Pharmacy Compounding Advisory Committee: IND Drug Development and Expanded Access (EA) June 8, 2022

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Disclosure

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

Objectives

- Explain alternative pathways (beyond bulk drug substance compounding under 503A and 503B) under which investigational drugs can be studied and used for treatment
- 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 provide access to 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 with 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 to treatment**

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 (Curriculum Vitae (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

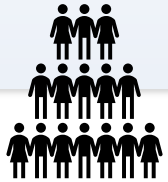
What is Expanded Access (EA)?

- **Expanded Access is the use of an investigational drug or biologic 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



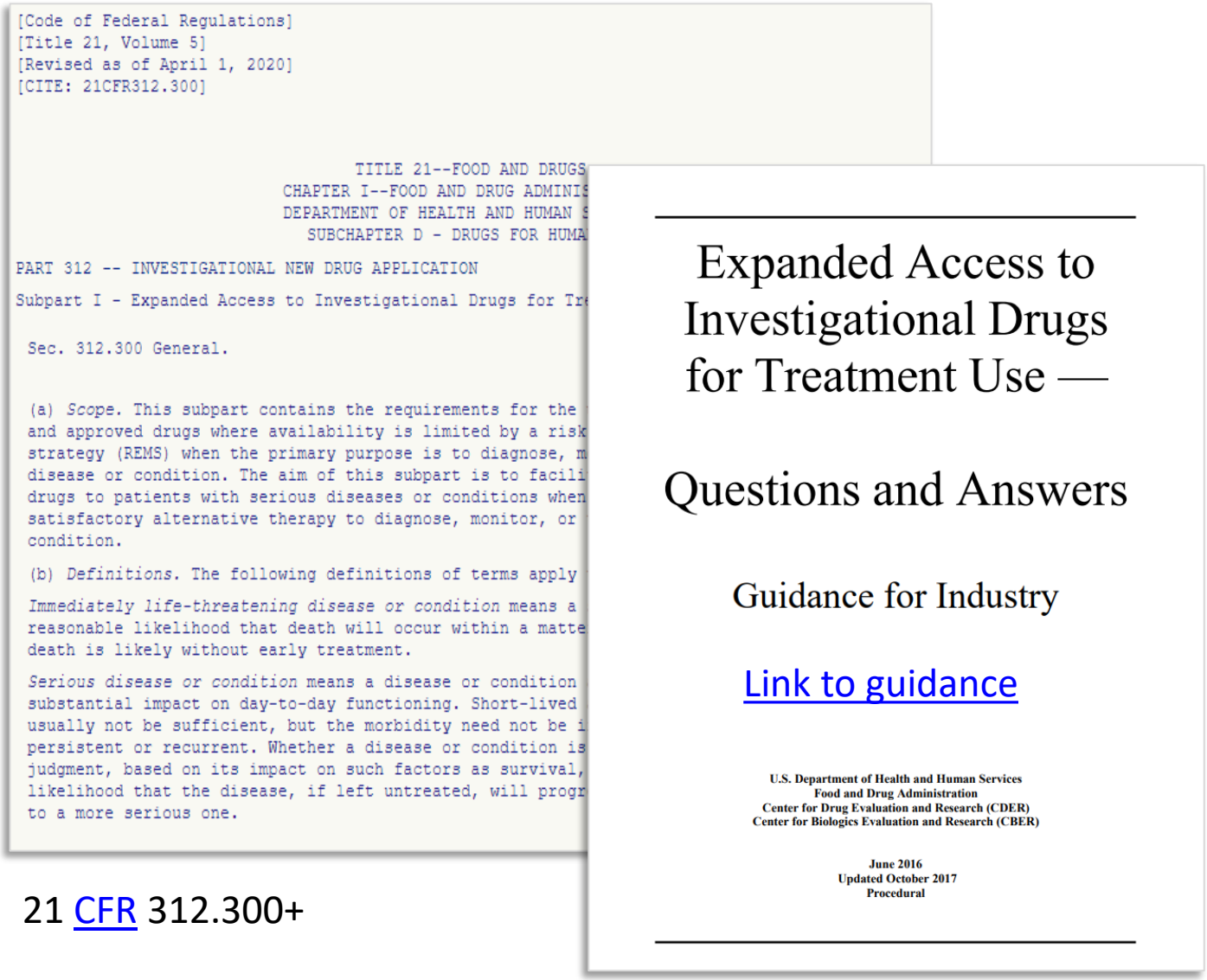
Treatment Investigational New Drug (IND) or Treatment Protocol

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 investigational product development program**

* 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 Expanded Access Programs (EAP), 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 Biologics)

- Creation of Form FDA 3926 for Individual Patient Expanded Access Investigational New Drug Application (IND) (2016)
- Updated guidances and website (2016, 2017)
- 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

- Expanded Access | Information for Patients
- Expanded Access | Information for Physicians
- Expanded Access | Information for Industry
- Expanded Access | How to Submit a Request (Forms)
- Expanded Access | Keywords, Definitions, and Resources
- FDA's Expanded Access Contact Information

Sometimes called "compassionate use", expanded access is a potential pathway for a patient with an **immediately life-threatening condition or serious 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 disease or condition, or whose life is immediately threatened by their 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.

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

Enclomiphene Citrate

Pharmacy Compounding Advisory Committee Meeting

June 8, 2022

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Special Thanks to:
Office of New Drugs- Division of Urology, Obstetrics and Gynecology

Nomination

- Enclomiphene citrate was 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)
- Enclomiphene citrate was evaluated for the following use: to increase serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to normal levels in the treatment of secondary hypogonadism
- The proposed dosage forms are capsules or tablets for oral administration in 12.5 mg, 25 mg, and 50 mg strengths

Evaluation Criteria

- Physical and chemical characterization
- Nonclinical and clinical safety
- Available evidence of effectiveness or lack of effectiveness
- Historical use in compounding

Physical and Chemical Characterization

Enclomiphene citrate:

- Is a small molecule
- Has no United States Pharmacopeia (USP) compendial monograph
- Can be made by separation from the mixture of geometric isomers: trans-clomiphene citrate (enclomiphene citrate) and cis-clomiphene citrate (zuclomiphene citrate). The mixture of these two isomers is clomiphene citrate
  - Clomiphene citrate has a USP monograph and is the active ingredient in an approved drug product
  - Based on USP monograph, the content of enclomiphene citrate in clomiphene citrate is about 50-70%
  - Clomiphene citrate is stable when stored at controlled room temperature and protected from light
  - Since enclomiphene citrate is one constituent of clomiphene citrate geometric isomeric mixture, it is expected to be stable when stored under the similar storage conditions

Physical and Chemical Characterization (2)

Enclomiphene citrate:

- Can be characterized by common analytical tools and techniques
- Is slightly soluble in water; therefore, particle size and polymorphism of the drug substance may be critical for solid oral dosage forms
- Impurity profile is expected to be similar to clomiphene citrate as outlined in USP monograph; in addition, likely impurities include residual cis-clomiphene citrate and binaphthyl-phosphoric acid used in the manufacturing process
- Impurities are unlikely to be toxic if adequately controlled

Conclusion: Enclomiphene citrate is a well-characterized small molecule and is expected to be stable under ordinary storage conditions when protected from light in the proposed dosage form.

Nonclinical – General Pharmacology

- Enclomiphene citrate is a selective estrogen receptor modulator (SERM) which acts by blocking the estrogenic suppression of the hypothalamic-pituitary-gonadal (HPG) axis
- Animal studies suggest that enclomiphene citrate can treat secondary hypogonadism by increasing circulating testosterone levels (Rodriguez et al. 2016)

Nonclinical – Pharmacokinetics and Safety

- Oral dosing of enclomiphene citrate in rodents showed rapid absorption and dose-related increase in plasma levels (European Medicines Agency [EMA] 2018)
- Repeat dose toxicity:
  - 26-week repeat oral dose toxicity in rats (0.5, 5, and 10 mg/kg/day):
    - No minimum no adverse effect level (NOAEL) due to drug-related toxicities at all doses
    - Reduced body weight and food consumption, decreased organ weight (prostate gland, pituitary gland, and epididymides), and histopathological findings (prostate, testes, seminal vesicles, and kidneys)
  - 9-month study oral dose toxicity in dogs (2, 10, and 40 reduced to 20 mg/kg/day due to morbidities in treated animals):
    - Deaths in high dose animals were related to hepatotoxicity
    - Mid-and high-dose treated dogs showed organ weight changes (adrenal/liver/prostate gland), delayed onset of puberty, and ophthalmic abnormalities (minimal lens fiber swelling)

Nonclinical Safety

- Genotoxicity:
  - Enclomiphene citrate was negative in a battery of genotoxicity assays
- Developmental and Reproductive Toxicity:
  - Doses of 200 mg/kg/day enclomiphene citrate resulted in mortality in male mice
  - Doses of 40 or 100 mg/kg/day were associated with altered sperm parameters, increased resorptions, and post-implantation loss
- Carcinogenicity:
  - A 26-week transgenic mouse carcinogenicity study (10, 50, 100, and 200 mg/kg/day enclomiphene) showed deaths among high-dose treated animals, possibly due to necrosis and inflammation of the intestines. Histopathology showed nonsignificant increased incidence of testicular interstitial cell adenomas
  - A 2-year rat carcinogenicity study (0, 0.0125, 0.025, and 0.05 mg/kg/day) did not have an increased incidence of tumors compared to controls
  - Enclomiphene citrate is not considered carcinogenic

Nonclinical Safety – Conclusion

- Nonclinical toxicity profile of enclomiphene citrate reflects its exaggerated pharmacological action as a SERM
- Reproductive adverse findings include decreases in organ weight (prostate gland, pituitary gland, and epididymides) and histopathological findings (prostate, testes, and seminal vesicles)
- Potential nonreproductive target organs in rats and dogs include liver, kidneys, and eyes
- Enclomiphene citrate is not considered genotoxic or carcinogenic

Clinical Safety – Pharmacokinetics

- Oral enclomiphene citrate is rapidly absorbed and has a half-life ($T_{½}$) of approximately 10 hours (Wiehle et al. 2014b)
- Maximum serum concentration occurs 2 to 3 hours after oral administration. Absorption is increased by the presence of food. Excretion is 61.5% in feces and 8.2% in urine (Earl and Kim 2019)
- Mean peak concentration (C_{max}) increased in a greater than dose proportional manner from 12.5 mg to 25 mg, and a less than dose proportional manner from 25 mg to 50 mg (Wiehle et al. 2014b)
- Main metabolite appears to be 4-OH enclomiphene formed primarily by CYP2D6 (EMA 2018)

Clinical Safety

- FDA Adverse Event Reporting System (FAERS)
  - Retrieved *no* adverse event (AE) reports for enclomiphene citrate
- Published clinical trials reported safety outcomes
- ClinicalTrials.gov safety study results
- Other safety information
  - AE and safety information on enclomiphene citrate from EMA in 2018

Clinical Safety – Clinical Trials

Kim et al. 2016:

- Two parallel, phase 3 randomized (R), double-blind (DB), placebo-controlled (PC) trials in patients with secondary hypogonadism
- Treatment received for 16 weeks:
  - oral enclomiphene citrate 12.5 mg (n=43), or
  - oral enclomiphene citrate 12.5 mg up-titrated to 25 mg (n=42), or
  - topical testosterone gel (n=85), or
  - placebo (n=86)

Clinical Safety – Clinical Trials (2)

Kim et al. 2016 - AEs reported:

- Enclomiphene citrate 12.5 mg:
  - 2 deaths (road traffic accident, deemed unrelated; cerebrovascular accident, unlikely related)
  - hypertriglyceridemia
  - anxiety
- Enclomiphene citrate 25 mg:
  - high hematocrit (Hct) or hemoglobin (discontinued due to AE)
  - high prostate-specific antigen (PSA) level (discontinued due to AE)
  - psoriatic arthropathy
  - depression
- Topical testosterone gel:
  - high Hct or hemoglobin (discontinued due to AE)
  - arthropod bite
  - coronary bypass
- Placebo:
  - muscle spasms

Clinical Safety – Clinical Trials (3)

Wiehle et al. 2014a:

- R, DB (for oral dosage), PC in patients with secondary hypogonadism
- Treatment received for 3 months:
  - oral enclomiphene citrate 12.5 (n=29) or 25 mg (n=33), or
  - topical testosterone (n=33), or
  - oral placebo (n=29)
- Reported AEs included:
  - enclomiphene citrate 25 mg:
    - inability to climax and loss of sensation during intercourse (patient discontinued)
    - mild nausea and mild dry heaving (patient discontinued)

