select critical quality attribute controls (for example, testing for BDS related impurities and endotoxin testing) of L-theanine for compounding proposed dosage forms

Historical Use in Compounding

- L-theanine is marketed as an ingredient in oral dietary supplement products
- L-theanine has been compounded in the United States
  - Oral formulations
  - Multiple ingredient injection solution products
- Oral formulations advertised for:
  - Sleep disorders
  - Managing symptoms of anxiety and stress
- Clinical studies evaluated compounded L-theanine for:
  - Age-related cognitive decline, attention-deficit/hyperactivity disorder (ADHD), and sleep in pediatric subjects with ADHD

Conclusion:

- L-theanine has been used in pharmacy compounding in the U.S. since at least 2017. It has been marketed as compounded oral and injectable formulations for various conditions. OFs have not reported compounding drug products containing L-theanine since 2020.

Nonclinical Safety (1): General Pharmacology

- In rodents, L-theanine:
  - Prolonged sleep (Zhang et al. 2021)
  - Decreased anxiety-like behavior (Wise et al. 2012)
  - Reduced depression-like behavior (Wakabayashi et al. 2012)
  - Improved memory (Zhu et al. 2018)

- However, the mechanisms underlying the pharmacological effects of L-theanine are poorly understood

Nonclinical Safety (2): Pharmacokinetics

- In rats, L-theanine is quickly absorbed following oral administration; plasma concentrations peak 30 minutes after dosing (Sato et al. 2021)
- L-theanine distributes well to all tissues, including the brain, the liver, and the kidney (Terashima et al. 1999; Zhu et al. 2022)
- In fasted rats, L-theanine delivered orally is metabolized to glutamic acid and ethylamine, which are eliminated in urine (Unno et al. 1999)
- Age and health status appear to affect the pharmacokinetics of L-theanine in rodents

Nonclinical Safety (3)

- In adult rats given L-theanine in their diet for 13 weeks (Borzelleca et al. 2006), the oral no-observed adverse effect level (NOAEL) was 4,000 mg/kg/day (the highest dose tested)
  - Using body surface area, the oral NOAEL translates to a human equivalent dose of 640 mg/kg that provides safety margins of ~96.8X (in adults) and ~48.8X (in children) for the highest oral dose of 400 mg used in most clinical studies
  - Although dietary consumption of L-theanine seems to be well tolerated, no information is available to compare systemic exposure from dietary consumption to once daily treatment at the same total dose

- Nonclinical reproductive and developmental toxicity studies of L-theanine delivered orally were not identified at the time of this evaluation

- The nominators did not submit, and FDA did not identify nonclinical toxicity studies of L-theanine delivered via the SL, topical, SC, or IM route of administration (ROA)

Conclusion:

- Nonclinical safety information was too limited at the time of this evaluation to inform safety considerations for the inclusion of L-theanine in the 503A Bulks List

Clinical Safety (1): PK, FAERS, CAERS

- Pharmacokinetics (PK)
  - PK data available for oral administration in adults
  - No pharmacokinetic data for children
  - No pharmacokinetic data for SL, topical, SC, or IM ROA in humans
- FDA Adverse Event Reporting System (FAERS)
  - 3 cases of adverse event (AE) reports for L-theanine
  - Adverse events: diabetic ketoacidosis, balance disorder, and feeling abnormal
  - Assessments were confounded by multiple other ingredients
- Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS)
  - 4 reports of L-theanine as the only active ingredient
  - Adverse events: allergic type reaction, increased anxiety and attention disturbance, and nausea and diarrhea

Clinical Safety (2): Clinical Studies

- Reported AEs in adults with medical conditions (oral ROA)
  - agitation, sedation, increased duration of sleep, vivid dreams, headache, exacerbations in obsessive compulsive disorder (OCD) requiring in-patient admission
  - appetite loss, nausea, vomiting, diarrhea, constipation, reflux
  - tachycardia, fatigue
  - neutropenia, elevated C-reactive protein
- Pediatric subjects with medical conditions (oral and sublingual ROA)
  - Reported AE: facial tic
- It is not known whether the reported AEs were due to L-theanine or due to other concomitant medications

Clinical Safety (3)

Conclusion:

- Oral and SL administration of L-theanine appears to be generally well tolerated
- No studies on L-theanine via the topical, IM, or SC ROA

Overview of Sleep Disorders

- Sleep disorders
  - Disorders that affect different parts of the normal sleep cycle
    - Insomnia
    - REM sleep disorders
    - Obstructive sleep apnea
    - Central disorders of hypersomnolence
    - Circadian rhythm sleep-wake disorders
    - Restless leg syndrome
    - Parasomnias

Clinical Effectiveness – Sleep Disorders (1)
Nominator Submitted Clinical Trial

Lyon et al. 2011:

