

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211843Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 12, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 211843
Product Name and Strength:	Thiola EC (Tiopronin) Enteric-coated, Delayed-release Tablets, 100 mg and 300 mg
Applicant/Sponsor Name:	Mission Pharmacal Company (Mission)
FDA Received Date:	June 7, 2019
OSE RCM #:	2018-1937-1
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels for Thiola EC (Tiopronin) Delayed-release Tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

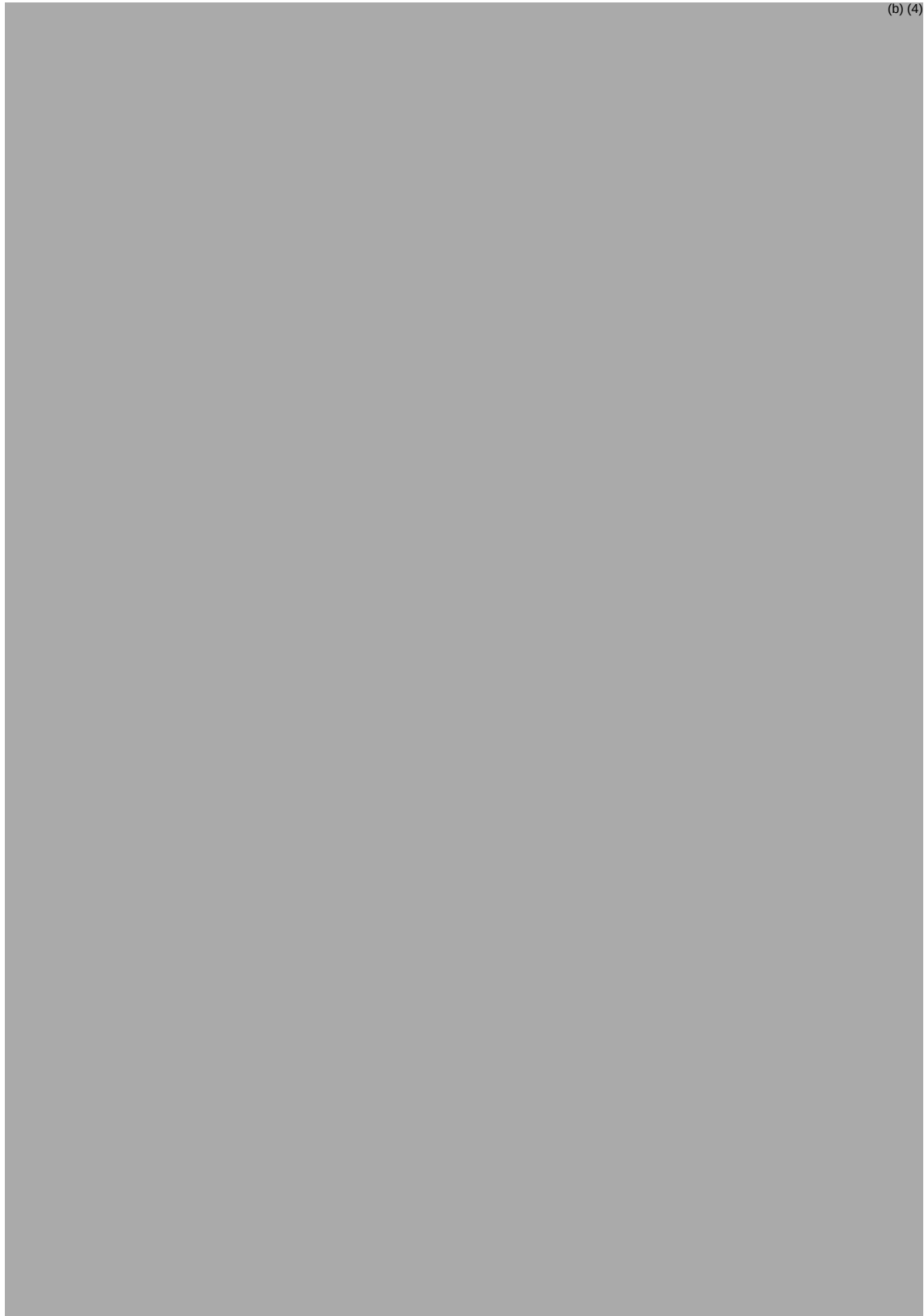
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Straka M. Label and Labeling Review for Thiola EC (tiopronin) (NDA 211843). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 22. RCM No.: 2018-1937.

APPENDIX A. IMAGES OF LABELS RECEIVED ON JUNE 7, 2019

Container labels



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/s/

MAXIMILIAN STRAKA
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CHI-MING TU
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 11, 2019

To: Sabry Soukehal, RAC, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

Michael Monteleone, MS, Associate Director for Labeling, (DCaRP)

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for THIOLA EC (tiopronin (b) (4))

NDA: 211843

In response to DCaRP's consult request dated September 12, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for THIOLA EC (tiopronin (b) (4))

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCaRP (Sabry Soukehal) on May 28, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 31, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
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**MEMORANDUM TO FILE
PEDIATRIC LABELING REVIEW**

From: Elizabeth L. Durmowicz, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ODE IV, OND

To: Division of Cardiovascular and Renal Products (DCaRP)
ODE I, OND

Subject: Pediatric Tiopronin Use and Labeling

NDA 211843

Applicant: Mission Pharmacal

Drug: Thiola EC¹ (tiopronin) Delayed Release Tablets

¹ FDA concluded that Thiola EC, the proposed proprietary name, is conditionally acceptable on December 10, 2018.

(b) (4)
CMC recommends FDA label the product as: THIOLA EC (tiopronin) Delayed Release Tablets
(OPQ Integrated Quality Review, June 5, 2019).

Proposed Indication: Prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria (b) (4)
(b) (4)
high fluid intake, alkali and diet modification, (b) (4)

Dosage Form: 100 mg and 300 mg delayed release oral tablets

Proposed Dosing:³ Adults: starting dose 800 mg/day
Pediatric patients: starting dose 15 mg/kg/day administered in 3 divided doses

Listed Drug: Thiola[®] (tiopronin) 100 mg immediate release (IR) oral tablets (NDA 019569)⁴

Consult Request:

DCaRP requested DPMH comment on whether the pediatric data submitted by the applicant raises efficacy or safety concerns that are not described in the approved tiopronin product United States Prescribing Information (USPI). DCaRP requested DPMH review the proposed USPI for this new tiopronin product and provide guidance on how to convey pediatric use information in labeling.