Clinical Safety – Clinical Trials (4)

Wiehle et al. 2014b:

- R, DB (for oral dosage), PC in patients with secondary hypogonadism
- Treatment received for 14 days:
  - oral enclomiphene citrate 12.5 mg (n=10), 25 mg (n=11), or 50 mg (n=11), or
  - topical testosterone gel (n=10), or
  - oral placebo (n=10)
- Reported AEs included:
  - enclomiphene citrate 12.5 mg
    - mildly increased estradiol
  - enclomiphene citrate 25 mg
    - mild sinus headache
  - enclomiphene citrate 50 mg
    - moderate headache

Clinical Safety – Safety Study

Safety Study from ClinicalTrials.gov (NCT01534208):

- Open-label, non-randomized phase 3 safety study. Patients with secondary hypogonadism received enclomiphene citrate 12.5 mg (n=216) or 12.5 mg up-titrated to 25 mg (n=283) for 26 weeks.
- Reported serious AEs included (1 report unless otherwise noted):

Enclomiphene citrate	12.5 mg	Enclomiphene citrate	25 mg
•Bradycardia •Chest pain •Biliary colic •Transient ischemic attack (TIA) •Seminoma	•Dyspnea •Knee arthroplasty •Deep vein thrombosis (DVT) •Hypotension	•Atrial flutter •Cholelithiasis •Diverticulitis (2) •Food poisoning •Kidney infection	•Pulmonary embolism (PE) •Cellulitis (2) •DVT

- Reported non-serious AEs for both groups included: Hot flushes (11), Upper respiratory tract infection (53), Influenza (12), Sinusitis (13), Muscle spasms (22), Headache (35), Dizziness (11), and Pollakiuria (daytime urinary frequency) (11)

Clinical Safety – Other Information

- In 2018, EMA reviewed enclomiphene for marketing authorization to treat secondary hypogonadism
- EMA Assessment Report concluded the safety of the product was not sufficiently demonstrated. The following is summary of AEs:
  - Most frequent AEs: headache, hot flushes, nausea, and muscle spasms
  - AEs leading to discontinuation: blurred vision, muscle spasm, headache**,** and aggression
  - Incidence of cardiac events and thromboembolic events in enclomiphene group was also slightly increased compared to patients treated with testosterone

Clinical Safety – Other Information (2)

- Additional safety information from EMA 2018 Report:
  - Ophthalmic abnormalities:
    - Cataracts were reported in nonclinical studies; and eye examinations were conducted during phase 2 and 3 clinical trials
    - EMA concluded that available data did not provide conclusive evidence that use of enclomiphene was associated with development of new or progression of existing cataracts
    - Recommended that ocular safety monitoring be included in a Risk Management Plan to collect additional data
  - Pharmacokinetic data: EMA considered data incomplete and further information needed to:
    - Inform dose adjustments in elderly patients, poor CYP2D6 metabolizers, and patients with renal and hepatic impairment. Pharmacokinetic studies indicated higher exposure for hepatic and renally-impaired patients than for healthy subjects
    - Exclude the possibility of a unique human metabolite of significance

Clinical Safety

Conclusion:

- Safety concerns include cardiac and thromboembolic events, elevated estradiol, increased PSA, and increased Hct
- Pharmacokinetic data are limited, including information on dose adjustments for patients with renal or hepatic impairment
- There are currently available FDA-approved therapies that meet established criteria for safety and efficacy and are labeled accordingly to inform their safe use

Overview of Hypogonadism

- Clinical syndrome that results from failure of testis to produce physiological concentrations of testosterone and/or a normal number of spermatozoa due to pathology in the HPG axis
- Classified as primary or secondary:
  - Primary: dysfunction arising from the level of the testes
    - Low testosterone, elevated gonadotropins (LH and FSH) (hypergonadotropic hypogonadism)
  - Secondary: dysfunction arising from the level of the hypothalamus or pituitary
    - Low testosterone, low or inappropriately normal LH and FSH (hypogonadotropic hypogonadism)

Diagnosis of Hypogonadism

- Diagnosis: based on assessment of signs and symptoms and low morning total testosterone levels on at least 2 occasions
  - American Urologic Association (AUA) recommends diagnosis of low testosterone below 300 ng/dL
  - Measurement of LH and FSH helps to differentiate between primary and secondary hypogonadism
- Signs and symptoms include:
  - decreased libido, decreased spontaneous erections, decrease in testicular volume, gynecomastia;
  - hot flashes, decreased bone mass, height loss, decreased pubic or axillary hair, decreased muscle mass; and
  - decreased energy and motivation

Treatment of Hypogonadism

- Treatment depends in part on underlying etiology and patient's goals for immediate fertility
- Products approved for treatment of hypogonadotropic hypogonadism:
  - Testosterone products
  - Human Chorionic Gonadotropin (HCG)
- Because testosterone can impair spermatogenesis, there is interest in non-testosterone alternatives for men with secondary hypogonadism, such as HCG or SERMs like enclomiphene citrate

Enclomiphene Citrate – Drug Applications

- Repros Therapeutics, Inc. submitted new drug application (NDA) 207959 for enclomiphene citrate 12.5 mg and 25 mg oral capsules, for the treatment of secondary hypogonadism in fertile men (>15 million sperm/mL)
  - December 2015: Repros announced a Complete Response from FDA that:
    - the design of Phase 3 studies was no longer adequate to demonstrate clinical benefit
    - FDA also noted concerns regarding study entry criteria, titration, and bioanalytical method validation in the Phase 3 program
- In 2016, Renable Pharma Limited applied to EMA for marketing authorization of enclomiphene for treatment of secondary hypogonadism in adult men
  - January 2018: EMA published an Assessment Report recommending the refusal of the authorization
    - EMA determined that the safety and efficacy of the product was not sufficiently demonstrated

Clinical Effectiveness – Clinical Trials

Kaminetsky et al. 2013:

- R, open-label, active-control trial to evaluate difference in changes in hormone levels and seminal parameters in patients with secondary hypogonadism
- Treatment received for 6 months:
  - enclomiphene citrate 25 mg (n=7) or
  - topical testosterone gel (n=5)
- Authors found:
  - Total testosterone levels: topical testosterone gel: 545 ± 269 ng/dL; enclomiphene citrate: 525 ± 256 ng/dL
  - Two men who received enclomiphene citrate did not achieve testosterone levels >300 ng/dL during treatment
  - LH and FSH increased in enclomiphene citrate group

Clinical Effectiveness – Clinical Trials (2)

Wiehle et al. 2013:

- R, single-blind trial to evaluate effects on 24-hour LH and total testosterone in patients with secondary hypogonadism
- Treatment received for 6 weeks:
  - enclomiphene citrate 6.25 mg (n=12), 12.5 mg (n=7), or 25 mg (n=12), or
  - transdermal testosterone (n=13)
- Authors found:
  - Mean testosterone levels increased in all treatment groups at 6 weeks (greater variability in serum testosterone levels in transdermal testosterone group)
  - LH and FSH increased in enclomiphene citrate groups

Clinical Effectiveness – Clinical Trials (3)

Wiehle et al. 2014a:

- R, DB (for oral dosage), PC trial to determine effect of enclomiphene citrate in men with secondary hypogonadism
- Treatment received for 3 months:
  - oral enclomiphene citrate 12.5 mg (n=29) or 25 mg (n=33), or
  - topical testosterone (n=33), or
  - placebo (n=29)
- Authors found:
  - Total testosterone level increased in all active treatment groups
  - LH and FSH levels increased in both enclomiphene citrate groups, and decreased in the topical testosterone group
  - Estradiol increased in all active treatment arms and remained elevated compared to baseline after 1 month of enclomiphene citrate discontinuation

Clinical Effectiveness – Clinical Trials (4)

Wiehle et al. 2014b:

- R, DB (for oral dosage), PC trial to evaluate safety, efficacy, and PK of oral enclomiphene citrate as an alternative to testosterone in patients with secondary hypogonadism
- Treatment received for 14 days:
  - oral enclomiphene citrate 12.5 mg (n=10), 25 mg (n=11), or 50 mg (n=11), or
  - topical testosterone gel (n=10), or
  - oral placebo (n=10)
- Authors found:
  - Serum total testosterone levels increased in active treatment groups
  - LH and FSH levels increased in enclomiphene citrate groups

Clinical Effectiveness – Clinical Trials (5)

Kim et al. 2016:

- Phase 3 R, DB, PC trials to compare effects of treatment on serum total testosterone, LH, FSH, and sperm counts in patients with secondary hypogonadism
- Treatment received for 16 weeks:
  - oral enclomiphene citrate 12.5 mg (n=43), or 12.5 mg up-titrated to 25 mg (n=42), or
  - topical testosterone gel (n=85), or
  - placebo (n=86)
- Authors found:
  - Total testosterone levels increased in all active treatment groups
  - LH and FSH increased in the enclomiphene citrate groups and decreased in the topical testosterone group
  - After cessation of treatment, total testosterone levels in the pooled enclomiphene citrate groups remained higher than baseline for at least 7 days

Clinical Effectiveness – Article Review

- Earl and Kim (2019) examined literature. Per authors:
  - Enclomiphene maintains the androgenic benefit of clomiphene citrate without the undesirable estrogen agonist effects attributable to zuclomiphene… the effects of zuclomiphene, "…are not fully understood"
  - Enclomiphene has been shown to preserve sperm concentration when compared with testosterone replacement
  - "Although the evidence is weak at best, early studies suggest that the side effect profile is not significantly worse than testosterone replacement therapy or clomiphene citrate. Ideally, future research will more clearly delineate and confirm this hypothesis"
  - Trials have shown enclomiphene achieves comparable testosterone levels to transdermal testosterone replacement while increasing physiologic production of LH and FSH
  - Further studies are necessary to fully characterize the impact on the subjective symptoms of hypogonadism, as well as to fully characterize potential AE profile

Clinical Effectiveness – Considerations

- FDA Guidance for industry (May 2018) provides recommendations for establishing clinical effectiveness for drugs intended to treat male hypogonadotropic hypogonadism attributed to nonstructural disorders of the hypothalamus or pituitary
  - This guidance incorporates advice FDA received at the Bone, Reproductive, and Urologic Drugs Advisory Committee December 2016 meeting on clinical trial design for drugs intended to treat secondary hypogonadism
  - It is unclear whether increasing testosterone confers clinical benefit
  - Trials should show clinically meaningful improvement in at least one symptom or sign of hypogonadism
  - FDA does not consider that changes in semen parameters alone are sufficient for establishing efficacy of drugs intended to treat functional secondary hypogonadism, since the intent of the drug is to improve fertility, and improvement in semen parameters does not ensure fertility
- Other regulatory body, EMA, also concluded that normalizing testosterone was not sufficient to conclude translation into clinically meaningful benefits for patients with secondary hypogonadism
- Enclomiphene citrate trials did not evaluate improvement in hypogonadal symptoms or quality of life

Clinical Effectiveness

Conclusion:

- While studies may suggest that enclomiphene citrate may increase testosterone levels with a concurrent increase in LH and FSH levels, it is unclear whether increasing testosterone concentrations alone in men with secondary hypogonadism confers clinical benefit
- Clinical trials did not demonstrate that enclomiphene citrate provides clinically meaningful improvement in symptoms or signs of hypogonadism
- There are currently FDA-approved therapies with established efficacy for the proposed use

Historical Use in Compounding

- There is insufficient information to determine length of use of enclomiphene citrate in pharmacy compounding
- It has been studied for effects on follicular development, ovulation induction, and secondary hypogonadism
  - Unclear whether the enclomiphene citrate drug product used in these studies was compounded
- Based on advertising information, enclomiphene citrate use is discussed for the treatment of male hypogonadism
  - Insufficient data about the length and extent of use in the United States and internationally
- Not recognized in the European or Japanese pharmacopeias

Recommendation

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Glutathione

Pharmacy Compounding Advisory Committee Meeting
June 8, 2022

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Special thanks to OND:

Division of Dermatology and Dentistry (DDD)

Division of Pulmonary, Allergy and Critical Care (DPACC)

Nomination

- Glutathione was 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)

- The proposed dosage forms include:
  - Oral: capsule, troche
  - Sublingual
  - Topical: cream, gel
  - Ophthalmic
  - Nasal spray
  - Inhalation preparations
  - Rectal
  - Injection: intravenous (IV), intramuscular (IM)

Nomination

Glutathione was evaluated for 24 uses:

- Skin lightening
- Cystic fibrosis
- Asthma
- Chronic obstructive pulmonary disease
- Chronic lung disease
- Oxidative stress
- Reduction of the side effects of chemotherapy
- Inhibition of chemical induced carcinogenesis
- Prevention of radiation injury
- Treatment of heavy metal poisoning (cadmium and mercury)
- Acetaminophen toxicity
- Autism spectrum disorder
- Alzheimer's disease
- Parkinson's disease
- Major depressive disorder
- Schizophrenia
- Helicobacter pylori infection
- Human immunodeficiency virus infection
- Tuberculosis
- Otitis media
- Peripheral obstructive arterial disease
- Anemia
- Diabetes
- Septic shock

Evaluation Criteria

- Physical and chemical characterization
- Nonclinical and clinical safety
- Available evidence of effectiveness or lack of effectiveness
- Historical use in compounding

Physical and Chemical Characterization

Glutathione:

- An endogenous tripeptide comprised of amino acids: cysteine, glutamic acid and glycine
- Bulk drug substance can be synthesized in well-developed protocols; impurities are unlikely to be toxic
- Stable at room temperature as a solid or in a solid dosage form when protected from oxygen
- As an aqueous solution, it is stable with proper formulation techniques including protection from oxygen, pH buffering and controlled storage temperature

Conclusion:

Glutathione is well characterized. It is likely to be stable when compounded as solid or liquid products with proper formulation and storage conditions (protection from air, controlled pH, and storage temperature).