- Double blind (DB), placebo controlled (PC) trial, 8 to 12-year-old boys with ADHD (n=98), treatment for 6 weeks
  - Oral L-theanine 200 mg twice daily (BID)
  - Placebo containing lactose
- Study Measurements: objective (actigraphy) and subjective (Pediatric Sleep Questionnaire: PSQ) measures of sleep quality
- Authors reported that participants in the L-theanine study arm
  - Had increased sleep efficiency, fewer bouts of nocturnal activity
  - However, there was no difference between treatment groups in sleep latency (time to fall asleep), or sleep duration (total sleep time), and PSQ data did not correlate with the actigraphy data

Clinical Effectiveness – Sleep Disorders (2)
Nominator Submitted Clinical Trial

Lyon et al. 2011:

- **Limitations**
  - Baseline measures on actigraphy, PSQ, core ADHD symptoms not reported
  - Did not discuss which type of stimulants the subjects were taking, did not show results by subgroup to discuss whether being on a stimulant had an effect on the study outcomes
  - Compliance with wearing the actigraph watch was not reported
  - Did not achieve the pre-specified statistical level of significance
  - No female subjects were included
  - Unclear whether slight changes in actigraphy measures in this small study are clinically meaningful
  - Unclear if results are generalizable to a larger population of children with ADHD and sleep disorders
  - Unclear if results are generalizable to populations with primary sleep disorders who do not have ADHD

Clinical Effectiveness – Sleep Disorders (3)
Other Studies

Thiagarajah et al. 2022:

- Randomized (R), DB, PC, crossover study, 39 adults with poor sleep quality received 4 weeks of:
  - Oral RLX2™ (150 mg alpha-s1-casein tryptic hydrolysate and 50 mg L-theanine)
  - Placebo
- The authors report sleep duration and sleep habitual efficiency were improved in the RLX2 group vs placebo

Ota et al. 2015:

- 8 week, open-label study, 17 adults with schizophrenia and 22 age and sex matched healthy subjects
- L-theanine (Suntheanine) 250 mg/day was added to the subjects' current treatment for schizophrenia
- The authors reported L-theanine ameliorated positive symptoms of schizophrenia and improved sleep quality

Limitations:

- Small sample size
- Absence of objective measures to assess sleep outcomes
- Authors do not report whether any study subjects had a primary sleep disorder
- L-theanine was given with another substance as part of the intervention in both studies
- Unknown if subjects were taking other medications that may have affected sleep
- Other underlying comorbidities or medical conditions
- Difficult to determine the contribution of L-theanine to the study outcomes
- Unclear whether study results generalizable to a population with primary sleep disorders

Clinical Effectiveness – Sleep Disorders (4)

Conclusion:

- There is insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of sleep disorders
- No studies in which subjects received L-theanine via the SL, topical, IM, or SC ROA
- Professional society guidelines do not discuss the use of L-theanine for sleep disorders
- There are FDA-approved therapies with established efficacy for many sleep disorders

Overview of Anxiety Disorders

- Anxiety disorders
  - Disorders that share features of excessive fear and anxiety
  - Anxiety disorders differ from one another in the types of objects or situations that induce fear, anxiety, or avoidance behavior
    - Separation Anxiety Disorder (SAD)
    - Selective Mutism (SM)
    - Specific Phobia (SP)
    - Social Anxiety Disorder (SD)
    - Panic Disorder (PD)
    - Agoraphobia
    - Generalized Anxiety Disorder (GAD)
    - Substance/Medication-Induced Anxiety Disorder
    - Anxiety Disorder Due to Another Medical Condition

Clinical Effectiveness – Anxiety Disorders (1) Clinical Trial

Sarris et al. 2019:

- R, DB, PC, pilot study, 46 adults with GAD who were non-responsive to their current medication evaluated anxiety and insomnia outcomes
- Treatment received for 4 – 8 weeks
  - Oral L-theanine 450 mg per day (given as one 225 mg capsule BID) + current medications
  - Placebo + current medications
- Treatment for second 4 weeks
  - Oral L-theanine 900 mg per day + current medications
  - Placebo + current medications
- Additional Treatments
  - Psychotherapy
- **Author Reported Conclusions**
  - For both anxiety and insomnia outcomes **no difference between L-theanine and placebo groups was observed**

Clinical Effectiveness – Anxiety Disorders (2)
Other Studies

Rizzo et al. 2022:

- Open-label study without placebo, 34 children with Tourette Syndrome or chronic tic disorder associated with anxiety symptoms, received L-theanine (200 mg/day) and vitamin B6 (2.8 mg/day) daily or psychoeducation for 2 months
- Authors report there was no difference in mean anxiety scores between treatment groups

Hidese et al. 2017:

- Open-label study without placebo, 20 adults with major depressive disorder received L-theanine orally (250 mg/day) for eight weeks
- Authors reported improvement in anxiety symptoms following administration of L-theanine

Ross et al. 2021:

- Case report without placebo of an adult with Post Traumatic Stress Disorder (PTSD), and Bipolar II disorder with generalized anxiety, received thirteen medications and dietary supplements including L-theanine, for three months
- Subject reported improvement in mood and anxiety

Limitations:

- Small sample size, lack of blinding, lack of placebo control
- Use of concomitant medications during the intervention confounds interpretation of the intervention
- Difficult to determine the contribution of L-theanine to the study outcomes
- Unclear whether study results would be generalizable to a population with primary anxiety disorders

Clinical Effectiveness – Anxiety Disorders (3)

Conclusion:

- There is insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of anxiety disorders
- No studies in which subjects received L-theanine via the other nominated ROAs
- Professional society guidelines do not discuss the use of L-theanine for anxiety disorders
- There are FDA-approved therapies with established efficacy for many anxiety disorders

Evaluation Summary

- **Physical and Chemical Characterization**
  - L-theanine is not well characterized due to lack of critical quality attribute controls (BDS related impurities and endotoxin testing) for compounding proposed dosage forms
- **Historical Use in Compounding**
  - L-theanine has been compounded in the United States
    - Oral formulations
    - Multiple ingredient injection solution products containing L-theanine
  - OFs have not reported compounding drug products containing L-theanine since 2020.
- **Safety**
  - The nominators did not submit, and FDA did not identify nonclinical toxicity studies of L-theanine delivered via the nominated SL, topical, SC, or IM route of administration
  - Nonclinical studies identified at the time of this evaluation were too limited to inform safety considerations for the inclusion of L-theanine in the 503A Bulks List
  - Oral and SL administration of L-theanine in humans appears to be generally well tolerated
  - No studies on L-theanine via the topical, IM, or SC ROA
- **Effectiveness**
  - There is insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of sleep disorders and anxiety disorders
  - No studies on L-theanine via the other nominated ROAs
  - Professional society guidelines do not discuss the use of L-theanine for sleep disorders or anxiety disorders
  - There are FDA-approved therapies with established efficacy for many sleep disorders and anxiety disorders

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs **against** L-theanine being added to the 503A Bulks List.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Ibutamoren Mesylate

Pharmacy Compounding Advisory Committee Meeting

October 29, 2024

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Special Thanks to: **Office of New Drugs - Division of General Endocrinology**

Nomination

Ibutamoren mesylate:

- Nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- Also known as MK-677, MK-0677, MK0677, and LUM-201
- Proposed dosage forms are oral capsules or tablets in 10 mg and 25 mg
- Evaluated for:
  - Growth hormone deficiency (GHD)
  - Osteoporosis
  - Hip fracture
  - Sarcopenia
  - Obesity
  - Alzheimer's disease (AD)

Evaluation Criteria

- Physical and chemical characterization
- Historical use in compounding
- Available evidence of effectiveness or lack of effectiveness
- Safety

Physical and Chemical Characterization (1)

Ibutamoren mesylate:

- Is a small chiral molecule containing serine and 2-aminoisobutyric acid as a substructure
- Has no U.S. Pharmacopeia (USP) compendial monograph
- Can reportedly be synthesized from commercially available starting material isonipecotic acid
- Is stable at -20°C for 4 years in powder form as reported in the literature
- Is soluble in water and ethanol

Physical and Chemical Characterization (2)

- Certificates of analysis (CoAs) provided by nominators include ID test and a purity test by HPLC, but no tests for chiral purity (% enantiomeric excess), drug substance related impurities, and residual solvents
- The likely impurity profile would be specific to and determined by the synthetic route used
- 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

Conclusion: Ibutamoren mesylate is not well characterized from a physical and chemical perspective because certain critical characterization data relating to the chiral purity, drug substance related impurities, or residual solvents were not found in the publicly available scientific literature nor provided in the CoAs.

Historical Use in Compounding (1)

Ibutamoren mesylate:

- Was first synthesized in 1995 by researchers at Merck in an attempt to identify an orally active growth hormone secretagogue (GHS)
- Has been studied for use in several conditions, including GHD, obesity, hip fracture, osteoporosis, and AD
  - None of the studies appear to have utilized a compounded formulation

Historical Use in Compounding (2)

- Ibutamoren mesylate is marketed online:
  - To reverse the aging process and as a supplement in bodybuilding and weightlifting
  - In capsule, tablet, powder, liquid, and injection forms
    - Some products are labeled for research use only
- It is unclear if any pharmacies are compounding such products
- Not recognized in the European or Japanese Pharmacopeias

Conclusion: The extent to which ibutamoren mesylate has been historically used in compounding is unclear. Currently available data are too limited to inform historical use for compounding.

