CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211843Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Division Memo

Date	June 24, 2019
From	Aliza Thompson, Deputy Director
Subject	Cross-Discipline Team Leader Review and Division Memo
NDA #	211843
Applicant	Mission Pharmacal Company
Date of Submission	August 31, 2018
PDUFA Goal Date	June 30, 2019
Proprietary Name	Thiola® EC
Established or Proper Name	Tiopronin
Dosage Form(s)	100- and 300-mg tablets
Applicant Proposed Indication(s)/Population(s)	prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria (b) (4) high fluid intake, alkali and diet modification, (b) (4)
Applicant Proposed Dosing Regimen(s)	(b) (4) dosage of 800 mg/day in adult patients (b) (4) (b) (4) average dose of THIOLA was about 1000 mg/day. (b) (4) initial dosage (b) (4) 15 mg/kg/day. THIOLA EC should be taken in 3 divided doses with or without food at the same times each day."
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s)	THIOLA EC is indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are not responsive to these measures alone.
Recommended Dosing Regimen(s)	Adults: The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dose was about 1,000 mg/day. Pediatrics: The recommended initial dosage in pediatric patients weighing 20 kg and greater is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients. Administer THIOLA EC in 3 divided doses at the same times each day, with or without food. Maintain a routine pattern with regard to meals. Swallow THIOLA EC tablets whole. Consider starting THIOLA EC at a lower dosage in patients with history of severe toxicity to d-penicillamine.

This secondary review is based on the following reviews:

Quality Assessment (6/5/19)	Sharon Kelly, Andrei Ponta, Anitha Govada, Ou Mei, Grafton Adams, Mohan Sapru (*Application Technical Lead*)
Office of Study Integrity and Surveillance (3/20/19)	Himanshu Gupta, Seongeun Cho, Sean Kassim
Office of Clinical Pharmacology Review (5/24/19)	Anusha Ande, Sudharshan Hariharan, Ramana Uppoor
Division of Pediatric and Maternal Health Reviews (5/24 and 6/6/19)	*Maternal Health:* Carrie Ceresa, Miriam Dinatale, Lynne Yao *Pediatric Labeling:* Elizabeth Durmowicz, Mona Khurana
Division of Medication Error Prevention and Analysis Reviews (12/10/18 and 3/22 and 6/12/19)	Sarah Thomas, Sevan Kolejian, Danielle Harris Maximilian Straka, Chi-Ming (Alice) Tu
Clinical Review (6/17/19)	Shen Xiao, Aliza Thompson
Office of Prescription Drug Promotion Review (6/11/19)	Puja Shah

1. Benefit-Risk Assessment[1]

Cystinuria is a rare, genetic disease characterized by decreased proximal tubular reabsorption of filtered cystine (a homodimer of the amino acid cysteine), resulting in increased urinary cystine excretion and cystine kidney stones. The disease often presents in childhood (median age of onset of kidney stones ~ 12 years), though patients can also present in infancy and late adulthood. Tiopronin is a reducing and complexing thiol compound that undergoes thiol-disulfide exchange with cystine to form a water-soluble mixed disulfide of tiopronin-cysteine, thus reducing the amount of sparingly soluble cystine in the urine.

Mission's application for Thiola EC (tiopronin) delayed release tablets relies on the Agency's previous finding of safety and effectiveness for Thiola (tiopronin) tablets. Studies conducted in healthy subjects provide the needed bridge to the approved product and published studies and case reports support an expansion of Thiola's current indication to include (b) (4) pediatric (b) (4).