General Pharmacology

Glutathione:

- Synthesized from precursor amino acids in nearly all cells of the human body, but liver is the main source (Lomaestro and Malone 1995)
- Exists in 2 forms: oxidized (glutathione disulfide) and reduced (glutathione, GSH)
- The reduced form is the subject of this nomination; main function is antioxidant
- Essential cofactor for numerous enzymes to inactivate various substances such as:
  - Reactive oxygen and nitrogen species, hydroxy radicals and peroxides that are formed during cellular metabolism
  - Environmental toxins, pharmaceuticals
- Affects regulation of cellular differentiation, proliferation, and apoptosis (Meister 1992)
- Disturbances in glutathione homeostasis have been suggested to be associated with the development or progression of human diseases (Ballatori et al. 2009)

Nonclinical Pharmacokinetics

- In rats, oral glutathione as liquid bolus (30 µmol) or in addition to food (2.5-50 mg/g of food) increased plasma concentration, with levels peaking at 2 hours and lasting for 3 hours (Hagen et al. 1990)

- Administration of the amino acid precursors of glutathione did not impact plasma glutathione levels (Hagen et al. 1990)

- Inhibition of glutathione synthesis resulted in an increase in plasma levels through absorption of intact glutathione rather than its constituents (Hagen et al. 1990)

- When administered via injection, it accumulated in the liver and spleen in mice; and in liver, spleen, and kidneys in rats (Cronkite et al. 1951)

Nonclinical Safety

- Acute toxicity studies showed that a single dose of glutathione is lethal in mice when injected subcutaneously (5 g/kg). A single dose of glutathione caused reversible accelerated respiratory parameters in dogs when injected Intravenously (IV) (1 and 2 g) (Cronkite et al. 1951).

- In a 26-week IV toxicity study (30, 100, and 300 mg/kg/day) in dogs, glutathione was not associated with adverse effects on body weight or food consumption; no other data were captured from this study (Suzuki et al. 1972).

- Genotoxicity data (Ames assay and mouse lymphoma assay) showed that it is not mutagenic in the absence of metabolic activation (Stark et al. 1989; Siefried et al. 2006).

- In hamsters, glutathione inhibited experimentally induced oral carcinogenesis (Charalapoulous et al. 2004).

- Insufficient nonclinical data exist to evaluate the toxicity profile of glutathione in reproductive or developmental toxicity studies.

Clinical Pharmacokinetics

Oral glutathione:

- In 7 healthy volunteers, single doses up to 3 g found nonsignificant increase in plasma; this suggests negligible systemic availability (Witschi et al. 1992)

- In 54 adults administered oral glutathione 1,000 mg, glutathione 250 mg or placebo for 6 months; glutathione measured at baseline and after 6 months (Richie et al. 2015)
  - Levels in the 1,000 mg group were increased more than with placebo in erythrocytes, plasma, lymphocytes and buccal cells
  - Levels in the 250 mg group were increased more than with placebo in whole blood
  - Levels returned to baseline following a one-month washout period
  - Authors concluded that “the extent to which direct absorption may be responsible for the present findings is not known”

- Hydrolysis of the tripeptide in intestine continues to be considered a primary obstacle to oral glutathione absorption (Buonocore et al. 2015)

Clinical Pharmacokinetics (2)

IV Glutathione:

- 10 healthy volunteers administered single high doses of 2 g/m^2
  - $T_{½}$ = 15 mins; was cleared from the systemic circulation with plasma cysteine and urinary excretion of cysteine becoming markedly increased (Aebi et al. 1991)

- 7 healthy volunteers received 50 mg/kg infused over 10 mins
  - $T_{½}$ = 10.9 mins; plasma levels returned to pre-dose values 30 mins after dosing (Hong et al. 2005)

Clinical Safety – FAERS

FDA Adverse Event Reporting System (FAERS) – Adverse event (AE) reports from 2000 – 2021:

- **IV Glutathione:**
  - Anaphylaxis or anaphylactic shock (2)
    - Dose unknown, time to onset was 30 minutes and 24 hours each after administration
    - Both discontinued, 1 re-challenged and then experienced anaphylaxis
  - Hepatoxicity (1)
    - Elevated liver enzymes: Aspartate transaminase (AST) 1,040 IU/L (26x normal) and alanine aminotransferase (ALT) 890 IU/L (22x normal)
    - 1,200 mg administered once/week, on concomitant medications
    - Hepatic injury resolved within 2 months of discontinuation of medications
  - Infusion Reactions (7)
    - Chest pain, shortness of breath, dizziness, “anaphylaxis”, nausea and vomiting
  - Hypersensitivity (3)
- **Inhaled:** Hypersensitivity (1)
- **Oral:** Hypersensitivity (1)

Clinical Safety – CAERS

The Center for Food Safety and Nutrition Adverse Event Reporting System (CAERS):

195 CAERS cases that included at least 1 AE in association with use of glutathione

- 194 cases describe use of products with multiple ingredients and/or use of multiple products such that the relationship to glutathione is confounded
  - 99 reported at least one “medically important event”
  - 77 reported “hospitalization”
  - 13 reported “life-threatening”
- 1 case listed glutathione as sole ingredient in the suspected product used to “even skin tone,” 3 AEs reported:
  - Rash
  - Scar
  - Skin hyperpigmentation

Clinical Safety – Clinical Studies (1)

IV Glutathione:

- 5 studies with safety assessments (1996 – 2018)
  - Severe AEs (warranted discontinuation):
    - "Deranged [abnormal] liver function tests" (8)
    - Anaphylaxis (1)
  - Other AEs:
    - Infusion site reactions (erythema, irritation, and skin eruptions), "feeling of heart sinking," hair loss, nausea, diarrhea, and abdominal cramps, sleep difficulties, vivid dreaming, sweating increased, dizziness, and upper respiratory infection
- In spite of widespread use, there are no studies on IV glutathione use for skin lightening or of its safety for chronic use (for any indication). The switch from brown to red melanin production may increase the risk of sun-induced skin cancers in previously protected individuals (Davids et al. 2016).

Clinical Safety – Clinical Studies (2)

Oral/Buccal: 3 studies with safety assessments (2010 – 2015)

- AEs: Non-specific gastrointestinal AEs (flatulence, gum soreness)

Nasal Inhalation Route: 2 studies (intranasal glutathione 300 mg or 600 mg/day, or saline placebo for 3 months)

- AEs (600 mg arm): a patient withdrew due to tachycardia and cardiomyopathy (resolved when glutathione stopped), labored breathing (2), sore throat (2), and increased thirst (2)

Oral Inhalation Route: 4 studies with safety assessments (1997 – 2015)

- Serious AEs: Bronchoconstriction with severe wheezing and breathlessness (1), facial palsy (1), hemoptysis (2)
- Non-serious AEs: Cough, constipation, headache, pyrexia, and abnormal sputum
- In one study, authors noted that a large percentage of subjects withdraw prematurely; difficult to assess the safety of interventions (Griese et al. 2013)

Clinical Safety – Other Information

Foreign Regulatory Authority:

- FDA of the Philippines (2018) warns against use of IV glutathione as a skin whitener due to non-approved indication, efficacy not well-established, and reported side effects. Multiple AEs identified with IV glutathione:
  - Stevens Johnson Syndrome (serious and potentially fatal)
  - Toxic epidermal necrolysis (serious and potentially fatal)
  - Skin rashes
  - Thyroid dysfunction
  - Kidney dysfunction
  - Severe abdominal pain
- Thailand authorities banned the use of IV glutathione for skin lightening “for fear of severe adverse reactions, including anaphylaxis” (Arjinpathana and Asawanonda 2012)

Clinical Safety

Conclusion:

- Oral glutathione is minimally absorbed and appears to be associated primarily with local, gastrointestinal AEs
- IV glutathione has resulted in hepatotoxicity and life-threatening anaphylaxis, despite rapid elimination from systemic circulation
- Nebulized oral inhalation of glutathione identified significant safety concerns of bronchoconstriction
- FDA has significant safety concerns, particularly for glutathione IV and inhalation formulations

Effectiveness

- FDA considers available evidence of the substance's effectiveness or lack of effectiveness for a particular use, including reports in peer-reviewed medical literature

- FDA evaluated 24 uses for glutathione

Effectiveness – Skin Lightening (1)

Skin lightening refers to the use of depigmenting agents. Skin-lightening (or "skin-bleaching") agents can be important tools in the management of disorders of hyperpigmentation, such as melasma and post inflammatory hyperpigmentation. There are FDA approved skin lightening agents such as for melasma of the face.

Use of skin-lightening agents to lighten one's natural skin color is a global phenomenon and a variety of substances have been used and been administered via topical, oral or IV routes.

Oral glutathione:

- Open-label (OL), single-arm study, N=30 (Handog et al. 2015)
  - Treatment for 8 weeks once/day with buccal lozenge 500 mg
  - There was decrease in melanin indices from baseline 2 weeks after initiation of treatment

  This is a small single-arm, short duration study; confirmatory trials would be needed.

Effectiveness – Skin Lightening (2)

IV glutathione:

- Placebo-controlled (PC) study in females for skin tone lightening, N=50 (Zubair et al. 2016)
  - Treatment twice weekly for 6 weeks:
    - IV "GSH Detox forte (aqua, glutathione 1200 mg, ascorbic acid, hydrolyzed collagen 35 mg and NaCl)" (n=25)
    - IV normal saline (placebo) (n=25)
  - A visual assessment tool was used to measure skin tone at body sites not exposed to the sun
    - 37.5% subjects in the glutathione group, 18.7% in placebo group showed skin lightening
    - Per authors: After stopping the treatment, this improvement was gradually lost at 6-month posttreatment, only 1 patient maintained this improvement

Effectiveness – Skin Lightening (3)

An article review concluded:

"There is little convincing evidence in favor of glutathione as a therapy for hyperpigmentation at the present time, and there are many unresolved controversies that surround its use. The trials… have numerous limitations… their efficacy (especially long-term) remains questionable. The extant evidence…of IV GSH as a therapeutic modality for improving skin tone or pigmentation is minimal and contradictory… More evidence in the form of high-quality trials with better study design, larger sample size, and long-term follow-up is vital…" (Sonthalia et al. 2018)

Conclusion:

A small IV glutathione clinical study appears to suggest it lightens the skin, but the effect seems to dissipate after discontinuation. Other studies failed to show a skin lightening effect with glutathione or were inadequately designed (i.e., uncontrolled). There are insufficient data to support the effectiveness of oral glutathione for skin lightening. In addition, the nominator has not provided data indicating that any effect that glutathione may have to lighten the skin provides a clinical benefit to address a disease or condition, such as managing disorders of hyperpigmentation.