General Pharmacology

- Based on nonclinical data, ibutamoren mesylate binds to and activates ghrelin receptors in anterior pituitary gland somatotrophs and in hypothalamic GH-releasing hormone (GHRH) neurons
  - It can induce GH release from anterior pituitary gland in vitro and in vivo (Holst et al. 2009)
  - It can trigger hypothalamic release of GHRH that, in turn, can stimulate GH release from somatotrophs (Bailey et al. 1999; Patchett et al. 1995)

- A single intravenous (IV) or oral dose increases serum GH levels in different animal species (Lee et al. 2018)

- However, following treatment of rats with the dose of 4 mg/kg/day (oral gavage) for 6 weeks, ibutamoren mesylate was unable to increase serum GH levels (Lee et al. 2018)
  - The loss of the desired clinical response of increased GH secretion following continuous treatment with ibutamoren mesylate may be due to increased expression of hypothalamic somatostatin (hormone that suppresses GH release) and/or receptor internalization and desensitization

Pharmacokinetics

- Nonclinical pharmacokinetic (PK) information:
  - Oral bioavailability in dogs: >60% (Patchett et al. 1995)
  - In vitro and in vivo, ibutamoren is metabolized primarily via CYP450 and glucuronidation (Cutler et al. 2022; Philip et al. 2021)

- Limited clinical PK information:
  - “High oral bioavailability” and “long duration of action” (Chapman et al. 1996); no details provided
  - Long-acting (24 hours) and is orally active (Thorner 1997); no details provided
  - No additional clinical PK data was identified in a medical literature search

Overview of GHD

- GHD:
  - Characterized by inadequate secretion of GH from pituitary gland
  - Can be congenital or acquired
    - Some cases have no known cause (idiopathic) and may be childhood- or adult-onset
  - Can be complete (inability to secrete GH) or partial
- Diagnosis: signs and symptoms and GH stimulation tests using provocative agents
  - Random GH level is not useful because levels fluctuate throughout day
  - Insulin-like growth factor 1 (IGF-1) levels are helpful in screening
- Signs and symptoms may include:
  - Childhood: low blood glucose levels in infants and toddlers, growth failure, short stature, and maturation delays
  - Adulthood: reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, lipid abnormalities, insulin resistance, and impaired cardiac function

Treatment of GHD

- Multiple recombinant human GH (rhGH) preparations approved for children with growth failure due to inadequate secretion of endogenous GH and adults with GHD

- In pediatric patients with GHD:
  - GH is used to normalize annual growth velocity and final adult height
  - Doses are titrated based on growth response. IGF-1 levels monitor adherence and safety

- In adults with GHD:
  - GH offers benefits in body composition, exercise capacity, and quality of life (Molitch et al. 2011)
  - GH dose is titrated according to clinical response, side effects, and IGF-1 levels

Clinical Effectiveness – GHD (1)

Ibutamoren mesylate (a GHS) has been studied for treatment of GHD

- Because it activates ghrelin receptors in the pituitary and hypothalamus to stimulate GH release, some residual endogenous GH secretion must be preserved (i.e., partial and not complete GHD)

- Chapman et al. 1996:
  - Randomized (R), double-blind (DB), placebo-controlled (PC) study evaluated oral MK-677 (2 to 25 mg) vs. placebo in 32 healthy adults (64-81 y/o) for two 14-day periods
  - Results showed MK-677 enhanced pulsatile GH secretion and increased IGF-1 levels
  - Study limitations: short duration, study population, lack of clinically meaningful endpoints

- Chapman et al. 1997:
  - R, DB, PC study evaluated effect of oral MK-677 on GH/IGF-1 axis in adults with severe GHD (N=9)
  - Received MK-677 10 mg or placebo (crossover fashion), or MK-677 10 mg then 50 mg for two 4-day periods
  - Authors found: IGF-1 and 24-hour mean GH concentrations increased with MK-677 vs. baseline; GH response greater in subjects least GH/IGF-1 deficient at baseline
  - Study limitations: short duration, small sample size, endpoints did not evaluate therapeutic effect

Clinical Effectiveness – GHD (2)

Codner et al. 2001:

- R, partially DB, PC study evaluated effect on GH/IGF-1 axis in 18 children with idiopathic GHD
- Received oral ibutamoren mesylate up to 0.8 mg/kg/day, up to 15 days

- Authors concluded:
  - Short-term administration can increase GH, IGF-1, and insulin-like growth factor-binding protein-3 (IGFBP-3) levels in some children with GHD
  - 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: short duration, small sample size, lack of clinically meaningful endpoints

Clinical Effectiveness – GHD (3)

Bright et al. 2021:

- Analysis of earlier completed R, DB, PC study of LUM-201 in 68 children with GHD
- After measuring peak GH response to LUM-201, subjects received for 6 months:
  - Oral LUM-201: 0.4 mg/kg/day (n=22) or 0.8 mg/kg/day (n=24); or placebo (n=22)
  - After 6 months, 20 subjects on placebo switched to subcutaneous (SC) rhGH 0.3 mg/kg/week