Materials Reviewed:

- Draft DCaRP Clinical Review (Shen Xiao, MD), May 29, 2019
- FDA's Information Request letter dated February 6, 2019 and the Applicant's Response (February 20, 2019, eCTD Seq#: 0008)
- Relevant documents in the original NDA 211843 submission (August 31, 2018; eCTD Seq#: 0001) including Section 4, "Pediatric Patients" in the Summary of Clinical Safety (Module 2.7.2) and select publications from the applicant's literature summary.
- Thiola[®]/NDA 019569 USPI⁵

(b) (4)

³ The proposed dosing for this product is the same dosing as the Thiola[®] IR tablet, NDA 19569.

⁴ Thiola[®] EC 100 mg oral tablet is a round, 8 mm, unscored tablet.

⁵ USPI dated October 2018 retrieved from [fdalabel](#). Accessed March 14, 2019.

Brief Regulatory History of Tiopronin

FDA approved tiopronin as Thiola® 100 mg IR oral tablets under NDA 019569 in August 1988 for use in patients (b) (4) for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria with urinary cystine greater than 500 mg/day, who are resistant to treatment with conservative measures of high fluid intake, alkali and diet modification, or who have adverse reactions to d-penicillamine. The FDA reviews supporting the original approval and labeling are not available electronically; however, data supporting the approval is available in the published literature.⁶

On August 31, 2018, the same application holder as the Thiola® (tiopronin) 100 mg IR oral tablets submitted the current marketing application, NDA 211843, to FDA under section 505(b)(2) of the Food Drug and Cosmetic Act relying on FDA's findings of safety and effectiveness for tiopronin 100 mg IR oral tablets. This NDA seeks FDA approval for a 100 mg and 300 mg enteric-coated oral tablet dosage form (b) (4) in the same patient population for which Thiola IR is currently approved. The NDA includes two pharmacokinetic (PK) studies⁷ and a summary of PK, safety, and efficacy data from the published literature. The applicant did not conduct any clinical safety or efficacy trials to support adult or pediatric approval of this marketing application with the NDA. The Prescription Drug User Fee Act goal date for this application is June 30, 2019, and the action goal date is June 28, 2019. (b) (4)

FDA granted orphan designation to tiopronin for "prevention of cystine nephrolithiasis in patients with homozygous cystinuria" in January 1986.⁸ The application holder submitted a prior approval supplement to NDA 19569 on December 20, 2018 to comply with the Physician Labeling Rule (PLR) format and address the requirements for the Pregnancy and Lactation Labeling Rule (PLLR).

Brief Overview of Homozygous Cystinuria

Cystinuria is a rare, autosomal recessive disorder characterized by defective renal reabsorption of cystine and dibasic amino acids leading to nephrolithiasis. Although the urine concentrations of all dibasic amino acids are elevated in cystinuric patients, only cystine leads to stone disease as it is relatively insoluble at physiological pH. The age of onset is variable, and stones may present

⁶ Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of Cystine Nephrolithiasis with Alpha-Mercaptopropionylglycine. *The Journal of Urology*. 1986;136:1003-1008.

⁷ The applicant submitted results from a food effect study (MPC-tiopronin-001) and a relative bioavailability (BA) study to bridge Thiola EC to Thiola IR (MPC-tiopronin-002).

⁸ Per my review of the [FDA Orphan Drug Designations and Approvals website](#) accessed on January 9, 2019.

in infancy or late adulthood.^{9,10} Stones occur bilaterally in more than 75% of cystinuric patients and can result in renal dysfunction, including end stage renal disease and poor quality of life.¹¹

Treatment measures are aimed at maintaining urinary cystine concentration below its solubility level (e.g., below 250 mg/dL), and include high fluid intake, dietary restriction and urinary alkalization.¹² If conservative measures are not effective, experts recommend treatment with a thiol-containing drug, such as tiopronin or d-penicillamine, to improve cystine solubility.¹³ Although penicillamine and tiopronin have similar, known toxicities, including dermatologic complications, hematologic abnormalities, myasthenia gravis and renal toxicity, use of tiopronin is preferred by some experts because the incidence of side effects is lower with tiopronin compared to d-penicillamine.¹² Captopril may be used off label in patients who cannot tolerate other cystine-binding agents.¹⁴ Tiopronin is FDA approved for treatment of cystinuria in patients (b) (4) and the USPI for penicillamine¹⁵ provides dosing recommendations for treatment of cystinuria in “pediatric patients” without any age limitations.

Reviewer Comment:

Because treatment options for patients with cystinuria are limited, the ongoing d-penicillamine shortages and anticipated removal of the tiopronin IR product from the market, DPMH recommends careful review of the totality of the pediatric data of tiopronin use and approving this product in as broad a pediatric patient population as possible.

DPMH Discussion of Tiopronin Use in Pediatric Patients

The applicant conducted a systematic review of the literature to identify published PK studies, efficacy and safety in pediatric patients.¹⁶ The applicant identified pediatric only (n=1) and pediatric and adult prospective studies (n=6), pediatric only (n=5) and pediatric and adult (n=6) retrospective studies, case reports (n=10) and publications reporting tiopronin use in pediatrics only (n=3) and pediatrics and adults (n=1). A description of the search strategy, publication

⁹ Dello Strologo L, Pras E, Pontesilli C, et al. Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: a need for a new classification. *J Am Soc Nephrol*. 2002;13(10):2547-2543.

¹⁰ Lambert EH, Asplin JR, Herrell SD, Miller NL. Analysis of 24-hour urine parameters as it relates to age of onset of cystine stone formation. *J Endourol*. 2010;24(7):1179-1182.

¹¹ Kim JH, Park E, Hyun SH, et al. Genotype and Phenotype Analysis in Pediatric Patients with Cystinuria. *J Korean Med Sci*. 2017; 32: 310-314

¹² Knoll T, Zollner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol*. 2005;20:19–24

¹³ Dello Strologo L, Laurenzi L, Legato A, Pastore A. Cystinuria in children and young adults: success of monitoring free-cystine urine levels. *Pediatr Nephrol*. 2007;22:1869–1873.

¹⁴ Sloan JA, Izzo JL. Captopril reduces urinary cystine excretion in cystinuria. *Arch Intern Med*. 1987;147(8):1409.

¹⁵ Per my review of the March 2018 Cuprimine USPI available at [FDALabel](#). Accessed May 28, 2019.

¹⁶ The applicant searched the pediatric literature from 1998 (the year FDA approved the tiopronin IR dosage form, NDA 019569) to May 2018.

selection and review process is described in the Clinical Overview (Module 2.5) and the summary of the pediatric data is provided in the Summary of Clinical Safety (Module 2.7.4).

Reviewer Comment

The applicant has provided a brief summary of the data from the publications they identified in the literature, but they did not provide a synthesis of the findings. The data in the literature to inform pediatric tiopronin labeling is limited. Limitations include the small number of publications identified/available in the literature, incomplete reporting of patient ages, dosing, and safety findings, and duplication of patient reports.