Effectiveness – Cystic Fibrosis (1)

- Cochrane Review identified 1 trial comparing nebulized glutathione to saline (Tam et al. 2013)
  - Authors found no evidence to recommend use of nebulized glutathione cystic fibrosis (CF); further research is required on improving outcomes

- Cochrane Review of antioxidant supplementation in CF, 3 studies on glutathione (Ciofu and Lykkesfeldt 2014)
  - Oral glutathione or placebo (N=47) (Visca et al. 2015)
    - Glutathione had positive effect on nutritional status and improvement in forced expiratory volume at one second (FEV1) after 6 months treatment. However, imbalance of the distribution of (more severe) delF508 homozygote subjects, and small sample size are potential biases.
  - Inhaled glutathione or placebo (N=19) (Bishop et al. 2005)
    - 3 of 4 endpoints were not statistically different; however, mean change for peak flow improved in the glutathione group. Per authors, limitations of study are optimal dose of inhaled glutathione is unknown and bias due to small sample.
  - Inhaled glutathione or placebo (N=153) (Griese et al. 2013)
    - Primary efficacy endpoints (FEV1) were not different between groups over 6 months. Large number of the subjects prematurely withdrew, 28% glutathione vs. 42% placebo.

Effectiveness – Cystic Fibrosis (2)

- Single-blind trial of inhaled glutathione vs placebo in CF for 12 months did not achieve measured improvement in FEV1 (Calabrese et al. 2015)

- Phase 2 study of oral glutathione or placebo in pancreatic insufficient CF patients found no differences between the groups in 6 months (Bozic et al. 2020)

- **The Cystic Fibrosis Foundation and Pulmonary Clinical Practice Guidelines Committee**
  Cystic Fibrosis Pulmonary Guidelines: Chronic Medication for Maintenance of Lung Health (2013)**:**
  – The evidence is insufficient to recommend for or against the chronic use of inhaled glutathione to improve lung function and quality of life or reduce exacerbations

Conclusion:
The beneficial effect of glutathione is very difficult to assess in patients with chronic condition without a very large population sample and a long-term study period. There is insufficient information to support its effectiveness for the treatment of CF.

Effectiveness – Asthma

- A 3-arm crossover study in 12 patients with mild to moderate bronchial asthma. Patients received single-dose inhaled glutathione 600 mg, sodium cromoglicate (SCG) 20 mg or placebo with at least 3 days between treatments, followed by a fog challenge (ultrasonically nebulized distilled water) 30 mins later

  – After fog challenge, placebo group had decrease mean in FEV1, 20.41%; glutathione 6.04%, and SCG 5.99% (Bagnato et al. 1999)

Conclusion:
One single-dose small study in 12 patients provides insufficient information about population, exposure or risk to support use of glutathione. Additional information provided by the nominator on the effect that glutathione may have on the structure or function of the body does not provide evidence of any clinical benefit on the use of glutathione in asthma.

Effectiveness – Oxidative Stress

Oxidative stress has been defined as the condition when the sum of free radicals in a cell exceeds the antioxidant capacity of the cell (Smeyne & Smeyne 2013)

- A trial of oral glutathione vs. placebo on oxidative stress in 40 healthy subjects (Allen and Bradley 2011)
  - Per authors: No significant changes in the measures of oxidative stress, including glutathione status (i.e., concentrations of glutathione)

- A 3-arm study (IV glutathione, oral N-acetylcysteine, or placebo) to evaluate prevention of contrast-induced nephropathy (CIN); serum creatinine and glutathione, and urinary lipid hydroperoxides were measured (N=21)
  Per authors: (Saitoh et al. 2011)
  - Renal oxidative stress may be a cause of CIN
  - Glutathione may be a potential strategy against CIN, but should be withheld until larger trials demonstrate its efficacy and safety
  - Limitations include small sample size and the most reliable markers of kidney damage were not evaluated (cystatin C and liver-fatty acid protein)

Conclusion:
Scientific publications were not found that define a population, dose or risk associated with glutathione for oxidative stress. Available data do not support the effectiveness of glutathione for oxidative stress. In addition, the nominator has not provided evidence of any clinical benefit associated with the use of glutathione to reduce oxidative stress.

Effectiveness – Reduction of Side Effects of Chemotherapy (1)

- A trial to evaluate IV glutathione vs. placebo in 185 patients undergoing chemo treatment did not reveal any evidence of benefit in any subgroup (Leal et al. 2014).

- A study to evaluate IV glutathione vs. placebo on prevention of neuropathy showed a lower incidence of neuropathy in the glutathione arm compared to placebo (N=50) (Cascinu et al. 1995).

- There are 5 other small studies of various cancers with different chemotherapeutic agents, each lacking a controlled group that showed potential benefit of glutathione use in prevention or reduction.

- A study to evaluate effect of glutathione vs saline in 27 patients with colorectal cancer. Although, glutathione group showed a reduction of neurotoxicity compared to placebo they also showed a significantly lowered level of the chemo agent. This is concerning as it may affect chemo efficacy (N=27) (Milla et al. 2009).

In summary, results of the studies for reduction of side effects of chemotherapy are mixed. Some show potential benefit but they are small studies and lack a control arm. The largest placebo-controlled study showed no benefit of glutathione.

Effectiveness – Reduction of Side Effects of Chemotherapy (2)

Chemotherapy Induced Peripheral Neuropathy (CIPN):

- **American Society of Clinical Oncology Clinical Practice Guideline (2014):**
  - Due to a lack of high-quality, consistent evidence, no established agents are recommended for the prevention of CIPN in people with cancer undergoing treatment with neurotoxic agents. Specific agents, including glutathione, should not be offered for prevention of CIPN.
- **American Cancer Society (2016):**
  - Study results are mixed on glutathione preventing CIPN, more research is needed.

Conclusion:
Available data are insufficient to support the effectiveness of glutathione for reduction of side effects of chemotherapy. FDA concurs with health professional organizations that there is lack of high-quality and consistent evidence to support the use of glutathione to prevent CIPN, and more research is needed.

Effectiveness – Prevention of Radiation Injury

- A study evaluated topical glutathione on decreasing the skin reaction caused by radiation in 30 women undergoing radiation for breast cancer received “RayGel” (glutathione and anthocyanins) gel or placebo (Enomoto et al. 2005)
  - Skin reaction severity score was lower in the glutathione group
  - Per authors:
    - Study was too small to demonstrate statistical difference
    - Patients were not stratified by risk factors associated with radiation damage or by the size of the breast
    - 2 initially randomized were excluded from the final analysis which may affect the results
    - The substances are absorbed, could get into cancer cells and provide them with protection during radiation, this defeats the purpose of radiotherapy

Conclusion:
Available data do not support the effectiveness of glutathione to prevent radiation injury.

Effectiveness – Autism Spectrum Disorder

- Johns Hopkins University Center for Excellence in Regulatory Science and Innovation (JHU CERSI) identified one study in which 26 children with Autism Spectrum Disorder were randomized to receive either transdermal or oral glutathione (Kern et al. 2011)
  - The publication did not report efficacy outcomes

Conclusion:
FDA did not identify any data to support the effectiveness of glutathione in the treatment of Autism Spectrum Disorder.

Effectiveness – Parkinson's Disease

- OL, uncontrolled small study of IV glutathione in 9 early untreated Parkinson's disease patients showed "decline of disability" (slowed disability progression) (Sechi et al.1996)

- Randomized (R), double-blind (DB), PC study of IV glutathione vs. placebo in 21 Parkinson's patients using Unified Parkinson's Disease Rating Scale (UPDRS) plus motor scores produced no significant difference between the groups (Hauser et al. 2009)

- R, DB, Phase I/IIa, 3-arm, intranasal glutathione in two doses (glutathione 300 or 600 mg/day) or placebo, study in 30 Parkinson's patients resulted in mild clinical improvement in UPDRS symptoms in both glutathione groups (Mischley et al. 2015)

- A follow-on Phase IIb study of 45 Parkinson's patients receiving intranasal glutathione vs. placebo resulted in neither treatment group being superior to placebo in UPDRS (Mischley et al. 2017)

Conclusion:
Available data do not support effectiveness. Additional information provided by the nominator on the use of glutathione to affect the structure or function of the body does not provide evidence of clinical benefit on its use in Parkinson's Disease.

Effectiveness – Human Immunodeficiency Virus (HIV) Infection

- A study of glutathione 600 mg in 4 mL saline was via aerosol in 14 HIV patients for 3 days
  - The authors noted that this study does not show clinical efficacy such as a reduction in the incidence of pulmonary opportunistic infections or evaluate the exact pattern of deposition of the glutathione in the lungs (Holroyd et al. 1993)

- DB, PC study of 30 HIV-infected individuals with CD4+ T cell counts below 350 cells/mm^3 were given either oral placebo or "liposomal glutathione" (Valdivia et al. 2017)
  - HIV-infected individuals resulted in an increase in the levels of IL-12, IL-2 and IFN-γ and a decrease in levels of IL-6, IL-10 and free radicals and no change in the levels of TGF-β, IL-1 and IL-17 when compared to their placebo counterparts

- While it was noted there is significant decrease of glutathione levels in blood cells of HIV patients, research has not yet shown glutathione is effective treatment for HIV infection (Morris et al. 2014b)

Conclusion:
While glutathione levels may be decreased in patients with HIV infection, no scientific literature was located that supported its clinical efficacy in these patients. Additional information provided by the nominator on the effect glutathione may have on the structure or function of the body does not provide evidence of clinical benefit on the use of glutathione in HIV infection.

Effectiveness – Otitis Media

- R, PC trial of glutathione treatment on chronic otitis media with effusion in 60 children who received nasal aerosol glutathione or placebo for 2 weeks (Testa et al. 2001)
  - One month follow-up found nasal aerosol administration of glutathione suggested improvement in two-thirds of the patients with otitis media

Conclusion:
The minimal data indicating effectiveness for some study participants are insufficient to support effectiveness of glutathione in treating otitis media.

Effectiveness – Peripheral Obstructive Arterial Disease

- R, DB, PC trial of IV glutathione vs placebo on walking-induced leg muscle pain relieved by rest was conducted in patients with peripheral artery disease over 5 days (N=40) (Arosio et al. 2002)
  - Glutathione group showed an increase in plethysmography values (measuring blood flow in the leg) after treadmill testing compared to rest measurements

Conclusion:
The minimal data indicating effectiveness for some study participants are insufficient to support effectiveness of glutathione in treating peripheral obstructive arterial disease.

Effectiveness – Anemia

- R, DB, PC study (n=20) of IV glutathione in acute hemolytic crisis and anemia found glutathione did not modify erythrocytes, platelets or hemoglobin during the hemolytic crisis and white blood cells and the level of Heinz bodies remained unchanged (Corbucci 1990)

- An uncontrolled study in patients on dialysis with chronic renal failure patients saw improved red blood cells (RBC), hemoglobin, hematocrit and reticulocytes after IV glutathione to treat anemia (Usberti et al. 1997)

- DB, R, PC study of IV glutathione on the anemic status in 20 patients with chronic renal failure showing anemia on hemodialysis received glutathione or placebo for 120 days (Costagliola et al. 1992)
  - The glutathione group showed increase in both hematocrit and hemoglobin on day 120, and a decline on days 150 and 180

Conclusion:
The minimal data indicating effectiveness for some study participants are insufficient to support effectiveness of glutathione in treating anemia.

Effectiveness – Septic Shock

- 3-arm study in 130 patients with septic shock evaluated the effect of IV glutathione on peroxidative indexes. Per authors, glutathione limited the peroxidative stress of patients (Ortolani et al. 1992).

- 3-arm study in 30 patients with septic shock evaluated the effect of IV glutathione. Protection against oxygen free radicals was evaluated; several markers measured. Per authors, variety of "indirect markers of protection against oxygen free radicals" were improved in those who received glutathione (Ortolani et al. 2000).

It is unclear whether measured laboratory endpoints were appropriate to adequately determine glutathione effect to change disease course.

Conclusion:
The minimal data indicating effectiveness for some study participants are insufficient to support effectiveness in treating septic shock.