- Authors found:
  - Mean annualized height velocity (HV) per year:
    - LUM-201: 6.0 cm to 6.9 cm
    - Placebo: 4.5 cm
    - rhGH: 11.1 cm
  - Peak GH ≥ 5 ng/mL with a single dose and a baseline IGF-1 > 30 ng/mL were positive predictive enrichment markers for increased HV on LUM-201
- Study limitations: retrospective analysis of data

Overview of Osteoporosis

- Bone mineral density (BMD) and bone mass decrease
- Diagnosis involves assessment of clinical history, signs and symptoms, and tests that measure BMD, such as dual-energy X-ray absorptiometry (DXA)
- Treatment aims to prevent fractures and may include:
  - Nutrition and exercise
  - Medications: bisphosphonates, calcitonin, estrogen agonists/antagonists, estrogen and combined estrogen and progestin, parathyroid hormone (PTH) analogs and PTH-related peptide (PTHrP) analogs, receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors, and sclerostin inhibitors

Clinical Effectiveness – Osteoporosis

Murphy et al. 2001: R, DB, PC study in 292 post-menopausal women with osteoporosis

- Oral treatment for up to 18 months: alendronate[1] and MK-677 25 mg, alone and in combination, or placebo
- Authors found:
  - Markers of bone formation and resorption increased (MK-677) vs. decreased (alendronate); reduction was mitigated with MK-677/alendronate
  - BMD increased at femoral neck 4.2% (MK-677/alendronate) vs. 2.5% (alendronate) at 18 months
    - Similar enhancement not seen in lumbar spine, total hip, or total body vs. alendronate alone
    - MK-677 alone for 12 months did not increase BMD at any site significantly vs. placebo
  - IGF-1 increased 40% with MK-677, with or without alendronate

- Authors concluded: anabolic effect of MK-677 attenuated indirect suppressive effect of alendronate on bone formation, but did not translate into significant increases in BMD other than the femoral neck
  - Per authors: although femoral neck is an important site for fracture prevention, lack of enhancement in bone mass at other sites compared with alendronate alone is a concern when weighed against potential side effects of enhanced GH secretion

[1] Alendronate is a bisphosphonate that is FDA-approved for the treatment of osteoporosis in post-menopausal women.

Overview of Hip Fracture

- Hip fractures often occur in patients ≥ 65 y/o as the result of falls
- Symptoms are typically acute pain at fracture site, and often not able to stand or bear weight
- Hip fractures are diagnosed on imaging studies such as X-rays
- Treatment is usually a combination of prompt surgical repair, rehabilitation, medication for pain, prevent blood clots and infection
- Successful long-term management of elderly patients has proved challenging; immobilization causes rapid muscle loss that may impact effective rehabilitation and functional recovery

Clinical Effectiveness – Hip Fracture (1)

Bach et al. 2004: R, DB, PC study evaluated oral MK-0677 on functional recovery in subjects ≥ 65 y/o recovering from hip fracture

- Treatment daily for 6 months: MK-0677 25 mg (n=84) or placebo (n=77)
- Authors found:
  - Both groups showed improvement over time with no differences in change in functional performance measures (FPMs) or Sickness Impact Profile for Nursing Homes (SIP-NH) score
  - MK-0677 group showed trends in greater improvement vs. placebo in 3 of 4 lower extremity FPMs, in physical domain of the SIP-NH, and in ability to live independently
  - IGF-1 levels increased by 84% in MK-0677 vs. 17% in placebo group

- Authors concluded:
  - Although MK-0677 treatment increased IGF-1, it was uncertain whether clinically significant effects on physical function were achieved
- Study limitations: unknown clinical relevance of measured changes in FPMs, measurement at discrete time points, lack of assessment of pre-fracture status

Clinical Effectiveness – Hip Fracture (2)

Adunsky et al. 2011: R, DB, PC study evaluated oral MK-0677 in patients ≥ 60 y/o recovering from unilateral hip fracture

- Treatment daily for 24 weeks: MK-0677 25 mg (n=62) or placebo (n=61)
- Authors found:
  - IGF-1 increased with MK-0677; was not paralleled by improvement in most FPMs
- Study was terminated early due to safety signal of congestive heart failure (CHF)
  - 4 patients [6.5%] in the MK-0677 group vs. 1 [1.7%] in placebo
- Authors concluded:
  "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."