From a product quality, pharmacology-toxicology, clinical pharmacology, and clinical safety and efficacy perspective, the application can be approved. Because the available dosage form and tablet strengths are not appropriate for use in patients weighing less than 20 kg or in patients who are unable to swallow solid oral dosage forms, the indicated population should be limited to adults and pediatric patients 20 kg and greater. Labeling will also indicate that the tablets should be swallowed whole, pending information on the relative bioavailability of the crushed tablets. As discussed under the labeling section of this review, the data submitted in support of safety do not raise new safety concerns; in fact, review of the submitted data

[1] This review does not include a Benefit-Risk Dimensions table or adhere to the recommended structure of the Benefit-Risk discussion as neither appeared to be well-suited for this application. We believe, nonetheless, that this review adequately addresses benefit-risk considerations and the basis for FDA's decision to approve the application.

and a report of adverse events in patients taking tiopronin from the FAERS database indicate that some of the risks included in the label for Thiola (tiopronin) should be removed from labeling.

2. Background

On August 31, 2018, Mission Pharmacal Company submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Thiola EC (tiopronin) delayed release 100-mg and 300-mg tablets for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria (b) (4) high fluid intake, alkali and diet modification, (b) (4). The application relies on the Agency's previous finding of safety and effectiveness for Thiola (NDA 019569, approved in 1988; currently held by Mission Pharmacal Company), two pharmacokinetic studies, data from the published literature and pharmacovigilance information from NDA 019569.

Per the applicant, Thiola EC tablets were developed by Mission as an enteric-coated tablet (b) (4) Thiola EC also comes in 2 strengths, whereas Thiola (tiopronin) is available in a single strength (100 mg).

The proposed indication statement for Thiola EC (tiopronin) mirrors the indication statement for Thiola (tiopronin), which is silent on the age range for which the product is approved. However, as discussed under "Pediatrics", the applicant has provided information from the published literature on safety and effectiveness in children and proposed changes to Section 8 of the label based on this information.

3. Product Quality

OPQ recommends approval of the application from a quality perspective, with the following postmarketing commitments:

1. Provide (b) (4) testing results for eight development/registration batches and six validation batches. Specifically, the eight development/registration batches are to be tested after ~24 months storage under long-term conditions. The six validation batches are to be manufactured June 2019 and are to be tested approximately one week after manufacturing as part of release testing. The agreed time frame for reporting the testing results is the 3rd quarter of 2019. These results are to be submitted to the NDA as an amendment.
2. Perform (b) (4) testing, as part of the stability protocol, for the validation batches with the six-month results to be made available around December 2019.
3. Submit all (b) (4) testing results, to set the final (b) (4) limit, as a Prior Approval Supplement (PAS) at the end of the 1st quarter of 2020.

Drug substance: Tiopronin is a white crystalline powder that is freely soluble in water.

Drug product: THIOLA EC tablets are round, white tablets that are manufactured as a delayed release solid oral dosage form containing 100-mg or 300-mg of tiopronin. One side of the tablet is imprinted with "T1" or "T3" (100 and 300-mg strength, respectively) in red ink.

Inactive ingredients include lactose, hydroxypropyl cellulose, hydroxypropyl cellulose (low substitute), magnesium stearate, hydroxypropyl methylcellulose E5, methacrylic acid: ethyl acrylate copolymer, talc, triethyl citrate. The enteric-coated tablet formulation (b) (4) .

Expiration Date and Storage Conditions: Available stability data support an expiration period of 18 months for the proposed product when stored at controlled room temperature (25°C or 77°F) in the commercial packaging, with excursions permitted to 15-30°C (59-86°F).

(b) (4)

Facilities review/inspection: According to the Office of Process and Facilities, the listed manufacturing facilities are considered acceptable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of the application.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) recommends approval of the application from a clinical pharmacology perspective. In support of the application, the applicant submitted the results of two clinical pharmacology studies-- a relative bioavailability study to bridge THIOLA EC to THIOLA IR tablets and a food effect study THIOLA EC tablets. The applicant has also submitted dissolution data and dose linearity information in support of a biowaiver request for the 100 mg strength of THIOLA EC tablets.

As discussed in the OCP review, the relative bioavailability study showed a lower peak Cmax (~20% decrease) for the THIOLA EC tablet as compared to the THIOLA IR tablet and similar total exposure. In the food effect study, administration of the THIOLA EC tablet in the fed state resulted in lower plasma exposure as compared to the fasted state (AUC0-t and AUC0-∞ lowered by ~20%; Cmax by ~10%). Based on these findings, OCP is recommending consistent administration of THIOLA EC tablets with or without food.