Dosage

The literature describes a range of tiopronin dosing in pediatric patients, including weight-based dosing from 10 mg/kg/day¹⁷ to 100 mg/kg/day,¹⁸ and doses of 400 mg to 1600 mg/day¹⁹ (see Appendix I for a tabular summary of tiopronin treated patients from the literature based on age, source and dosing). The literature suggests that doses less than 15 mg/kg/day may be inadequate.^{13,20} One publication noted that younger pediatric patients require higher tiopronin dosage per kilogram (kg) of body weight compared to older pediatric patients.¹³ The authors noted that they did not conduct PK studies and were unable to conclude that the higher dose per body weight in younger pediatric patients was due to lower absorption or faster clearance. The literature recommends and reports that prescribers individualize the dosage to effect,^{13,18,21,22} and limit dosing in pediatric patients to < 50 mg/kg/day (see Safety and Effectiveness, below).^{18,23}

Safety and Effectiveness

Data from the published literature suggest that the effectiveness and safety of tiopronin use in the pediatric population is similar to that in adults and identify that tiopronin has been used in

¹⁷ Onal B, Dogan C, Citgez S, et al. Percutaneous Nephrolithotomy in Children with Cystine Stone: Long-Term Outcomes from a Single Institution. *The Journal of Urology*. 2013; 190:234-238.

¹⁸ Pavanello L, Rizzoni G, Dussini N, et al. Cystinuria in Children. *Eur.Urol*. 1981; 7:139-143.

¹⁹ Araki T, Tanahashi T, Ishito N, et al. Treatment of Cystine Calculi with Tiopronin. *The Japanese Journal of Urology*. 1981;72: 221-236.

²⁰ Tekin A, Tekgul S, Atsu N, Sahin A, Bakkaloglu M. Cystine calculi in children: the results of a metabolic evaluation and response to medical therapy. *J Urol*. 2001;165:2328-2330.

²¹ Kinoshita K, Yachiku S, Sonoda T, Takeuchi M, Kotake T. [Treatment of cystinuria with α -mercaptopyropionylglycine (MPG)]. *Nihon Rinsho*. 1972;30(11):2324-2328. Japanese.

²² Lindell A, Denneberg T, Hellgren E, Jeppsson JO, Tiselius HG. Clinical course and cystine stone formation during tiopronin treatment. *Urol Res*. 1995;23(2):111-117.

²³ Rizzoni G, Pavanello L, Dussini N, Chiandetti L, Zacchello G. Nephrotic syndrome during treatment with alphanmercaptopyropionylglycine. *J Urol*. 1979;122(3):381-382.

pediatric patients less than 9 years of age, including infants and young children¹¹ (see Appendix II for a tabular summary of tiopronin treated patients from the literature based on age). Based on their review of the literature, the applicant estimates that over 200 pediatric patients have been treated with tiopronin. The applicant's review of the literature did not identify unique safety concerns in pediatric patients, or a subpopulation of pediatric patients, compared to adult patients. The adverse reactions associated with tiopronin use in pediatric patients identified in the applicant's literature search are included in the approved tiopronin IR USPI.

The literature identifies reports of specified and unspecified proteinuria, including nephrotic syndrome, in adults and pediatric patients.^{13,18,22,23,24,25,26,27} Two reports of pediatric proteinuria occurred in the setting of higher tiopronin dosing (i.e., > 50 mg/kg/day),^{18,23} and one report describes a 4 year old who developed nephrotic syndrome on tiopronin "10 mg/kg".²⁷ The proteinuria in these cases resolved after discontinuation of tiopronin. This drug-related renal adverse event may be dose-dependent,^{18,23} appears to be reversible after tiopronin withdrawal,^{22,24,25,26,27} and to usually not recur with restart of tiopronin at a lower dosage (e.g., 20 mg/kg/day).^{18,23} Although biopsies have been conducted in adult patients who developed proteinuria during tiopronin treatment, the literature reports do not identify that biopsies were conducted in pediatric patients treated with tiopronin that developed proteinuria. The adult biopsy findings reported in the literature in patients with cystinuria treated with tiopronin include "idiopathic membranous glomerulonephritis" (n=2 patients),²² "membranous nephropathy" (n=1 adult patients),²⁸ "glomerulopathy with minimum lesions" (n=1 adult patient).²⁵

Administration

FDA issued an Information Request Letter²⁹ asking the applicant to address how this product is to be administered to patients too young to swallow solid oral dosage forms. The applicant responded³⁰ that the literature provides limited information about tiopronin administration to patients unable to swallow solid oral dosage forms; however, one publication notes administration of "Thiola syrup".³¹ (b) (4)

²⁴ Asanuma H, Nakai H, Takeda M, et al. [Clinical study on cystinuria in children--the stone management and the prevention of calculi recurrence]. *Japanese Journal of Urology*. 1998;89(9):758-765. Japanese.

²⁵ Bruno M, Fruttero B, Marangella M, Linari F. [Cystinuria: clinical and therapeutic aspects]. *Boll Chim Farm*. 1982;121(2):1S-8S. Italian.

²⁶ Kallistratos G, Dimopoulos C, Kalfakakou-Vadalouka V. et al. Familial cystinuria in Ioannina District (Greece) diagnosis and treatment. *Urol. Res*. 1983;11: 291-296.

²⁷ Tasic V, Lozaonovski VJ, Ristoska-Bojkovska N, Sahpazova E, Gucev Z. Nephrotic syndrome occurring during tiopronin treatment for cystinuria. *Eur J Pediatr*. 2011;170:247-249.

²⁸ Zheng Z, Xue Y, Jia J, Weil L, Shang W, Lin S. Tiopronin-induced membranous nephropathy: a case report. *Ren Fail*. 2014;36(9):1455-1460.

²⁹ FDA issued the letter to the applicant on February 6, 2019.

³⁰ Applicant's response to the Information Request Letter submitted to FDA February 20, 2019 (eCTD Seq#: 0008).

³¹ Barbero S, Domeneghetti G, Sardi R. [Cystinuria. Description of a case]. *Minerva Pediatr*. 1979;31(3):229-233. Italian.

(b) (4) As such, the applicant proposed to conduct stability and dissolution testing of Thiola EC when crushed and mixed with applesauce to support administration to patients unable to swallow solid oral dosage forms.

FDA met with the applicant by teleconference on April 9, 2019 to discuss strategies for dosing pediatric patients unable to swallow oral dosage forms. FDA noted that because this product has orphan drug designation we cannot require, but we can encourage the applicant develop an age-appropriate formulation for young pediatric patients. FDA agreed with the applicant's proposal to conduct stability and dissolution testing of crushed Thiola EC in applesauce, but noted that an *in vivo* bioavailability study would also be required to support this method of administration (and including this administration method in labeling). (b) (4)

A limited response from an informal global survey of practicing pediatric nephrologists³⁴ suggests that tiopronin may not be used frequently in patients less than 6 years of age. Tablet crushing is possible but is reportedly associated with a foul sulfur odor which limits the palatability of the product and precludes providers from recommending product administration via this method unless necessary. The informal survey suggests that admixing³⁵ is not frequently employed.