Overview of Sarcopenia

- Age-associated loss of skeletal muscle function and muscle mass, which is progressive and generalized
- Likely multifactorial etiology, with causes such as declines in activity and nutritional intake, disease triggers, inflammatory pathway activation, and hormonal changes
- Symptoms may include strength and functional declines that can contribute to adverse health outcomes such as loss of function, disability, and frailty
- Treatment:
  - No FDA-approved drugs indicated for sarcopenia
  - Current treatment interventions focus on increasing activity and providing adequate nutrition

Clinical Effectiveness – Sarcopenia

References submitted by the nominator did not include studies conducted in subjects with sarcopenia:

- Plotkin et al. 1997 (abstract): oral MK-677 vs. placebo in 104 men and women with strength deficits (ages 65-95 y/o): IGF-1 levels increased in dose-dependent manner after 2 weeks and mean 24-hour GH levels increased with MK-677 vs. baseline

- Murphy et al. 1998: oral MK-677 vs. placebo in 8 healthy males with diet-induced protein catabolism: MK-677 for 7 days reversed diet-induced nitrogen wasting, with less weight loss in MK-677 group vs. placebo
  Authors noted future studies should determine whether anabolic effects of MK-677 will persist with prolonged treatment, and if they will be associated with clinical benefits

- Nass et al. 2008 proof-of-concept study: oral MK-677 vs. placebo in 71 healthy adults (ages 60-81 y/o): MK-677 increased 24-hour mean GH and fat-free mass (FFM) over 12 months, although increased FFM did not result in changes in strength or function

Overview of Obesity

- Chronic health condition that increases the risk for heart disease and is linked to other health problems, such as type 2 diabetes and cancer
- Diagnosis based on medical history and high body mass index (BMI) (for adults, ≥ 30 kg/m^2)
- Treatment may involve:
  - Dietary or nutritional counseling, behavioral weight-loss programs, surgery
  - FDA-approved drug products as adjunctive therapy for weight loss, including:
    - Glucagon-like peptide-1 (GLP-1) receptor agonist (e.g., liraglutide (Saxenda), semaglutide (Ozempic, Wegovy))
    - Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (tirzepatide (Zepbound))
    - Naltrexone HCl and bupropion HCl (Contrave): an opioid antagonist (naltrexone) and an aminoketone antidepressant (bupropion)
    - Orlistat (Xenical): an inhibitor of gastrointestinal lipases
    - Phentermine and topiramate (Qsymia): a sympathomimetic amine anorectic (phentermine) with a sulfamate-substituted monosaccharide (topiramate)

Clinical Effectiveness – Obesity

Svensson et al. 1998b: R, DB, PC parallel study evaluated GH secretion and body composition in males with obesity (18-50 y/o)

- Treatment daily for 8 weeks: oral MK-677 25 mg (n=12) or placebo (n=12)

- Authors found in MK-677 group vs. placebo:
  - Peak GH increased after initial dose and through study
  - IGF-1 increased approximately 40%
  - FFM increased (determined with DXA or using a four-compartment model)
  - No change in total body fat and visceral fat
- Authors noted: further studies are needed to evaluate whether higher dose of MK-677 or prolonged treatment period can promote a reduction in body fat
- Study limitations: small sample size, short study duration, studied only males ≤ 50 y/o

Overview of Alzheimer's Disease

- Progressive disease that affects memory, thinking, and behavior
- Specific causes not fully understood but likely include combination of age-related changes in the brain and genetic, environmental, and lifestyle factors
- Symptoms may include memory loss and mild cognitive impairment, progressing to behavior changes and inability to communicate
- Diagnosis is typically made by detailed clinical assessment
- Treatment:
  - Depends in part on the stage of disease; medications are approved 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)
  - Medications are approved to treat symptoms associated with AD (e.g., brexipiprazole)

Clinical Effectiveness – Alzheimer's Disease

Sevigny et al. 2008: R, DB, PC multi-center study evaluated disease progression in 563 subjects with mild to moderate AD

- Treatment daily for 12 months: oral MK-677 25 mg (n=282) or placebo (n=281) Cholinesterase inhibitors or memantine were allowed if on stable doses
- Efficacy measures—change from baseline at month 12 on:
  - Clinician's Interview Based Impression of Change with caregiver input (CIBIC-plus), cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and Clinical Dementia Rating-sum of boxes (CDR-sob)

- Authors found:
  - MK-677 25 mg resulted in 60.1% increase in IGF-1 at 6 weeks and 72.9% at 12 months
  - No significant differences between treatment groups on efficacy measures
- Authors concluded: despite noting a robust increase in IGF-1, MK-677 was ineffective at slowing the rate of progression of AD

Effectiveness

Conclusion:

- There is insufficient information to support the effectiveness of ibutamoren mesylate for the treatment of GHD, osteoporosis, hip fracture, sarcopenia, obesity, and AD
- 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
- The uses under consideration have the potential to be serious
- In addition, there are currently FDA-approved drugs with established efficacy for GHD, osteoporosis, obesity, and AD, and alternative treatment methods for hip fracture and sarcopenia

Nonclinical Safety (1)