As discussed in the OCP and DPMH reviews, the available dosage form and tablet strengths are not appropriate for use in patients weighing less than 20 kg or in patients who are unable to swallow solid oral dosage forms. OCP is recommending a randomized, 2-way crossover single oral dose study in healthy subjects to evaluate the relative bioavailability of 300 mg THIOLA EC (crushed) mixed in apple sauce compared to 300 mg THIOLA EC intact tablet as a post-marketing commitment (PMC) to support providing dosing instructions to pediatric

patients weighing less than 20 kg or who cannot swallow the tablet whole. The applicant has agreed to conduct this study.

6. Clinical/Statistical- Efficacy

As previously noted, the application relies on the Agency's previous determination of effectiveness for Thiola (troponin) tablets. Studies conducted in healthy subjects provide the needed bridge to the approved product. The applicant also submitted published studies and case reports to support an expansion of Thiola's current indication to include (b) (4) pediatric (b) (4). See "Pediatrics" for further discussion.

7. Safety

The application relies on the Agency's previous determination of safety for Thiola (tiopronin) tablets. As discussed in the Clinical Review, the applicant also conducted a search of the published literature to address the postmarketing safety experience with Thiola. The applicant's search did not raise new safety concerns; in fact, review of the submitted data and and a report of adverse events in patients taking tiopronin from the FAERS database indicate that some of the previously included risks should be removed from labeling (see discussion under "Labeling"). For information on data supporting safety across pediatric age groups, see "Pediatrics".

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held.

9. Pediatrics

The current label for Thiola (tiopronin) includes the following text under Pediatric Use: "Safety and effectiveness below the age of 9 have not been established." The applicant proposed to revise this language as follows: (b) (4) and submitted a summary of available literature to support this text/proposed modification (b) (4). The Division of Pediatric and Maternal Health (DPMH) was asked to evaluate these data and comment on any concerns raised regarding efficacy in the proposed pediatric population and any specific safety concerns that are not described in labeling, including pediatric-specific safety issues.

In their reviews, Dr. Durmowicz (DPMH) and Dr. Xiao (Clinical Review) discuss the limitations of the submitted data, but also conclude that the data are sufficient to support safety, effectiveness and dosing (b) (4). I agree with their assessment of the data and their conclusion. As in adults, proteinuria, including nephrotic syndrome, has been reported in pediatric patients taking tiopronin, with higher doses of tiopronin (> 50 mg/kg/day in pediatric patients) associated with greater risk. In general, proteinuria appears to be reversible following drug withdrawal and available data indicate that tiopronin can be restarted in patients at a lower dose following resolution of proteinuria.

10. Other Relevant Regulatory Issues

On December 20, 2018, Mission submitted a labeling supplement to update the Thiola (tiopronin) tablet label to comply with the Physician Labeling Rule format and address the requirements for the Pregnancy and Lactation Labeling Rule. The label for Thiola (tiopronin) will be updated accordingly.

11. Labeling

The approved label for Thiola (tiopronin) is not in the Physician Labeling Rule (PLR) format and substantial edits were made to convert the Thiola EC (tiopronin) label to PLR format and update the label to reflect the data submitted in support of safety in adults and in support of safety, efficacy and dosing in pediatric patients. The label was also revised to address the Pregnancy and Lactation Labeling Rule.

I thank the members of the review team and, in particular, Michael Monteleone, Associate Director for Labeling, and Mary Ross Southworth, Deputy Director for Safety, for their work on the label.