DPMH Discussion about Pediatric Labeling for Thiola EC

Although the available dosing, efficacy, and safety data are adequate to label tiopronin for use in the full pediatric age range, the EC dosage form and 100 mg and 300 mg tablet strengths of this tiopronin product are not appropriate for use in patients weighing less than 20 kg or in patients who are unable to swallow solid oral dosage forms. Based on the proposed weight-based dosing of 15 mg/kg/day, the starting dose for a patient weighing 20 kg is 100 mg (administered three

³² Per teleconference with the applicant on April 9, 2019.

³³ OPQ Integrated Quality Review, June 5, 2019.

³⁴ In order to better understand how tiopronin is being administered to pediatric patients, Mona Khurana, MD, sent an inquiry in February 2019 to pedneph@lists.uchicago.edu. This is a listserv for the dissemination of information about the practice and science of pediatric nephrology worldwide. Dr. Khurana's inquiry received responses from 11 pediatric nephrologists. There are approximately 767 practicing pediatric nephrologists in the US (source: https://www.asn-online.org/education/training/workforce/Nephrology_Workforce_Study_Report_2014.pdf)

³⁵ Admixing is the appropriate term for "compounding".

times per day). Because the tablet is not scored and tablet splitting would result in loss of the EC properties, the dosage strengths can only provide appropriate dosing for patients weighing 20 kg or greater (see Table).

(b) (4)

Furthermore, because the currently available data do not support crushing this product and administration with a liquid or soft solid, patients must swallow the tablet whole. As such, Thiola EC is not appropriate for use in patients unable to swallow solid oral dosage forms (generally patients < 6 years of age).³⁷

DPMH Conclusions

- The available data support the safety, effectiveness, and dosing of Thiola EC in pediatric patients (b) (4).
- Based on the recommended weight-based pediatric dosing of 15 mg/kg/day, the Thiola EC 100 mg and 300 mg tablets can only provide appropriate dosing in patients weighing 20 kg or greater who are able to swallow pills.
- Data from the literature provide evidence that higher dosages of tiopronin (i.e., > 50 mg/kg/day) are associated with a greater risk of proteinuria and that this drug-related renal adverse event appears to be reversible after drug withdrawal. DCaRP should include this information in the USPI. No other safety concerns were identified in the literature that are not already addressed in labeling.
- Although data in the literature suggest that pediatric patients require higher doses based on weight compared to adults, given that tiopronin is dosed to effect and no efficacy

³⁶ Per CDC growth charts for male children. Available at: https://www.cdc.gov/growthcharts/cdc_charts.htm
Accessed January 18, 2019.

³⁷ Meltzer EO, Welch MJ, Ostrom NK. Pill Swallowing Ability and Training in Children 6 to 11 Years of Age. *Clinical Pediatrics*, 2006;45(8):725–733.

concerns were identified in the literature that are not already included in labeling, no additional labeling information about pediatric dosing or efficacy is needed.

- The limitations of the proposed dosage strengths and the dosage form likely preclude tiopronin administration to the youngest pediatric patients (i.e. patients less than 6 years of age based on weight and the ability to swallow tablets). However, the lack of an age-appropriate formulation for this age cohort does not appear to be a public health need given the rarity of cystinuria in this subpopulation and the available data suggesting that tiopronin is not frequently used in this age cohort. .
- Crushing Thiola EC and mixing it in applesauce may be a viable strategy for administering this product in patients unable to swallow tablets if results from the sponsor's planned relative BA study support acceptable relative bioavailability and palatability; however, if crushing the tablet results in a foul odor, pediatric patients may be reluctant or refuse to take the product.

DPMH Recommendations

- Label this product for use in pediatric patients with cystinuria weighing ≥ 20 kg.
- Include the following information and instructions in the USPI:
 - Patients must swallow tablets whole
 - Evaluate for proteinuria before tiopronin initiation and monitor for the development of proteinuria during treatment
 - In patients who develop proteinuria during tiopronin treatment
 - discontinue tiopronin and monitor renal function and proteinuria until resolution
 - consider restarting tiopronin at a lower dosage after resolution of proteinuria
 - Avoid tiopronin dosages greater than 50 mg/kg/day in pediatric patients due to the risk of renal toxicity, specifically proteinuria and nephrotic syndrome
- If a BA study demonstrates that Thiola EC has the same or adequately similar bioavailability to Thiola IR, include information about administration via crushing and in appropriate soft solids in the USPI.

DPMH participated in review team and labeling meetings with DCaRP and other members of the review team between January 2019 and May 2019. DPMH agrees with the May 30, 2019 draft USPI. Final labeling will be negotiated with the applicant and may not fully reflect changes reflected in this draft. DPMH's input will be reflected in the final labeling and the approval letter.

Appendix I: Number of Patients Treated with Tiopronin From Published Pediatric Clinical Studies and Case Reports: FDA Age Categorization, Source, and Dose Regimen³⁸

Age Category at Treatment	Source	Tiopronin Treatment Dose/Frequency/Duration	Number of Treated Patients
Infants (1 Month up to 2 Years of Age)	Nalcacioglu, et al., 2013	NA/NA/5 months (n = 1), 12 months (n = 1)	2
	Asanuma, et al., 1998	NA/day/~1-1.5 years	1
	Dello Strologo, et al., 2007	NA/NA/NA (follow up 38 months)	1 ^a
Children (2 up to 12 Years of Age)	Hayase, et al., 1980	5% Tiopronin, 23,500 mL/NA/47 days (bladder irrigation)	1 ^b
	Rizzoni, et al., 1979	50 mg/kg/day/3 months and later 100 mg/kg/day/NA (n = 1); ~40-80 and later 50 mg/kg/day/total of 6 months (n = 1)	2
	Tasic, et al., 2011	10 mg/kg/day/9 months	1
	Larsson, et al., 1985 (Note: Other disease)	150 mg/Day 1, 300 mg/ Day 2, and 600 mg/Day 3 (n = 1); 300 and 600 mg/day/3 months for each dose (n = 2; second phase of study)	2
	de Temple, et al., 1989	NA/NA/~20 days	1
	Bianchi and Franceschini, 1975	2 g/day/2 months	1
	Berio, 1979	500-1,000 up to 2,000 mg (dose titrated with urinary cystine)/day/7 months	1
	Kinoshita, et al., 1972	0-900 mg/day/3-14 days; later 0-1,200/day/7 months	2
	Tizzani, et al., 1976	2000 mg/day/~3.5 months	1
	Dello Strologo, et al., 2007	NA/NA/NA (follow up 14-86 months)	6 ^c
	Barbero, et al., 1979	NA/NA/4 months (syrup)	1
	Araki, et al., 1981	0.1 g/day/19 months (n = 1); 0.5 g reduced to 0.4 g/day/ 19 months (n = 1); 1.6 g/day/41 months (n = 1)	3