- In rats, ibutamoren mesylate and other ghrelin receptor agonists induce hypotension (Sales da Silva et al. 2020)
- Ghrelin receptors are expressed in the brain reward system (Zigman et al. 2006), and, in rodents and in humans, the ghrelin receptor agonist ghrelin has been shown to induce pharmacological responses typically evoked by drugs of abuse (Edvardsson et al. 2021; Maric et al. 2012; Malik et al. 2008)
  - By activating ghrelin receptors in the brain reward system, ibutamoren mesylate could stimulate reward processing and potentially induce reinforcing and addictive behaviors. However, nonclinical studies were lacking to demonstrate whether ibutamoren mesylate has reinforcing and/or addictive properties

Nonclinical Safety (2)

- Nonclinical acute toxicity, repeat-dose toxicity, genotoxicity, or carcinogenicity studies were not found in publicly available scientific literature

- Nonclinical developmental and reproductive toxicity studies with ibutamoren mesylate were not found in the literature
  - However, treatment of mice at different stages of the reproductive cycle and gestation with ghrelin, a substance that like ibutamoren mesylate acts as a ghrelin receptor agonist, resulted in negative effects on fertilization, implantation, and embryofetal development (Luque et al. 2014)

Nonclinical Safety – Conclusion

- As discussed in general pharmacology (slide 49), according to nonclinical pharmacological studies, the desired clinical response of increased GH secretion may be lost during continuous oral treatment with ibutamoren mesylate
- Ibutamoren mesylate can induce hypotension in rats
- Via activation of ghrelin receptors in brain reward regions, ibutamoren mesylate may have behavioral reinforcing/addictive properties
- The finding of developmental toxicity following gestational treatment of rodents with a substance that, like ibutamoren mesylate, acts as a ghrelin receptor agonist raises additional safety concerns

Clinical Safety

- FDA Adverse Event Reporting System (FAERS)
- Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS)
- Published case reports
- Published clinical studies that reported safety outcomes
- Other safety information

Clinical Safety – Safety Reports

- FAERS: Search retrieved three adverse event (AE) reports (doses unspecified)
  - Vomiting and upper abdominal pain
  - Could not “feel one of his fingers”
  - Intracranial infarct in 68-year-old male with underlying medical conditions on concomitant medications

- CAERS: Search retrieved two additional reports in males
  - Weight loss, diarrhea, headache, and abdominal discomfort (25 mg)
  - Decreased activity and mood alteration (dose unspecified)

- Published case reports: Retrieved three reports with one or more of the following AEs
  - Hepatomegaly, elevated liver enzymes, dyslipidemia, hyperglycemia, elevated glycosylated hemoglobin A1c (HbA1c)

Our ability to interpret AE reports is limited by factors such as insufficient case details and concomitant medications

Clinical Safety – Clinical Studies (1)

3 studies in patients with GHD treated for 4 days to 6 months

- Oral doses up to 0.8 mg/kg/day in children and up to 50 mg/day in adults

  (Chapman et al. 1997 [N=9]; Codner et al. 2001 [N=18]; Bright et al. 2021 [N=68])
- AEs reported:
  - Increased appetite, vomiting, diarrhea
  - Headache, dry skin, night sweats
  - Numbness on right hand
  - Increased transaminases, white blood cell (WBC) count, creatinine

Clinical Safety – Clinical Studies (2)

1 study in 292 women with osteoporosis treated with oral alendronate and MK-677 25 mg (individually and in combination) for 6-18 months (Murphy et al. 2001)

- Per authors, GH-mediated AEs were noted in MK-677 groups:
  - Weight gain, edema, abdominal distension, carpal tunnel syndrome
- Discontinuations due to AEs judged to be related to treatment:
  - MK-677: Headache, night sweats, hip/leg pain, abdominal pain, hyperprolactinemia, transaminase elevation > 3 times upper limit of normal
  - Alendronate: Fluid retention, headache, night sweats, hip/leg pain, abdominal pain, heartburn, esophageal ulcer
  - MK-677/alendronate: Hyperglycemia, hypertension, fluid retention, headache, night sweats, hip/leg pain, heartburn, rash, hyperprolactinemia
  - Placebo: abdominal pain, esophageal ulcer, rash

Clinical Safety – Clinical Studies (3)

2 studies in patients ≥ 60 y/o with hip fracture treated with oral ibutamoren mesylate 25 mg for 6 months

- Bach et al. 2004
  - Serious AEs (SAEs): 24% (MK-0677) versus 18% (placebo)
    - Thrombosis (MK-0677 = 4; placebo = 0); reported as non-drug related
    - Deaths (MK-677 = 3 during treatment; placebo = 3 during months 7-12); assessed as not related to treatment
  - MK-0677 group: increases in serum glucose, insulin, and HbA1c
  - More reports of edema and fluid overload in MK-0677 group (n=16) vs. placebo (n=10)

- Adunsky et al. 2011:
  - The study was terminated early due to a **safety signal of CHF (MK-0677 = 4; placebo = 1)**
  - AEs which may possibly be mechanism-based include (per authors):
    - CHF and increased blood pressure
  - AEs with higher frequency in MK-0677 group: elevated blood glucose and HbA1c, myalgia, arthralgia
  - Authors concluded the AEs "…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