Effectiveness – Other Uses

- For the remaining 11 of the 24 uses, please see FDA's memo for our evaluation of the available evidence of effectiveness or lack of effectiveness of drug products compounded with glutathione. As described in the memo, there is either no available information, or insufficient evidence of effectiveness of glutathione in association with these nominated uses:

  - Chronic Obstructive Pulmonary Disease
  - Chronic Lung Disease
  - Treatment of heavy metal poisoning
  - Inhibition of chemical induced carcinogenesis
  - Acetaminophen toxicity
  - Alzheimer's disease
  - Major depressive disorder
  - Schizophrenia
  - Helicobacter pylori infection
  - Tuberculosis
  - Diabetes

Historical Use in Compounding (1)

- JHU CERSI evaluated the use of glutathione in autism spectrum disorder (ASD)
  - < 1% of parents used glutathione injection for a child with ASD in a clinical sample of 1,788 ASD patients < 17 years old (y/o) at the Kennedy Krieger Institute Center for Autism and Related Disorders
  - Use of glutathione was rare: <2% of responses in a population sample of 1,487 parents of children < 18 y/o with autism
  - Use of glutathione was <1% among children with and without ASD in a national sample of Medicaid claims for 2010 – 2014
  - In phone interviews with three currently practicing physicians and researchers with expertise in ASD and complementary and alternative medicine, little was known about glutathione treatment as it is rarely prescribed or recommended for ASD in clinical practice
- According to outsourcing facility (OF) reports submitted to FDA, several OFs prepared single ingredient drug products compounded in injection, suppository, cream, and capsules containing glutathione. OFs also reported preparing injection products containing glutathione and other drugs.

Historical Use in Compounding (2)

- There have been published references to glutathione compounding since 2010
- The International Journal of Pharmaceutical Compounding has published compounding formulations for topical gels, transdermal creams, inhalation solutions and troches
- Glutathione is listed in the Japanese and European pharmacopoeia
- Online promotions for compounding pharmacies and treatment clinics in the U.S. promote use of glutathione in a wide variety of conditions and diseases. Use of various dosage forms including oral, inhalation, nebulized, nasal spray, transdermal, topical, IV, intramuscular and rectal formulations are promoted
- Use of IV glutathione for skin lightening is prevalent in the U.S. Medical spas across the country offer glutathione injection and infusion for skin lightening treatments
- In 2019, FDA issued a Compounding Risk Alert for glutathione powder due to potentially high levels of endotoxins in the bulk drug substance and reported AEs

Conclusion:

Glutathione is promoted in the U.S. to treat wide variety of conditions in various dosage forms, including IV infusion. It is used in many regions around the world, and certain authorities have issued warnings against IV glutathione. JHU CERSI report found it is rarely used to treat ASD.

Evaluation Summary

- Glutathione is well-characterized and likely to be stable when compounded as solid or liquid dosage forms with protection from oxygen and proper storage conditions.

- Serious safety issues with glutathione use include anaphylaxis/hypersensitivity, hepatoxicity, severe wheezing, and breathlessness. Glutathione injection and inhalation in particular raise safety concerns.

- There is either no available information or insufficient evidence of effectiveness of glutathione with any of the proposed uses. Bioavailability of oral dosage form is minimal and systemic exposure from injection formulations is associated with rapid metabolism. Approved drugs are available to treat several of the conditions that the glutathione is proposed to treat, many of which are serious or life-threatening.

- Available literature indicates that glutathione has been used since at least 1965 and compounding can be traced back to at least 2010.

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs ***against*** glutathione being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Ammonium Tetrathiomolybdate (ATTM)

Pharmacy Compounding Advisory Committee Meeting

June 8, 2022

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Special Thanks to:

Division of Hepatology and Nutrition
Division of Neurology 1
Division of Oncology 1

Nomination

- ATTM was 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)
- ATTM was evaluated for:
  - Treatment of Wilson Disease, and
  - Copper chelation therapy
    - Breast cancer, kidney cancer, prostate cancer, colorectal cancer, esophageal cancer, and malignant pleural mesothelioma
- The proposed dosage form is capsule for oral administration in 20 mg to 60 mg dosage strengths

Evaluation Criteria

- Physical and chemical characterization
- Nonclinical and clinical safety
- Available evidence of effectiveness or lack of effectiveness
- Historical use in compounding

Physical and Chemical Characterization

ATTM:

- Is the ammonium salt of tetrathiomolybdate, referred to as TTM[a] which is the active moiety
- Is a copper chelating agent
- Is sensitive to oxygen and decomposes at room temperature
  - When compounded as capsules, it is likely to be stable only if protected from moisture and air
- Likely impurities include ammonium molybdate and molybdenum trisulfide
  - Impurities unlikely to be toxic

Conclusion:

ATTM can be characterized using readily available analytical techniques

ATTM is likely to be stable if protected from moisture and air when compounded as capsules

[a] Due to structural relevance, some discussion in this evaluation is from references that use the term TTM instead of ATTM. Such discussion is only to provide supportive information for the evaluation for ATTM. Any conclusion that is drawn only pertains to the substance ATTM.

Nonclinical Pharmacokinetics

TTM

- Has been studied in animal models where it was shown to form a complex with food protein and copper to prevent copper absorption
- In rats, oral dosing decreased copper hepatic and renal uptake (Mills 1981)
- In dogs, oral and intravenous administration increased serum copper concentration (Chan 2015); indicating copper mobilization from tissue
- In sheep, prolonged subcutaneous dosing of TTM resulted in molybdate accumulation in multiple organs including the brain and pituitary (Haywood 1998)

Nonclinical Safety (1)

- Acute toxicity information was not found
- Repeat oral dose toxicity in dogs (Langlois 2019):
  - In a 12-week (wk) study in dogs, 1/10 developed immune-mediated anemia and thrombocytopenia
  - In a 6-week study in a dog model of copper-associated hepatopathy (CAH):
    - Several TTM-treated dogs showed decreased copper levels from baseline
    - Hepatic molybdenum increased >50-fold
    - No significant changes in histological scores, hematologic or biochemical markers
    - These findings suggest that TTM can decrease copper in some dogs with CAH

Nonclinical Safety (2)

- Developmental and Reproductive Toxicity
  - Toxicology profile described in presence of copper, not ATTM alone
    - In weanling rats, exposure to ATTM with copper resulted in malformations of growing bones (Spence 1980)
    - In sheep, exposure to ATTM with copper resulted in adverse fertility outcome in both sexes, marked morbidity with atrophy or degeneration of the pituitary and adrenal glands, testicular atrophy, and ovarian cysts (Haywood 2004)
- Genotoxicity
  - No studies were found in the literature
- Carcinogenicity
  - No studies were found in the literature

Nonclinical Safety (3)

Conclusion:

- TTM may be associated with an increased incidence of immune-mediated anemia and thrombocytopenia in dogs
- Exposure to TTM with copper resulted in developmental malformations of growing bones as well as pituitary, adrenal, and fertility adverse effects in rats and sheep
- No studies were found assessing the genotoxicity or carcinogenicity potential for TTM

General Pharmacology

- We did not find pharmacokinetic data on ATTM in humans
- TTM does not circulate in the free form in vivo (Maiti and Moura 2021)
- Two possible mechanisms of TTM with copper (Brewer, et al. 1991; Pan et al. 2002):
  - Given with food, it binds with copper and food protein, preventing copper absorption, then mixes with bile and is eliminated in the stools
  - Given without food, it is absorbed into the blood and complexes available copper and albumin, making free copper unavailable for cellular uptake. This tripartite complex is slowly metabolized and finally excreted into the bile

Clinical Safety

- FDA Adverse Event Reporting System (FAERS)
- Published clinical trials reported safety outcomes
- ClinicalTrials.gov safety study results
- Other sources of safety information

Clinical Safety – FAERS (1)

FDA Adverse Event Reporting System (FAERS)[b]

- 16 reports with ATTM as a suspected drug from 2000 to 2021
  - Reasons for use: malignancy (13), Wilson disease (2), not reported (1)
  - Total daily dose: 40 mg to 280 mg
  - All cases reported serious outcomes including 1 death
    - Death in a patient with hepatocellular carcinoma due to bacteremia
- Adverse events (AEs) reported:
  - Hematologic abnormalities (8)
  - Thromboembolic/cardiac disorder (3)
  - Hepatic abnormalities (2)
  - Cutaneous reaction (1); Fever, diarrhea, and dehydration (1)

[b]FAERS is a database that contains information on adverse event and medication error reports submitted to FDA

Clinical Safety – FAERS (2)

Hematologic abnormalities (n = 8):

- Anemia, leukopenia, neutropenia
  - The time to onset of the anemia and leukopenia was 14 days after initiation of ATTM, suggesting a temporal association
    - Treatment of anemia included blood transfusion (3) or hospitalization (1)
  - ATTM discontinued in 7 patients; 5 re-challenged with a lower dose, 1 had persistent anemia

Thromboembolic/cardiac disorder (n = 3):

- Acute pulmonary embolism, chronic pulmonary embolic disease, palpitations
  - Cases confounded by underlying disease states, concomitant medication, or limited by insufficient documentation

Clinical Safety – FAERS (3)

Hepatic abnormalities (n=2):

- A patient with Wilson disease (WD) had elevated AST[c] and ALT[d] (4x baseline) 3 wks after daily treatment with ATTM 120 mg. Levels returned to baseline after temporary hold and dose reduction. Concomitant medications were not reported.
- A patient with WD had significant elevation of AST, ALT, and bilirubin 1 wk after ATTM dose was increased from 120 mg to 180 mg/day.
  - AST and ALT peaked above 1,000 IU/L (normal range: AST 12 to 38 IU/L and ALT 7 to 41 IU/L).
  - Patient baseline AST and ALT not specified.
  - ATTM was discontinued and liver function slowly returned to baseline.

[c] Aspartate aminotransferase; [d] Alanine aminotransferase

Clinical Safety – Clinical Studies (1)
Wilson Disease

5 studies with safety assessment in patients with WD treated with ATTM for 8 weeks (1994 - 2020)

- ATTM dose 120 to 410 mg/day
- AEs reported:
  - Brewer et al. 1994, open-label (OL) (n=17): Per authors “no toxicity”
  - Brewer et al. 1996, OL (n=33, includes 16 new patients and 17 patients from Brewer 1994):
    - 1 of the 16 new patients had significant anemia, decrease hemoglobin (Hgb) 13 to 7.5 g/dL (ref. 12-18 g/dL) 30 days after treatment
      - Anemia improved soon after cessation of ATTM (11.5 g/dL by Day 40) but recurred with re-initiation
      - Bone marrow exam showed depression of hematopoiesis in red blood cell line
    - 9 of the 16 new patients had elevated ALT
      - Mean ALT increased 46 to 123 U/L (reference 2-35 U/L) at 5 weeks
      - ALT returned to baseline after discontinuation

Clinical Safety – Clinical Studies (2)
Wilson Disease

Continued:

- AEs (during 8-week treatment) reported per study:
  - Brewer et al. 2003, OL (N=55, includes 22 new patients and 33 patients from Brewer 1994; 1996)
    - 5 of the 22 new patients had bone marrow suppression during 3-6 weeks of treatment (mean blood counts):
      - Decrease Hgb from 13.8 to 9.8 g/dL
      - Decrease white blood cells: 5,800 to 3,500/µL (ref. 4000 – 10,000/µL)
      - Decrease platelet count: 112,000 to 86,000/µL
    - 3 of the 22 new patients had elevated liver enzymes
      - Increase mean ALT peak 413 IU/L (ref. 7 - 41 IU/L) by 5 weeks (10x normal)
      - Increase AST, lactate dehydrogenase, and alkaline phosphatase
  - Per authors, bone marrow suppression and liver enzyme elevations can occur with rapid escalation of dose

Clinical Safety – Clinical Studies (3)
Wilson Disease

Continued:

- AEs reported per study:
  - Brewer et al. 2006, Randomized (R), double-blind (DB), 2-arm controlled, compared ATTM and trientine (N=48)
    - During 8-week treatment
      - Anemia and neutropenia: 3 ATTM vs. 1 trientine
      - Elevated liver enzymes: 4 ATTM vs. 0 trientine
    - During follow-up (6-22 months)
      - Deaths: 2 ATTM vs. 4 trientine
        - Determined to be unrelated to ATTM
  - De Fabregues et al. 2020 (N=5)
    - 1 patient developed anemia, leukopenia, and liver enzyme elevation 3 wks after starting ATTM
    - AEs resolved after withholding ATTM x1 week and resuming at half the dose

Clinical Safety – Clinical Studies (4)
Wilson Disease

Safety Summary of ATTM use in WD:

- Available data are limited to a few small studies, mostly open-label and uncontrolled
- Despite the paucity of data, studies have raised considerable safety concerns, particularly potential bone marrow suppression and liver dysfunction, that appear to be related to ATTM use
- There is concern regarding the lack of safety data on the use of ATTM in pediatric population and pregnant women