³⁸ Table 26 from the Summary of Clinical Safety (Module 2.7.4)

Age Category at Treatment	Source	Tiopronin Treatment Dose/Frequency/Duration	Number of Treated Patients
Adolescents (12 Years up to 16 Years of Age)	de Temple, et al., 1989	NA/NA/3 months	1
	Carratù, et al., 1977	100 mg/kg/day reduced to 75 mg/kg/day after <3 months/day/8 months	1
	Berio, 1979	500-1,000 up to 2,000 mg (dose titrated with urinary cystine)/day/NA	1
	Dello Strologo, et al., 2007	NA/NA/NA (follow up 12-86 months)	3 ^c
	Kinoshita, et al., 1972	0-1,200 mg/day/3-14 days (n = 2); later 0-1,200/day/7 months (n = 1)	2
	Araki, et al., 1981	1.6 g/day/63 months	1
Infants and Children (1 Month up to 12 Years of Age)	Pavanello, et al., 1981	5-100 mg/kg/day/22-65 months	7
	Dello Strologo, et al., 2007	NA/NA/NA (follow up 12-86 months)	6 ^c
	Spacagna, 1978 (Note: Other disease)	100-800 mg/day/6-20 days (IM, Inh, IM + Inh)	24
Children and Adolescents (2 up to 16 Years of Age)	Yuruk, et al., 2017	20 mg/kg/day/25.7 ± 5.2 (9-69) months	4
	Costantini, et al., 1982 (Note: Other disease)	150 mg/ Twice daily/9 days (inhaled via nebulizer)	8
	Gargani, et al., 1980 (Note: Other disease)	400 mg/day/20 days (IM) and NA/Day/20 days (Inh) (n = 9); 200 mg day/14 days (IV with antibiotic) and NA/Day/14 days (Inh) (n = 16)	25
	Araki, et al., 1981	0.1 g/day/19 months (n = 1); 0.5 g reduced to 0.4 g/day/19 months (n = 1); 1.6 g/day/63 months (n = 1); 1.6 g/day/41 months (n = 1)	4
	Dello Strologo, et al., 2007	NA/NA/NA (follow up 12-86 months)	11 ^c

Age Category at Treatment	Source	Tiopronin Treatment Dose/Frequency/Duration	Number of Treated Patients
Pediatrics (All Ages)	Öner, et al., 1997	NA/NA/NA	2
	Tekin, et al., 2001	10-15 mg/kg/day/median 15 (3-35) months	18
	Daudon, et al., 2003	Tiopronin/ Median 1,000 mg (500-1500)/day/NA	15 ^d
	Dello Strologo, et al., 2007	NA/NA/NA (follow up 12-86 months)	11 ^c
	Kim, et al., 2017	2.6-10.5 mg/kg/day/ 3.8-13.8 years	7
	Precchia, et al., 1977 (Note: Other disease)	~300-1,000 mg/day/ 3 months	50
	Laurenti, et al., 1984	50-60 mg/kg/day/ 3-6 months (calculolytic therapy); 30 mg/kg/day/NA (Preventative therapy)	14 ^e
	Asanuma, et al., 1998	25-3600 mg/day/NA (follow up 3 months-16 years)	10 ^f
	Araki, et al., 1981	0.1 g/day/19 months (n = 1); 0.5 g reduced to 0.4 g/day/ 19 months (n = 1); 1.6 g/day/ 63 months (n = 1); 1.6 g/ day/41 months (n = 1)	4
Pediatrics and Adults	Dello Strologo, et al., 2007	24.65 (13.8-51) mg/kg/day/ median 36 (12-86) months	18 ^c
	Pak, et al., 1986	100-2,000 mg/day/ 4-36 months	66
	Chow and Stroom, 1996	800-1,200 mg/day/ 7-141 months	14 ^d
	Pierides and Deltas, 1997	NA/NA/NA (follow up ~12 years)	9 ^g
	Onal, et al., 2013	10 mg/kg/NA/95 (6-136) months	35
	Kallistratos, et al., 1983	300 mg (initial dose), 1,200 mg (maximal dose), or NA (maintenance dose)/day/NA	3 ^h
	Kinoshita, et al., 1972	0-1,600 mg/day/3-14 days (n = 13); later 0-1,600/day/ 6-23 months (n = 7)	13 ⁱ
	Bruno, et al., 1982	1-2 g, further reduced to 1 g/day/NA	36
	Pontoni, et al., 2000	20-30 mg/kg/day/>2 years (>50 months in 5 patients)	10
	Araki, et al., 1981	0.1-2.8 g/day/19-70 months	21 ^j
	Daudon, et al., 2003	Tiopronin/ Median 1,000 mg (500-1500)/day/NA	57 ^d

IM = Intramuscular; Inh = Inhalation.

- a One patient or none aged from 1 month to 2 years was treated with tiopronin; it is unknown whether this patient received D-penicillamine instead of tiopronin.
- b Tiopronin was used for bladder irrigation.
- c It is unknown whether 1 or 2 of the patients received D-penicillamine instead of tiopronin.
- d Patient number for tiopronin or D-penicillamine treatments.
- e The patients were children, but the age was not specified. One patient had gastric intolerance to tiopronin and treatment was changed to D-penicillamine.
- f Pediatrics, age not specified.
- g No information on age was provided; it was assumed that the tiopronin treated patients were a mixed population.
- h Total of 210 patients included 3 Thiola-treated males with cystinuria and urolithiasis of unknown age (1 known adult; 2 in which pediatric or adult status cannot be determined) and urine-tested untreated patients with and without cystinuria.
- i Four pediatric patients included.
- j Four of the 21 adult patients received tiopronin for a brief period of time; for 2 of them treatment was stopped due to rash and for the third case, per patient request (wish to become pregnant). The fourth patient had low cystine urine excretion (<200 mg/day) and tiopronin was not further administered.

Appendix II: Number of Patients Treated with Tiopronin from Published Pediatric Clinical Trials and Case Reports Based on FDA Age Categorization³⁹

Age Category at Treatment	Number of Treated Patients^a
Infants (1 Month up to 2 Years of Age)	4
Children (2 up to 12 Years of Age)	22
Adolescents (12 Years up to 16 Years of Age)	9
Infants and Children (1 Month up to 12 Years of Age)	37
Children and Adolescents (2 up to 16 Years of Age)	52
Pediatrics (All Ages)	131
Pediatrics and Adults	282

a. A patient can be counted in more than 1 category.