Clinical Safety – Clinical Studies (4)

1 study in males with obesity treated with oral ibutamoren mesylate 25 mg for 8 weeks

(Svensson et al. 1998b)

- AEs reported with MK-677:
  - Peak prolactin and cortisol increased after first administration but not significantly different vs. placebo at 2 or 8 weeks
  - Oral glucose tolerance test showed impairment of glucose homeostasis at 2 and 8 weeks
  - 5 subjects had mild AEs considered to be drug-related:
    - Glucose 180 mg/dL at 6 weeks (spontaneous decrease 1 week later)
    - Transient increase alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (asymptomatic)
    - Transient gastritis at 4 weeks and mild sweating at 6 weeks

1 study in patients with mild to moderate AD who received MK-677 25 mg (n=282) or placebo (n=281) daily for 12 months (Sevigny et al. 2008)

- Incidence of AEs, SAEs, and serious drug-related AEs were comparable between groups
- Deaths (MK-677 = 3, placebo = 7); none were considered to be drug-related
- Drug-related laboratory AEs MK-677 (22.1%) vs. placebo (10%) – almost exclusively increased glucose and HbA1c

Clinical Safety – Clinical Studies (5)

5 studies in adult subjects who received oral ibutamoren mesylate 2 mg to 50 mg, for 1 week to 2 years

3 studies in healthy adults ≥ 60 y/o and adults with functional impairment
(Chapman et al. 1996, N=32; Murphy et al. 1999, N=187; Nass et al. 2008, N=71)

- AEs: increased appetite, mild transient lower extremity edema, abdominal pain, transient muscle pain, carpal tunnel syndrome, lightheadedness, shortness of breath, warm sensation
- Laboratory AEs: increased fasting blood glucose (leading to discontinuation in some subjects), cortisol, HbA1c (increased glucose correlated with BMI, per authors suggesting GH stimulatory effects may result in impaired glucose tolerance in individuals with predisposing risk factors)
- MK-677 dose down-titrated due to increased fasting blood glucose or joint pain
- AEs with no causality assessment: cancer (adenocarcinoma of tongue, colon cancer), myocardial infarction

1 study (abstract) in adults ≥ 65 y/o with strength deficits (Plotkin et al. 1997, N=104)

- MK-677 group: increased fasting blood glucose

1 study in adults 24-39 y/o with diet-induced protein catabolism (Murphy et al. 1998, N=8)

- MK-677 group: increased fasting blood glucose; stomachache and dizziness
- Placebo: diarrhea, headache

Summary of Safety Information from Clinical Studies

- 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
  - Single or multiple doses from 2 mg to 50 mg per day or weight-based doses from 0.2 to 0.8 mg/kg/day with durations up to 2 years
- Serious AEs included CHF, thrombosis, cancer, and myocardial infarction
- AEs leading to discontinuation included:
  - Hyperglycemia, hyperprolactinemia, increased transaminase levels
  - Hypertension, bloating/fluid retention, headache, night sweats, abdominal pain, heartburn, rash, lightheadedness, shortness of breath, warm sensation
- Commonly reported AEs included hyperglycemia, increased HbA1c, increased insulin, increased transaminase levels, headache, musculoskeletal complaints, fluid retention, and increased appetite

Additional Safety Information on IGF-1

- Increased IGF-1 and safety:
  - There are known potential risks associated with elevated GH and IGF-1
  - Warnings and precautions in FDA-approved recombinant human GH (rhGH) label include 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
  - We note a number of AEs known to be associated with rhGH were reported with ibutamoren mesylate in clinical studies (e.g., hyperglycemia and fluid retention)

- IGF-1 levels in older adults:
  - Older individuals with high IGF-1 are observed to be at increased risk for incident disease (such as dementia, vascular disease, and osteoporosis) or death. Higher IGF-1 appeared to be associated with cancer risk across ages (Zhang et al. 2021)
  - There is a lack of safety data on use of ibutamoren mesylate and its risks associated with higher IGF-1

Clinical Safety – Conclusion

- There are serious safety concerns related to ibutamoren mesylate use including CHF, hyperglycemia, elevated liver enzymes, edema and fluid overload. AEs reported in clinical studies include musculoskeletal pain, increase in appetite, and hyperprolactinemia
- 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
- 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
- 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 AD

Evaluation Summary

On balance, the physicochemical 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, ibutamoren mesylate is not well characterized from a physicochemical perspective, there are potential serious safety risks associated with its use, and there is limited evidence of benefit with its use for the nominated conditions, which are serious. These are particularly concerning given the availability of FDA-approved drug products that are indicated to treat many of these uses.

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs **against** ibutamoren mesylate being added to the 503A Bulks List.


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