Labeled risks
Thiola (tiopronin) was approved for the treatment of cystinuria in 1988 and the label references toxicities observed with penicillamine, another agent approved for the treatment of cystinuria. For example, the Thiola (tiopronin) label states that "Despite apparent lower toxicity of THIOLA, THIOLA may potentially cause all the serious adverse reactions reported for d-penicillamine. Thus, although no death has been reported to result directly from THIOLA treatment, a fatal outcome from THIOLA is possible, as has been reported with d-penicillamine therapy from such complications as aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome or myasthenia gravis."

The available data, including the published clinical experience and pharmacovigilance data supplied by the applicant, Dr. Chalon Rodriguez's Clinical Review of NDA 019569, and a report of adverse events in patients taking tiopronin from the FAERS database, were reviewed to determine whether such toxicities should remain in labeling. Based on this information and exchanges with the applicant pertaining to toxicities observed in patients with cystinuria treated with tiopronin[2], the decision was made to revise the Contraindications,

[2] The safety database supporting approval was not derived from randomized controlled trials comparing tiopronin to placebo or penicillamine. In reviewing the safety data, emphasis was placed on toxicities

Warnings and Precautions, Adverse Reactions and Dosing (recommended monitoring) Sections of the label as outlined below.

Prescribing Information: Overview of key changes

- Indications and Usage
  - Inclusion of pediatric patients 20 kg and greater in the indicated population
  - Removal of disease etiology and practice of medicine language
- Dosage and Administration
  - Inclusion of dosing instructions for pediatric patients and text indicating that tablet should be swallowed whole
  - Revised monitoring advice
    - Clarified recommendations for monitoring and subsequent action with respect to proteinuria
    - Removed recommendations to monitor peripheral blood counts, direct platelet count, hemoglobin, serum albumin and liver function tests
- Contraindications
  - Inclusion of contraindication in patients with tiopronin or Thiola EC component hypersensitivity
  - Removal of contraindications for pregnancy (see below), agranulocytosis, aplastic anemia or thrombocytopenia
- Warnings and Precautions
  - Warning with respect to proteinuria has been revised and expanded to include information with respect to pediatric patients
  - Removal of warnings with respect to Hematologic Toxicity, Goodpasture's Syndrome and Myasthenia Gravis
- Adverse Reactions
  - This section has been substantially revised following a review of the literature and revisions for alignment with the current *Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format.*
- Use in Specific Populations
  - Pregnancy/Lactation – Previous labeling stated that use of tiopronin in pregnancy is contraindicated except where the anticipated benefit clearly outweighs the risks. Revised labeling describes that available published case report data have not identified a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes and that renal stones in pregnancy may result in adverse pregnancy outcomes. The recommendation remains to not breastfeed during treatment.
  - Pediatric Use – This section has been revised to indicate that Thiola EC is indicated for use in pediatric patients weighing 20 kg or more, that proteinuria, including nephrotic syndrome, has been reported in pediatric patients and that pediatric patients receiving greater than 50 mg/kg tiopronin per day may be at greater risk of this toxicity. The label also indicates that the tablets are not approved for use in pediatric patients weighing less than 20 kg or in pediatric patients unable to swallow tablets.

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observed in patients with cystinuria treated with tiopronin because it was difficult to determine whether adverse events reported in other disease settings were caused by tiopronin, the underlying disease, or other administered therapies.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
A REMS is not needed to ensure that the product's benefits outweigh its risks.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The applicant has agreed to conduct the PMCs discussed in the Product Quality and Clinical Pharmacology Sections of this review.

Recommended Comments to the Applicant
In light of the changes that have been made to product labeling, particularly the removal of language on monitoring for hematologic and hepatic adverse effects, the Reporting Requirements section of the approval letter should contain text similar to the following:

> We request that for a period of 5 years from the U.S. approval date, you provide detailed analyses of events of blood disorders and hepatic adverse events reported from clinical study and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Thiola EC (tiopronin) as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of blood disorders and hepatic adverse events reported with Thiola EC (tiopronin) should also be provided in the periodic safety report.

The Division of Cardiovascular and Renal Products will also work with the Division of Pharmacovigilance in OSE to assess these adverse events of interest in the postmarketing period.

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/s/

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