³⁹ Table 25 from the Summary of Clinical Safety (Module 2.7.4). It is unclear to me why the applicant organized the table in these age groups.

APPEARS THIS WAY ON ORIGINAL

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Review

Date: May 23, 2019 **Date consulted:** September 25, 2018

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: THIOLA EC (tiopronin), enteric coated, delayed-release tablets

NDA: 211843

Applicant: Mission Pharmacal Company

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Indication: for the prevention of cystine (kidney) stone formation in patients with severe
homozygous cystinuria (b) (4)
[REDACTED] high fluid intake, alkali and
diet modification, (b) (4)
[REDACTED]

**Materials
Reviewed:**

- August 31, 2018, 505(b)(2) submission for Thiola EC tablets, NDA 211843
- September 25, 2018, DPMH consult for NDA 211843, DARRTS Reference 4325409
- May 21, 2019, submission for Thiola EC tablets, NDA 211843, Clinical Information Amendment

Consult Question: “Please evaluate the submitted data on use/risks of tiopronin during pregnancy, lactation and reproductive risks and comment on proposed labeling describing those risks (PLLR conversion) in the Thiola EC label.”

INTRODUCTION AND BACKGROUND

On August 31, 2019, Mission Pharmacal Company submitted a 505(b)(2) New Drug Application for Thiola EC (tiopronin) 100 and 300 mg tablets, delayed release, 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 enteric coated tablet is a new delayed release formulation as the currently approved tiopronin is an immediate release formulation. (b) (4)

The Division Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 25, 2018, to assist with the Pregnancy and Lactation subsections of labeling. The listed drug-relied upon, Thiola (tiopronin) immediate release tablets NDA 19569, was originally approved on August 11, 1988.

- Tiopronin is an active reducing agent that undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of thiola-cysteine. This reaction causes a water-soluble mixed disulfide to form and reduces the amount of sparingly soluble cystine. Tiopronin has the following drug characteristics:
 - 163.20 Daltons
 - Peak plasma concentration range of 3-6 hours based on a single dose with food
 - Bioavailability of 97%
 - Severe adverse reactions: hematologic toxicity (aplastic anemia, agranulocytosis, and thrombocytopenia), which can result in death; proteinuria with nephrotic syndrome
 - Common adverse reactions include nausea, diarrhea, soft stools, oral ulcers, rash, fatigue, fever, arthralgia, proteinuria and emesis.

Current State of the Labeling

The Listed Drug label is not in the Physicians Labeling Rule (PLR) format or the PLLR format.

- There is a contraindication with regard to tiopronin exposure during pregnancy, “except in those with severe cystinuria where the anticipated benefit of inhibited stone formation
- clearly outweighs the possible hazards of treatment.” In addition, labeling notes that “Mothers maintained on THIOLA treatment should not nurse their infants.”
- There are no human data; however, there are animal data.
- There are no existing pregnancy testing/contraception recommendations.
- There are no known drug-drug interactions with hormonal contraceptives.

REVIEW

PREGNANCY

Cystinuria and Pregnancy

- Cystinuria is a rare inherited metabolic disorder that affects males and females equally. People with cystinuria expel unusually high levels of cystine in the urine.¹
- Individuals with cystinuria typically form small, jagged crystalline stones. This causes sharp pains in the lower back or side of the abdomen and can also cause blood in the urine or infections in the urinary tract.¹
- Standard treatment includes large amounts of fluids, and urinary alkalinization, in order to help cystine dissolve readily in the urine in order to prevent the formation of stones.¹
- Another treatment option includes administration of D-penicillamine. Although D-penicillamine has been shown to cause skeletal defects and cleft palates in the fetuses of pregnant rats who were administered the drug at 10 times the recommended human dose,¹ these effects have not been observed in human fetuses according to limited published literature.

Renal Stones and Pregnancy

The presence of renal stones in pregnant women has been associated with an increase in the risk of adverse outcomes such as premature rupture of membranes, spontaneous abortion, pre-eclampsia, hypertension, gestational diabetes mellitus, and caesarean deliveries.^{2,3,4,5} However, these findings are not seen consistently among the various studies and the data are conflicting.⁶ Low birth weight and preterm delivery have also been reported in pregnant women with renal stones throughout published literature and this data appears consistent among the various publications. Preterm delivery rates range between 2.5 and 40% throughout published literature.^{3,4,6,7,8,9}

Nonclinical Experience

In animal reproduction studies, there was no evidence of teratogenicity with administration of tiopronin to pregnant mice and rats during organogenesis at doses up to 10 times the highest recommended human dose; however, high doses have been shown to interfere with maintenance of pregnancy and viability of the fetus. The reader is referred to the Pharmacology/Toxicology review by Rama Dwivedi, Ph.D., DARRTS.

¹ Cystinuria. National Organization for Rare Disorders. <https://rarediseases.org/rare-diseases/cystinuria/>. Accessed 26 April 2019.

² Rosenberg, et al. Nephrolithiasis during pregnancy: characteristics, complications, and pregnancy outcomes. *World J Urol*. 2011. 29(6): 743-747. *Acta Obstet Gynecol Scand*. 2013 Jan;92(1):69-74

³ Chung, et al. Urinary calculi increase the risk for adverse pregnancy outcomes: a nationwide study. *Obstet Gynecol*. 2007 May;109(5):1099-104.

⁴ Swartz et al. Admission for nephrolithiasis in pregnancy and risk of adverse birth outcomes.

⁵ Bánhidý F, Acs N, Puhó EH, et al. Maternal kidney stones during pregnancy and adverse birth outcomes, particularly congenital abnormalities in the offspring. *Arch Gynecol Obstet* 2007; 275: 481–487.

⁶ Meher S et al. Renal stones in pregnancy. *Obstet Med*. 2014, 7(3):103-110.

⁷ Drago JR, Rohner TJ, Chez RA. Management of urinary calculi in pregnancy. *Urology* 1982; 20: 578–581.

⁸ Hendricks SK, Ross SO, Krieger JN. An algorithm for diagnosis and therapy of management and complications of urolithiasis during pregnancy. *Surg Gynecol Obstet* 1991; 172: 49–54.

⁹ Stothers L, Lee L. Renal colic in pregnancy. *J Urol* 1992; 148: 1383–1387.

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature. The reader is referred to the applicant's submission for specific search parameters. In one publication by Araki et al (1981),¹⁰ 17 subjects were treated with tiopronin and five subjects were treated with hydration only for cystinuric stones. One of the adult subjects (24-year-old female) was pregnant during treatment and received tiopronin 0.8 g/day through gestational month three. She delivered a set of healthy twins with no abnormalities reported. No further information was provided.