Clinical Safety - Clinical Studies
Cancer

- 7 studies with safety assessment of ATTM in patients with various types of cancers, including breast, kidney, prostate, malignant pleural mesothelioma, colorectal, and esophageal (2000-2017)
- Doses of ATTM administered, study size, and length of treatment varied
- Most common AEs:
  - Bone marrow suppression - neutropenia, lymphopenia, granulocytopenia, anemia
  - Sulfur burps (foul rotten-egg smell), nausea, vomiting, diarrhea
- Other adverse events:
  - Dizziness, deep venous thrombosis (DVT)
    - It is unknown whether DVT may be related to ATTM (Gartner et al. 2009)

Clinical Safety – Case Report

- A 56-year-old female with metastatic cancer self-treated with TTM 120 mg/day (obtained via internet) and developed (Lang et al. 2004) :
  - Severe neutropenia
  - Severe copper deficiency[e]
    - Decreased serum copper[f] 6x from baseline
    - Decreased ceruloplasmin[g] 8x from baseline
- This illustrates concern for potential misuse and clinically significant copper depletion associated with ATTM

[e]Hematologic hallmark of copper deficiency is anemia and leukopenia; copper deficiency may also lead to neurologic damage

[f]Copper is an essential trace element, necessary for the activity of many key enzymes

[g]Ceruloplasmin is the major copper carrying protein in the blood and a marker of copper status

Clinical Safety

Conclusion:

- Safety concerns associated with the use of ATTM include significant bone marrow suppression (i.e., anemia, leukopenia, and thrombocytopenia) and hepatoxicity, which are potentially serious
- Concerns about adverse effects of significant copper removal associated with the use of ATTM, its long-term effects, and the lack of safety data associated with use in pregnant women and children
- There are FDA-approved therapies currently available for the treatment of Wilson disease and for the types of cancer evaluated that meet established criteria for safety and effectiveness, and are labeled accordingly to inform their safe use

Wilson Disease – Overview

- Rare autosomal recessive disorder caused by mutations of copper transporter gene *ATP7B* leading to copper excess and accumulation in tissue
- Copper build-up can lead to damage of the liver, brain, and eyes
- Signs and symptoms include chronic liver disease, neurologic abnormalities, and psychiatric disturbances
- It is a serious progressive condition; may be fatal if untreated
- Treatment goal is to reduce the amount of copper that has accumulated and to maintain normal copper (National Institutes of Health Genetic Rare Disease Information Center)
- Diagnosed between the ages of 5 and 35 years (mean age of 13 years) (Lin et al. 2014)

Wilson Disease – Treatment

The American Association for the Study of Liver Diseases (AASLD 2008) recommends:

- Avoid intake of food and water with high concentrations of copper
- For symptomatic patient, a chelating agent, D-penicillamine or trientine, is the initial treatment. Trientine may be better tolerated
- For pre-symptomatic patients or for maintenance, use a chelating agent or zinc
- Treatment continued during pregnancy; dosage reduction is advised for D-penicillamine and trientine
- Acute liver failure or cirrhosis should be referred for liver transplantation
- Treatment is lifelong and should not be discontinued unless a liver transplant has been performed

ATTM Drug Applications

- There are no FDA-approved drug products that contain ATTM as active ingredient
- ATTM has been studied for breast cancer under Investigational New Drug (IND) Application (Jain 2013 and Chang 2017)
- Pipex Pharmaceuticals submitted New Drug Application (NDA) for Coprexa (oral tetrathiomolybdate) for the treatment of initially presenting neurologic WD
- In 2008, Pipex announced that the NDA was issued a Refuse to File letter, which cited, among other deficiencies, issues concerning the adequacy of clinical evidence of safety and efficacy, and a request for an additional short-term reproductive drug safety study in animals

Effectiveness in Wilson Disease (1)

3 phase 2, OL, single-arm studies (Brewer et al. 1994; Brewer et al. 1996; Brewer et al. 2003)

- Efficacy of ATTM in a total of 55 patients (cumulative) presenting with neurological signs and symptoms
- Main study objectives were to test the efficacy and toxic effects of ATTM in patients with neurologic signs and symptoms caused by WD
- Neurologic assessment
  - Subjective quantitative neurologic test and quantitative speech examination at baseline and weekly for 8 weeks; yearly thereafter
  - Subjective quantitative brain MRI scoring at baseline and yearly (1994 and 1996 studies)

Effectiveness in Wilson Disease (2)

Continued:

3 phase 2, OL, single-arm studies (Brewer 1994; 1996; 2003)

- Treatment regimen
  - ATTM 120 to 410 mg/day for 8 weeks followed by oral zinc acetate 50 mg 3x/day maintenance
- Patients were followed for 1-8 years
- Authors found:
  - 2/55 (4%) showed neurologic deterioration, gradual improvement on quantitative neurologic and speech scores over time

In summary,

- 3 studies showed no significant change in mean neurology, speech and MRI scores in most patients during the 8 weeks of ATTM treatment. However, these studies are of limited utility because:
  - Treatment was too short. It is difficult to evaluate efficacy based on an 8-week trial that is looking for evidence of neurologic deterioration in a chronic neurologic condition like WD.
  - Single arm studies; interpretation of efficacy is difficult without a comparator.
  - Scales of limited utility as they lack validation.
  - Missing examination data, i.e., 50% or more missing weekly and yearly assessments.

Effectiveness in Wilson Disease (3)

Randomized (R), double-blind (DB), 2-arm controlled trial comparing frequency of neurologic worsening and degree of neurologic recovery in 48 patients treated with ATTM vs trientine (Brewer et al. 2006)

- Treated for 8 weeks with either
  - ATTM, 120 mg/day PLUS zinc acetate (n=25) or
  - Trientine 1000 mg/day PLUS zinc acetate (n=23)
- All patients continued zinc acetate maintenance
- Neurologic assessment: Quantitative neurologic and speech exam weekly for 8 wks. then yearly x 3yrs
- Authors found:
  - Neurologic deterioration 1/25 in ATTM vs. 6/23 in trientine group

Study Limitations:

- Treatment was too short; difficult to evaluate efficacy on an 8-week trial that is looking for evidence of neurologic deterioration in a chronic neurologic condition
- Scales of limited utility as they lack validation

Effectiveness in Wilson Disease (4)

Uncontrolled, longitudinal study describing case series of 5 patients with neurological symptoms receiving ATTM (De Fabregues et al. 2020)

- 120 mg/day in 6 divided doses;
- 4 patients treated for 8 wks, 1 patient treated for 16 wks
- Oral zinc maintenance
- Neurologic assessment (before starting ATTM and 3 months later): Unified Wilson's Disease Rating Scale (UWDRS), Global Assessment Scale (GAS) for WD and the Brewer-adapted Unified Huntington's Disease Rating Scale (UHDRS) for WD; brain MRI
- Authors found:
  - Neurological clinical improvement in all patients at 3 months
  - Neuroimaging improvement (2/5)
- Study Limitations:
  - Open label, very small, short duration and follow-up; should be confirmed in a large randomized clinical trial to establish a better benefit-risk balance

Cancer and Copper

- Cancer involves abnormal cell growth along with invasion, dissemination, and metastasis (Blockhuys et al. 2017)
- It has been hypothesized that the progression of cancer cells is dependent on copper (Ishida et al. 2010)
- It has been shown that the copper level in a cancer cell is higher (up to 2–3-fold) than copper level in a healthy normal cell (Kuo et al. 2002)
- Copper is an important cofactor for angiogenic growth factors and cytokines, such as VEGF[h], bFGF[i], interleukins (IL)-6 and 8, which are critical for tumor angiogenesis (Gartner et al. 2009)
- Angiogenesis, the formation of new capillary branches from existing blood vessels, is tightly controlled by a net balance between angiogenic stimulating factors and inhibitors (Folkman 1995, Carmeliet 2003, Urso and Maffia 2015)
- Imbalanced angiogenic stimulating factors and inhibitors leads to local progression and metastasis (Hanahan and Folkman 1996, Iruela-Arispe 1997, Denoyer et al. 2015, Urso and Maffia 2015)

[h] vascular endothelial growth factor; [i] basic fibroblast growth factor

Effectiveness in Cancer Treatment (1)

Breast Cancer

Phase 2, OL, single-arm study to evaluate the effect of ATTM associated copper depletion on circulating markers of angiogenesis in 39 patients at high risk of breast cancer recurrence (Jain et al. 2013)

- Treatment received
  - Standard cancer treatment completed at least 6 weeks prior to study; concurrent hormonal therapy permitted
  - ATTM 180 mg daily induction; then 100 ±20 mg daily for 2 years or until relapse
- Authors found:
  - Copper depletion in 75% by 1 month
  - ATTM reduced bone marrow-derived endothelial progenitor cells (EPCs), considered critical for metastatic progression
  - 27/39 (69%) had no relapse through the course of the study
- Authors concluded:
  - ATTM may promote tumor dormancy and ultimately prevent relapse, but a large, randomized, multicenter trial would be necessary

Effectiveness in Cancer Treatment (2)

Breast Cancer

Phase 2, OL, single-arm study to evaluate the effect of ATTM-associated copper depletion on circulating markers of angiogenesis in 75 breast cancer patients, at high risk of relapse (Chan et al. 2017)

- Treatment received:
- Standard cancer treatment completed prior to study – only concurrent hormonal therapy was permitted
  - ATTM 180 mg daily induction; then 100 ±20 mg daily for 2 years or until relapse
- Authors found:
  - Copper depletion correlates with reduced EPCs and other biomarkers
  - Event-free survival (EFS) was 72% and overall survival 84% at median follow-up of 6.3 years
- Authors concluded:
  - While these results are encouraging, they need to be confirmed in a larger randomized, placebo-controlled study

These studies do not provide adequate evidence that ATTM contributes to a clinical response because the trials were single arms and patients continued to receive other cancer therapy.

Effectiveness in Cancer Treatment (3)

Kidney Cancer

Phase 2, single-arm study to evaluate antitumor activity and effect on several angiogenic factors in 15 patients with advanced kidney cancer (Redman et al. 2003)

- Treatment received:
  Standard cancer therapy completed 4 weeks prior to study
  – TTM 180 mg/day for 6 months
- Authors found: Overall, 6-month progression-free survival rate was 31%, median disease progression was 13 wks
- Authors' conclusion: TTM alone showed no efficacy in patients with advanced kidney cancer

Prostate Cancer

Phase 2, single-arm study to evaluate antitumor activity and effect on several angiogenic factors in 19 patients with hormone-refractory prostate cancer (HRPC) (Henry et al. 2006)

- Treatment received: TTM 180 mg/day (median duration 13.7 weeks; range 8.1 to 33.9 weeks)
- Authors found: No difference in VEGF, bFGF, IL-6 and IL-8 levels within the first 3 months; cancer of 14/19 evaluable patients progressed; study terminated after enrollment of 19 patients because more than 11 patients had progressed
- Authors' conclusion: Copper depletion with TTM did not delay disease progression in patients with asymptomatic metastatic HRPC

Effectiveness in Cancer Treatment (4)

Malignant Pleural Mesothelioma (MPM)

- Phase 2, single-arm study to evaluate the effect of copper depletion on progression and survival after cytoreductive surgery in 30 patients with MPM (Pass et al. 2008)
- Treatment received:
  - Oral TTM 180 mg/day in divided doses, 4-6 weeks after surgery, then 60 mg/day
- Comparison with 169 historical controls treated with cytoreductive surgery
- Authors found:
  - Copper reduction is associated with reduction in serum VEGF levels
  - Time to progression (Stage I and II): median 20 months TTM vs. 10 months in historical controls
  - Time to progression (Stage III): median 7 months, no difference from controls
- Authors concluded:
  - TTM has antiangiogenic effects in MPM after surgical resection, but the study had potential for bias because it was not a randomized trial
  - Recommended validating this trial in a larger randomized study

Effectiveness in Cancer Treatment (5)

Colorectal Cancer (Metastatic)

Exploratory (pilot) study to evaluate the tolerability of TTM in combination with chemotherapy, time to disease progression, and effect on angiogenic factors in 24 patients (Gartner et al. 2009)

- Treatment received:
  - Irinotecan, 5-fluorouracil, and leucovorin
  - TTM 180 mg/day
- Authors found: No significant correlation between baseline serum cytokine levels and time to disease progression; 6 patients who continued TTM alone had tumor progression within the next 5 months

Esophageal Cancer

Phase 2 study to evaluate progression after surgical resection and chemoradiation in 69 patients (Schneider 2013)