Drug Utilization Rates in Females of Reproductive Potential

The applicant provided a summary of drug utilization rates amongst females of reproductive potential (ages 15 to 44). Estimates were provided based on tablet manufacturing data from initial approval in 1988 through 2013. Data from 2014 to 2019 was provided from recent marketing demographic data. According to estimate calculations, from 1988 to 2013, approximate use of tiopronin in females of reproductive potential was (b) (4) females per year for the first five years followed by (b) (4) females per year from 1993 to 2013. In addition, the applicant estimates that approximately (b) (4) females of reproductive potential received tiopronin between the years 2014 to present. See Table 1 below for more details.

Table 1. Tiopronin drug utilization rates among all patients and women of childbearing age (WCBA) from 2014 to 2019* (corresponds to Table 1, page 4, applicant's May 21, 2019 submission)

Year	All Patients	WCBA Patients
2014	(b) (4)	(b) (4)
2015		
2016		
2017		
2018		
2019 ^a		
^a Reported to date		

*2019 includes data for only part of the year

DPMH's Review of Literature

DPMH conducted a review of published literature using PubMed and Embase regarding tiopronin exposure during pregnancy using the following search terms, "tiopronin and fetal malformations," "tiopronin and spontaneous abortion and miscarriage," "tiopronin and embryo-fetotoxicity. No additional data were found. Also, no additional information was found for review in Micromedex or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.

¹⁰ Araki T et al. Treatment of Cystine Calculi with Tiopronin. The Japanese Journal of Urology. 1981, 72(2):221-236.

Reviewer comment:

The applicant provided an adequate review of the literature to address the PLLR requirements with regard to tiopronin exposure during pregnancy. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

There are no available animal data with regard to tiopronin and animal milk.

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature. The reader is referred to the applicant's submission for specific search parameters. A publication by Akrivis et al. (2000),¹¹ measured the effects of orally administered tiopronin on the suppression of lactation and plasma prolactin in a group of women in the puerperium, a period of 6 weeks after childbirth. A total of 100 women ages 17 to 37 were enrolled in the study into four different groups (25 in each group). None of the women in the study wished to breastfeed for various reasons. Group I consisted of women who received no medication but had restricted fluid intake, ice-bags applied to the breasts and tight breast binders. Group II consisted of those who received tiopronin (200 mg/day) for 14 days. Group III consisted of women who received tiopronin (500 mg/day) for 14 days. Group IV consisted of women who received bromocriptine (5 mg/day) for 14 days. Suppression of lactation was measured before and after days 1, 2, 3, 4 and 14 of treatment. Significantly higher percentages of lactation suppression were measured in the tiopronin group at 84% (200mg/day group) and 88% (500mg/day group) and in the bromocriptine group at 96% compared to group I (60%). During treatment, there was a statistically significant decrease in prolactin levels in all four groups; however, in women who received tiopronin and bromocriptine, the levels of prolactin after 14 days of therapy were lower compared to group I. The authors concluded that administration of tiopronin in low to moderate doses was effective in suppressing lactation. The study is limited by the small number of subjects enrolled in each group, which makes it difficult to draw definite conclusions. See Table 2 below.

¹¹ Akrivis C et al. Inhibition of puerperal lactation with 2-mercaptopropionyl-glycine. Eur J Clin Pharmacol. 2000. 56: 621-623.

Table 2. Serum prolactin levels (ng/ml) in the four groups during treatment [corresponds to Table 1, page 2, Akrivis et al (2000)¹¹]

Group	Baseline	Day 1	Day 2	Day 3	Day 4	Day 14
I	128 (44)	112 (39)	107 (35)	109 (43)	93 (34)	56 (34)
II	125 (53)	95 (52)	96 (50)	84 (47) ^b	69.9 (31) ^b	32 (29) ^c
III	117 (50)	117 (51)	89 (49)	81 (46) ^b	78 (50) ^b	21 (12) ^c
IV	119 (57) ^a	32 (34) ^a	24 (38) ^a	12 (9) ^a	21 (29) ^a	17 (16) ^{d, e}

All values are expressed as mean (± SD). Group I (women treated with conservative measures), Group II (women treated with 200 mg/day of 2-MPG), Group III (women treated with 500 mg/day of 2-MPG), and Group IV (women treated with bromocriptine)

^a $P < 0.001$ compared to group I, II, III

^b $P < 0.05$ compared to group I

^c $P < 0.02$ compared to group I

^d $P < 0.001$ compared to group I

^e $P < 0.05$ compared to group II

DPMH review of literature

DPMH conducted a review of published literature with regards to tiopronin and breast milk, and no data were found. Also, there are no additional data found in *LactMed*, *Medication and Mothers Milk*, or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.

Reviewer comment:

The applicant conducted a review of the literature to address the PLLR requirements with regard to tiopronin and breastfeeding. The applicant submitted one article that studied the effects of tiopronin on lactation suppression; however, this study was conducted in women immediately after birth who were not breastfeeding. Drug levels in milk were not measured in this study. Instead the study evaluated serum levels of prolactin and effects on milk suppression. The study is limited by the small number of women enrolled in each group.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In two published animal fertility studies, rats were administered tiopronin 20 mg/kg/day intramuscularly (IM) for 60 days; tiopronin interfered with male infertility causing reductions in testis, epididymis, vas deferens, and accessory sex glands weights and in the count and motility of cauda epididymal sperm. Histological and morphological changes were noted in reproductive organs. The reader is referred to the Pharmacology/Toxicology review by Rama Dwivedi, Ph.D., DARRTS.

Review of Literature

The applicant and DPMH conducted a review of the literature that revealed no clinical data regarding tiopronin exposure and effects on fertility.

Reviewer comment:

The applicant conducted a review of the literature to address the PLLR requirements with regards to tiopronin and females and males of reproductive potential, and no clinical data were found. After discussion with the DCRP Pharmacology/Toxicology team it was decided that the nonclinical fertility data are not clinically relevant since the drug was given via IM administration in rats and is administered orally in humans. In addition, the Pharmacology/Toxicology team was unable to calculate human dose multiples. See the Discussion and Conclusions section below for further information.

DISCUSSION AND CONCLUSIONS

Pregnancy

In animal reproduction studies in pregnant rats and mice administered tiopronin at 10 times the recommended human dose, teratogenicity was not observed; however, high doses have been shown to interfere with maintenance of pregnancy and viability of the fetus. In a published case report, a pregnant woman who received tiopronin 0.8 g/day through gestational month three delivered a set of healthy twins with no abnormalities reported. There are not enough data to draw conclusions on drug associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Lactation

There are no data on the presence of tiopronin in either human or animal milk or on the effects of the breastfed child. There is one publication that suggests that tiopronin may suppress lactation. however, the study was conducted in a small number of women. Current labeling contraindicates breastfeeding with use of Thiola due to the potential for hematologic toxicity. Given the drug's characteristics (molecular weight <800 Daltons), it is possible that the drug will be present in human milk. Given the potential for hematologic toxicity, DPMH recommends that breastfeeding is not recommended during Thiola use.