- Treatment received:
  - Cisplatin, paclitaxel, and radiotherapy for 3 weeks followed by surgical removal of the esophagus
  - Oral TTM 20 mg/day started 4 weeks post-op; continued for 2 years
- Comparison was made to 69 historical controls treated with a similar protocol minus TTM
- Authors found: No statistically significant difference in disease-free or overall survival at 3 years and no association between decreased level of ceruloplasmin with recurrence free survival or overall survival

Effectiveness

Conclusion:

- There is insufficient information to support the effectiveness of ATTM:
  - For the treatment of Wilson disease
  - For use as chelation therapy for the treatment of breast, kidney, hormone refractory prostate cancer, malignant pleural mesothelioma, colorectal, and esophageal cancer
- There are currently FDA approved therapies with established efficacy for the treatment of Wilson disease and the types of cancer addressed in the nomination

Historical Use in Compounding

- ATTM has been used in pharmacy compounding from 1984 to at least April 2021
- Compounded ATTM has been used orally to treat various conditions, including Wilson disease, breast cancer, malignant pleural mesothelioma, and primary biliary cirrhosis, according to literature articles and clinical trials that evaluated ATTM as a new treatment
- 1 outsourcing facility reported compounding an ATTM capsule in 2017
- Results from an internet search for compounded drug products containing ATTM revealed 4 compounding pharmacies within the United States compounding ATTM
  - 1 of the 4 specified dosage form, the intended route of administration, and strength (e.g., “40 mg oral capsules”) of the drug product

Historical Use in Compounding

- One Australian compounding pharmacy advertised compounding ATTM 2.5, 5, and 10 mg capsules
- The International Journal of Pharmaceutical Compounding (IJPC) published compounding formulations for ATTM 20 mg and 50 mg oral capsules
- There is no compounded drug product monograph for any ATTM dosage form in the United States Pharmacopeia-National Formulary (USP-NF)

Conclusion:

There is evidence of the historical and current use of ATTM in compounding as an oral formulation for the treatment of Wilson disease or as copper chelation therapy for treatment of cancer both within and outside the United States.

Evaluation Summary

- **Physical-Chemical Characterization:** ATTM can be characterized using readily available analytical techniques; likely to be stable if protected from moisture and air when compounded as capsules
- **Safety**:
  - Nonclinical studies have shown that ATTM produces epiphyseal damage in growing bones
  - Concerns with ATTM use include hepatoxicity and bone marrow suppression, i.e., anemia, leukopenia, and thrombocytopenia, which are potentially serious
  - Concerns with adverse effects of significant copper removal with use of ATTM and its long-term effects
  - Lack of data on ATTM use in pregnant women and children
- **Evidence of Effectiveness:**
  - Insufficient information to support the effectiveness of oral ATTM for the treatment of Wilson disease and as chelation therapy for the treatment of breast, colorectal, esophageal, kidney, MPM, and prostate cancer
  - There are currently available FDA-approved therapies with established efficacy for the treatment of Wilson disease and cancers addressed in evaluation
- **Historical Use:**
  - ATTM used in pharmacy compounding since 1984 in oral dosage forms
  - There is evidence of the historical and current use of ATTM in compounding as an oral formulation for the treatment of Wilson disease or as copper chelation therapy for treatment of cancer both within and outside the United States

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria **weighs against** ammonium tetrathiomolybdate being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Ferric Subsulfate

Pharmacy Compounding Advisory Committee Meeting

June 8, 2022

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Pharmacy Compounding Review Team (PCRT)
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Special thanks to:
Division of Urology, Obstetrics, and Gynecology (DUOG) in OND

Nomination

- Ferric subsulfate *solid or powder* was 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)
- Ferric subsulfate was proposed for use as an astringent and hemostatic agent during minor surgical procedures
- Proposed route of administration was for topical use in the following dosage forms, as a solution and powder (10-21%)

Evaluation Criteria

- Physical and chemical characterization
- Nonclinical and clinical safety
- Available evidence of effectiveness or lack of effectiveness
- Historical use in compounding

Physical and Chemical Characterization (1)

- **Ferric subsulfate** is also called iron subsulfate, Monsel's salt, basic ferric sulfate, or iron hydroxide sulfate
- $Fe_4(OH)_2(SO_4)_5$ (CAS number 1310-45-8)[1]
- There is no ferric subsulfate drug substance monograph in the United States Pharmacopoeia (USP), National Formulary, British Pharmacopoeia, or European Pharmacopoeia

[1] CAS = Chemical Abstracts Service

Physical and Chemical Characterization (2)
Ferric Subsulfate Solid or Powder

- Ferric subsulfate solid or powder used in industrial waste processing as coagulant and pigment in pickling baths for steel and aluminum
- Very limited information in public databases
  - Stable at room temperature in light-resistant containers
  - Exposure to light accelerates decomposition
  - Unclear how ferric subsulfate solid or powder is isolated and purified
- No reference found for synthesis of solid or powder
- Lack of information regarding manufacturing, quality, and characterization

Conclusion: Because ferric subsulfate solid or powder is not well characterized chemically and physically, we do not have assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency

Bulk Drug Substance Evaluation
Ferric Subsulfate Solution (Monsel's)

- Lack of clarity in nomination and literature
  - Unclear whether the nominator intended for FDA to consider ferric subsulfate and Monsel's (solution, paste) to refer to a bulk drug substance and a drug product compounded from that substance, respectively, or whether the nominator intended to mean that they are the same products, and the names are used interchangeably

Conclusion: FDA interprets the nomination to be for the bulk drug substance ferric subsulfate solid or powder, and data submitted by Fagron on "Monsel's" will be considered for the overall assessment and recommendation with respect to the use proposed by the nominator

Physical and Chemical Characterization (3)
Ferric Subsulfate Solution

USP drug product monograph for ferric subsulfate solution or Monsel's solution

$$12\ FeSO_4 + 4\ HNO_3 + 3\ H_2SO_4 \rightarrow 3\ Fe_4(OH)_2(SO_4)_5 + 4\ NO + 2H_2O$$

{ferrous sulfate} {ferric subsulfate solution}

- USP drug product monograph for ferric subsulfate solution describes a procedure that starts with *ferrous sulfate* to prepare ferric subsulfate solution
- Ferric subsulfate solution contains, in each 100 mL, basic ferric sulfate equivalent to not less than 20 g and not more than 22 g of iron (Fe)
- Stable in light-resistant containers above 22°C
- No additional information found on ferric subsulfate in databases searched

Ferric subsulfate solution is chemically and physically well-characterized when USP drug product monograph is followed, but solution is made starting from *ferrous sulfate* rather than ferric subsulfate solid or powder, which we construe to be subject of nomination

Nonclinical Pharmacology and Safety

- Hemostasis was improved when ferric subsulfate (Monsel's solution) was used in rat tail bleeding model (Byun et al. 2018)
- Hemostatic effect of ferric subsulfate (Monsel's solution) on rate of wound healing in pig model (Sawchuck 1986)
  - Application of ferric subsulfate (Monsel's solution) on punch biopsy wounds resulted in delayed tissue re-epithelialization
- No data found in the literature that described acute toxicity, repeat dose toxicity, reproductive toxicity, genetic toxicology, or carcinogenicity aspects of ferric subsulfate

Clinical Safety (1)
CAERS / FAERS

- No cases related to ingredient were found in Center for Food Safety and Nutrition Adverse Event Reporting System (CAERS)
- FDA Adverse Event Reporting System (FAERS):
  - 15 cases of potential drug-event associations reported through August 2021; causality often unclear
  - Minor adverse events (AEs) cases of application site reactions (e.g., inflammation, pain, irritation, chemical burn, dysuria)
  - Of the 10 serious AEs (SAEs) reported, 3 involved ferric subsulfate from compounded ferric subsulfate products & resulted in hospitalizations

Clinical Safety (2)
SAEs - FAERS Reports

- 31-year-old; Case ID 15334124 (U.S.; 2018)
  - Monsel's solution applied to urethra after intrauterine device (IUD) removal
  - Swelling in urethra, dysuria, and skin pigmentation
  - Hospitalization for chemical burn
- 33-year-old; Case ID 15395442 (U.S.; 2018)
  - Monsel's solution applied to cervix prior to IUD placement
  - Burning sensation and intense pain with small amounts of tissue and blood coming out of her vagina
  - Evaluated in emergency room for application site burn
- 29-year-old; Case ID 17999873 (U.S.; 2020)
  - Monsel's paste applied to cervix to control bleeding
  - Evaluated in hospital for burning sensation

Clinical Safety (3)
Topical Application – Peritoneal Perforation

Peritoneal perforation and mortality (Shuhaiber 2005)

- 46-year-old patient died after complication from large cervical biopsy
  - Pads soaked with Monsel's solution used to control complications of persistent bleeding, after unsuccessful hemostasis with suture and other surgical interventions

Conclusion: Peritoneal cavity must not be exposed to Monsel's solution

- Leak of Monsel's solution into the peritoneal cavity could lead to areas of bowel damage and necrosis after topical application
- Uterine perforation **must be excluded** before the use of Monsel's solution (Disu 2007 and Miller 2015)

Clinical Safety (4)
Other Safety Information

1. Monsel's solution used for hemostasis during *in vitro* fertilization (IVF) may affect pregnancy outcomes (Cook 2013)
   - Pregnancy outcomes reduced during IVF for Monsel's group compared to control patients (did not receive Monsel's solution)
     - 15.2% vs. 33.6%
2. Pathological artifacts and diagnostic challenges
   - Ferric Subsulfate causes dyspigmentation and may distort pathology on re-excision
     - Histologic changes in tissue may persist up to 3 weeks
     - Depth calculation error of melanoma obscures interpretation
   - Conclusion: Recommend avoiding cervical smears on patients with recent treatments of ferric subsulfate on the cervix in order to avoid confusion on future diagnosis

Clinical Safety (5)

Conclusion:

- There are no published clinical trials conducted to specifically assess the safety of ferric subsulfate drug products in humans
- AEs primarily consisted of acute reactions to ferric subsulfate exposure rather than exposure data for longer-term effects
  - Majority of cases identified suspect product as “Monsel’s solution” or “paste”
- Possible postoperative discharge (1-3 days), delayed wound healing, and vaginal irritation
- Monsel’s solution should not be used intra-abdominally because a leak into peritoneal cavity could lead to bowel damage and necrosis

Overview of Intraoperative Procedures for CIN Complication - Bleeding

- Cervical precancerous lesions or intraepithelial neoplasia (CIN)
  - Atypical squamous changes in cervix transformation zone
- Women in reproductive and postmenopausal ages diagnosed using cervical biopsies with surgical procedures
  - Cold knife conizations
  - Laser conization
  - Loop electrical excision procedure [LEEP] with electrocautery
- Short-term complications: bleeding (intraoperative and postoperative) and infection
- Control of intraoperative bleeding
  - Surgical techniques (e.g., sutures, clips, or electrocautery)
  - Adjunct use of topical hemostatic agents

Topical Hemostatic Agents to Control Intraoperative Bleeding

ACOG* Committee on Gynecologic Practice's conclusions and recommendations (2020):

- Topical hemostatic agents are used when electrocautery or sutures for hemostatic control of surgical bleeding not ideal or safe
  - Not for routine prophylaxis of postoperative bleeding because increase risk of infection, adhesion formation, and other complications
- Topical caustic hemostatic agents used on cervix and vagina:
  - *Ferric subsulfate 20% (Monsel's solution)*, aluminum chloride, silver nitrate, and zinc chloride paste
  - Not for intrabdominal use

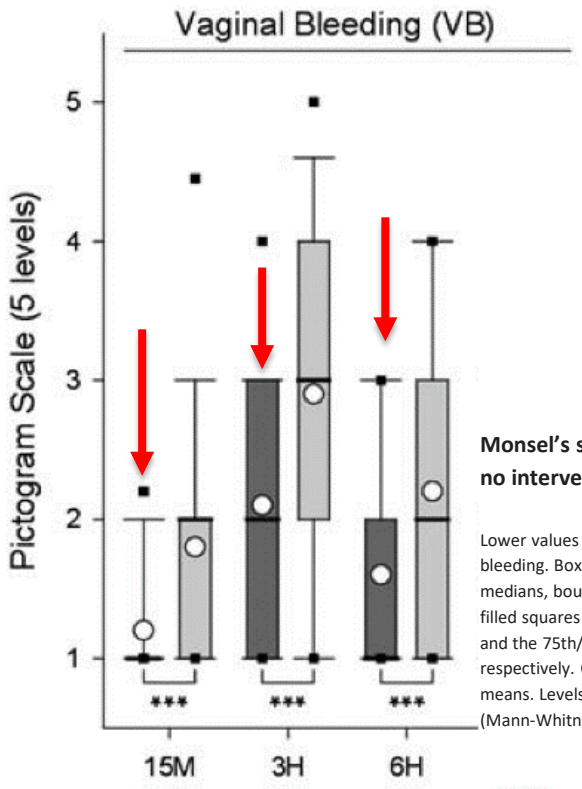
*American College of Obstetricians and Gynecologists

Clinical Effectiveness – Clinical Trials (1)

(Hilal 2016) randomized, controlled trial of 20% Monsel's solution (ferric subsulfate) group (N=75) vs. "wait and see" control group (N=70) in the reduction of VB

- Endpoint was VB after 15 minutes
  - Measured by scoring sanitary pad with modified 5-level pictogram as objective measure
- Monsel's solution group experienced less VB, mean score 1.2 ± 0.6 vs. 1.8 ± 1.0 in control group

Conclusion: Support efficacy of ferric subsulfate as hemostatic agent in the reduction of vaginal bleeding in the short-term



Monsel's solution (dark gray) vs. no intervention (light gray)

Lower values correspond to lower amount bleeding. Box plots: thick lines indicate medians, boundaries, and whiskers, and filled squares indicate the 25th/10th/5th; and the 75th/90th/95th percentiles, respectively. Open circles represent the means. Levels of significance are indicated (Mann-Whitney U test) ***p≤0.001.

Clinical Effectiveness – Clinical Trials (2)

Kietpeerakool (2007) Randomized to Monsel's solution (N=140) vs. control (povidone-iodine solution) (N=145) to study occurrence of postoperative bleeding after LEEP

- Uncomplicated VB (defined as postoperative VB that did not require any treatment)
- Persistent VB (defined as postoperative VB of at least 2-weeks duration and did not require any treatment)

Symptoms‡

Variable	Monsel's group ($n = 128$)	Control group ($n = 128$)	Difference (95% CI)	*P*-value
Uncomplicated vaginal bleeding (days)	2.73 ± 3.25	5.06 ± 4.35	2.33 (1.43–3.23)	<0.001
Persistent vaginal bleeding	4 (3.13)	14 (10.94)	0.26 (0.07–0.89)	0.014

†Values are given as mean ± SD or number (percentage) unless stated otherwise.

‡Excluding menstrual bleeding and women who had any complications. CI, confidence interval.

Conclusion: Supports efficacy of ferric subsulfate in reduction of bleeding following LEEP

Clinical Effectiveness (3)
Nominator Submitted Trials

Mitchell 1998 (Randomized, controlled trial (RCT))

- 390 women randomized to ablation treatments: cryotherapy (N=139), laser vaporization (N=121), or LEEP (N=130)
- Ferric subsulfate solution applied postoperatively only in laser vaporization and LEEP

Martin-Hirsch and Bryant 2013 (Cochrane review – included 3 studies of ferric subsulfate)

– Gilbert 1989
  - 200 women underwent cold-knife conization, were evenly randomized to the treatment group "pack" with Monsel's solution (ferric subsulfate) compared to standard suture technique group

– Lipscomb 2006
  - Ferric subsulfate (N=47) compared to fulguration with ball electrode (electrocautery) (N=53) for hemostasis following LEEP

– Doyle 1992
  - 125 healthy women undergoing LEEP for cervical biopsies were randomized to either the Monsel's solution group or the control group

Conclusion: These studies did not have adequate controls, or it was not possible to estimate the contribution of ferric subsulfate solution towards hemostasis as opposed to other factors (pressure exerted on the wound by the gauze pack, size of the biopsy excision, types of surgery procedures). One study in the Cochrane review showed both fulguration with ball electrode and Monsel's paste to be equally effective for hemostasis after LEEP.

Clinical Effectiveness

Conclusion:

- There is evidence of effectiveness for use of ferric subsulfate (Monsel's solution) as topical hemostatic agent based on data from RCTs to reduce bleeding following minor gynecological surgical procedures (cervical biopsies)

Historical Use in Compounding

- No information on which products are compounded starting from ferric subsulfate solid or powder
- Some available information suggests ferric subsulfate has been used as hemostatic agent since the 19th century
- Compounded as a topical solution and gel to stop bleeding after minor surgical procedures in the U.S.
- Ferric subsulfate is the active ingredient in unapproved prescription and non-prescription products marketed in U.S. for human and animal use for hemostasis

Recommendation

Based on this information we have considered, a balancing of the four evaluation criteria weighs ***against*** ferric subsulfate *solid or powder* being added to the 503A Bulks List primarily because of the lack of information on the physical and chemical characterization of ferric subsulfate solid or powder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Process for Identifying Drugs for the Withdrawn or Removed List

Pharmacy Compounding Advisory Committee Meeting

June 8, 2022

Gabrielle Cosel, MSc
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CDER

Statutory Framework

- One of the conditions that must be satisfied for a drug product to qualify for the exemptions under sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) is that the compounder does not compound a drug product that appears on a list published by the Secretary of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (Withdrawn or Removed List), codified at § 216.24.
- A drug product that is included in the Withdrawn or Removed List is not eligible for the exemptions provided in sections 503A or 503B.
- FDA has reviewed and added 85 bulk drug substances to the Withdrawn or Removed List to date.

Process for Developing the Withdrawn or Removed List

- FDA periodically reviews available information on drugs withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective with the goal of identifying possible new entries for the list.
- The information reviewed may include:
  - *Federal Register* notices announcing withdrawal of approval of a new drug application (NDA) or abbreviated new drug application (ANDA) for safety or effectiveness reasons
  - *Federal Register* notices announcing an Agency determination that a drug product that was voluntarily withdrawn from sale was withdrawn for reasons of safety or effectiveness

Process for Developing the Withdrawn or Removed List

- FDA also reviews available information to determine whether any approvals of new drug applications would warrant modifications to existing entries on the list
- Appropriate divisions within the Office of New Drugs (OND) evaluate each identified candidate or proposed modification using the available information about the drug.
- The responsible division will prepare a review of the information that documents its recommendations as to whether to include the drug on the withdrawn or removed list, or remove a drug from the list, or modify an entry.

Process for Updating the Withdrawn or Removed List

FDA will update the Withdrawn or Removed List through notice and comment rulemaking (as stated in a final rule published in October 2016).

- FDA intends to propose regulations to revise the list when we identify drugs that we tentatively determine should be listed.
- FDA also intends to propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing.
- Generally, FDA will finalize any additions or modifications to the list after consulting the Advisory Committee about the relevant drug, and after providing an opportunity for public comments to be submitted on a proposed rule.

Current Drug Identified for the Withdrawn or Removed List

FDA is considering including on the list:

Lorcaserin Hydrochloride: all drug products containing lorcaserin hydrochloride

U.S. FOOD & DRUG ADMINISTRATION

Lorcaserin Hydrochloride

Pharmacy Compounding Advisory Committee Meeting
June 8, 2022

Marianne San Antonio, DO
Physician
Pharmacy Compounding Review Team
Office of Specialty Medicine, Office of New Drugs, CDER, FDA

Overview of Withdrawn or Removed List

- The Withdrawn or Removed List (21 CFR 216.24)[1]
  - Under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, FDA has established a list of drug products that were withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective
- Drugs on the Withdrawn or Removed List cannot qualify for the exemptions under sections 503A or 503B

[1] CFR = Code of Federal Regulations

Lorcaserin Hydrochloride (BELVIQ)

- Selective agonist of 5-hydroxytryptamine (5-HT) 2C receptors
  - BELVIQ 10 mg tablets (NDA 022529 approved on June 27, 2012)
  - BELVIQ XR 20 mg extended-release (ER) tablets (NDA 208524 approved on July 15, 2016)
  - Approval for NDA 022529 included a postmarketing requirement to investigate cardiovascular adverse events
- Indicated for use
  - Adjunct to a reduced-calorie diet + increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of
    - 30 kg/m^2 or greater (obese) or
    - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes)

Lorcaserin Hydrochloride Marketing Withdrawal

- Postmarketing study (CAMELLIA-TIMI 61)[2] was conducted by the sponsor to investigate cardiovascular adverse events
- Safety concerns identified in the postmarketing study
  - Primary safety concern: possible increased risk of malignancy
- Lorcaserin hydrochloride products were withdrawn from the market for safety reasons

[2] CAMELLIA-TIMI 61 = Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61

Lorcaserin Hydrochloride Postmarketing Study CAMELLIA-TIMI 61

- The study was required by FDA because of occurrence of cardiovascular adverse events during treatment with other FDA-approved medications for weight loss
- Study population
  - 12,000 overweight or obese subjects
  - With or at risk for atherosclerotic vascular disease
- Neither pulmonary hypertension nor valvular heart defects occurred at an increased rate in patients treated with lorcaserin hydrochloride compared to placebo[3]

3. Bohula, EA, SD Wiviott, DK McGuire, et al., 2018b, Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients, N Engl J Med, 379(12):1107-1117

Lorcaserin Hydrochloride Postmarketing Study CAMELLIA-TIMI 61 and Malignancy Risk

- FDA's analysis of the CAMELLIA-TIMI 61 clinical study data identified an imbalance in cancer in humans[4]
- Rates higher in the lorcaserin hydrochloride group for
  - Colorectal cancer
  - Pancreatic cancer
  - Lung cancer
- First 180 days
  - Number with a new cancer diagnosis was similar in lorcaserin hydrochloride and placebo groups
- Beyond 180 days
  - Cancer risk elevated in the lorcaserin hydrochloride group

4. Sharretts, J, O Galescu, S Gomatam, et al., 2020, Cancer Risk Associated with Lorcaserin - the FDA's Review of the CAMELLIA-TIMI 61 Trial, N Engl J Med, 383(11):1000-1002.

Lorcaserin Hydrochloride Postmarketing Study CAMELLIA-TIMI 61 and Malignancy Risk

- Mechanism of association with cancer unclear
- Cancer signal persisted through multiple analyses
- Clinical findings corroborated by evidence from animal models
- Necessary safety endpoints (cancer) unlikely to be readily or ethically investigated in a clinical trial

Summary of Withdrawal Timelines

June 27, 2012	• BELVIQ (lorcaserin hydrochloride) tablets, 10 mg approval (NDA 022529) • Included a **postmarketing requirement** to investigate cardiovascular adverse events
2014	• **CAMELLIA-TIMI 61 Postmarketing study** • Data collection between 2014-2018 • Primary outcome: evaluate the **risk of cardiovascular problems**
July 15, 2016	• BELVIQ XR (lorcaserin hydrochloride) extended-release tablets, 20 mg (NDA 208524) approved
2020	• FDA's analysis of CAMELLIA-TIMI 61: **imbalance in cancer in humans**
January 14, 2020	• Drug safety communication: **possible increased risk of cancer** with lorcaserin hydrochloride

February 13, 2020	• FDA asked sponsor to voluntarily withdraw lorcaserin hydrochloride from the U.S. market
	• Sponsor requested FDA to **withdraw approval** of
	  ◦ NDA 022529 BELVIQ (lorcaserin hydrochloride) tablets, 10 mg and
	  ◦ NDA 208524 BELVIQ XR (lorcaserin hydrochloride) extended-release tablets, 20 mg

September 17, 2020	• FDA published Federal Register notice (85 FR 58063) withdrawing approval of the lorcaserin hydrochloride applications
March 4, 2021	• **Withdrawn from sale for reasons of safety or effectiveness** (86 FR 12697) • **Removed from the Orange Book**

Assessment

- CAMELLIA-TIMI 61 clinical study and nonclinical data suggest an increased risk of malignancy with use of lorcaserin hydrochloride
- FDA concluded that lorcaserin hydrochloride's benefits do not outweigh the risks for the approved indications (86 FR 12697, March 4, 2021)
- We are not aware of data suggesting that increased risk of malignancy is restricted to particular lorcaserin hydrochloride drug products
- Lorcaserin hydrochloride withdrawn from the market due to safety concerns

Recommendation

- FDA recommends that all drug products containing lorcaserin hydrochloride be included on the Withdrawn or Removed List using the following entry

Lorcaserin hydrochloride: All drug products containing lorcaserin hydrochloride


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