Females and Males of Reproductive Potential

There are no human data on the effects of tiopronin on females and males of reproductive potential. Although published animal fertility studies suggest that male rat fertility may be affected with tiopronin use, a different route of administration was used in animals and a human dose multiple could not be calculated. After discussion with the DCRP Pharmacology/Toxicology team, it was decided that the nonclinical fertility data are not clinically relevant and will be summarized in subsection 13.1. Subsection 8.3 Females and Males of Reproductive Potential will be omitted from labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

Lactation: Breastfeeding is not recommended (8.2).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available published case report data with tiopronin over decades of use have not identified a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Renal stones in pregnancy may result in adverse pregnancy outcomes (*see Clinical Considerations*). In animal reproduction studies, there were no adverse developmental outcomes with oral administration of tiopronin to pregnant mice and rats during organogenesis at doses (b) (4) times the recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Renal stones in pregnancy may increase the risk of adverse pregnancy outcomes, such as preterm birth and low birth weight.

Data

Animal Data

[Refer to the Pharmacology/Toxicology review]

8.2 Lactation

Risk Summary

There are no data on the presence of tiopronin in either human or animal milk or on the effects of the breastfed child. (b) (4) published study suggests that tiopronin may suppress milk production. Because of the potential for serious adverse reactions, including (b) (4) (b) (4) advise patients that breastfeeding is not recommended during treatment with Thiola.

17 PATIENT COUNSELING INFORMATION

Lactation: Advise women that breastfeeding is not recommended during treatment with Thiola [*see Use in Specific Populations (8.2)*].

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/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 22, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 211843
Product Name and Strength:	Thiola EC (Tiopronin) Enteric-coated, Delayed-release Tablets, 100 mg and 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mission Pharmacal Company (Mission)
FDA Received Date:	August 31, 2018
OSE RCM #:	2018-1937
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 REASON FOR REVIEW

As part of the New Drug Application (NDA) review, this review evaluates the proposed Thiola EC container labels and prescribing information (PI) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Thiola EC (tiopronin) enteric-coated, delayed-release tablets 100 mg and 300 mg were developed by Mission as an enteric-coated tablet (b) (4). In addition, the 300 mg tablet provides a lower number of tablets per dose. The approved indication remains unchanged from the original Thiola tablets.

The approved Thiola Prescribing Information (PI) (NDA 019569) served as the basis for the Thiola EC PI. The PI is specific to Thiola EC as it contains new clinical pharmacokinetic study information, updated data from literature and pharmacovigilance information, and is incorporated into the Physician Labeling Rule (PLR) format.

Mission intends to introduce the Thiola EC into the marketplace upon notification of approval by the FDA. (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials submitted found the proposed container labels and PI may be improved to promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

The proposed Thiola EC (tiopronin) prescribing information and container labels can be improved to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. General Comments

- a. We note that the terms “enteric-coated” and “delayed-release” are

(b) (4)

- b.

(b) (4)

2. Dosage and Administration Section

- a. Consider stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100”.

- b.

(b) (4)

^a Mission Pharmcal Company. Clinical Information Amendment: Response to FDA Information Request Dated February 6, 2019. San Antonio (TX): Mission Pharmcal Company. 2019 FEB 21. Available from: \\cdsesub1\evsprod\nda211843\0008\m1\us\111-information-amendment\clinical-information-amendment-2019-02-20.pdf

- c. We recommend including the response to FDA Comment 3 provided in the Information Request Response^b t (b) (4)

4.2 RECOMMENDATIONS FOR MISSION PHARMACAL COMPANY (MISSION)

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. Assigning National Drug Codes with sequential drug product codes (middle digits) for different strengths of the same drug product do not adequately distinguish the products. The middle digits are traditionally used by healthcare providers to check the correct product and strength, and so similarity of product code numbers has led to selection and dispensing errors of the wrong strength. To better differentiate National Drug Codes, we recommend changing the product codes (middle digits) so that they are not sequential. Alternatively, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits or format them in bold type.^c
2. Revise the principal display panel (PDP) to provide adequate strength differentiation to prevent wrong strength selection medication errors, by:
 - a. Change one or both background colors highlighting the strengths “100 mg” and “300 mg” to provide adequate color differentiation between the strengths. As currently presented, the (b) (4) (100 mg) and (b) (4) (300 mg) background colors do not provide adequate color differentiation.
 - b. Remove the redundant word “Tablets” from the proposed strength statements “100 mg Tablets” and “300 mg Tablets”. The dosage form is already presented as a part of the established name on the PDP.
 - c. Display the strength statement with adequate prominence. Because there is numerical overlap (300) in your proposed 100 mg in 300-count and the 300 mg product, present the strength in adequate prominence on the PDP to prevent wrong selection errors due to confusion between the strength and quantity statement. Alternatively, you may consider changing the net quantity of the 100 mg tablets so there’s no numerical overlap with the strength “300 mg”. If more space is needed to display the strength statement in adequate prominence, then relocate the statement “Distributed by Retrophin, Inc.” to a side panel.

^b Mission Pharmacal Company. Clinical Information Amendment: Response to FDA Information Request Dated February 6, 2019. San Antonio (TX): Mission Pharmacal Company. 2019 FEB 21. Available from: \\cdsesub1\evsprod\nda211843\0008\m1\us\111-information-amendment\clinical-information-amendment-2019-02-20.pdf

^c Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

- d. Consider relocating the strength statement to directly below the established name. We recommend that the PDP include critical information such as proprietary name, established name, and product strength, usually displayed in this order, as the most prominent information on the PDP.

Example layout below is just to demonstrate our recommendations above, not true to font type, size, or color.



3. Ensure the container labels contain a linear barcode per 21 CFR 201.25.
4. Ensure that the lot number and expiration date are presented on container labels and carton labeling per 21 CFR 201.10(i) and 21 CFR 201.17. We recommend the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the

expiration date.^d Ensure that the expiration date is clearly differentiated from the lot number.^e

5. Revise the statement: (b) (4),” to read
“Usual dosage: See prescribing information”.
6. Remove the statement: (b) (4)
(b) (4) to ensure that patients receive the correct number of tablets based on their individualized dose, and for consistency with the proposed PI (Section 16 does not mention storing in original container). If a pharmacy receives a prescription for less than the package size, there will be a delay in therapy as the pharmacy contacts the prescriber to change the quantity.
7. Remove the statement (b) (4) because the package insert (assuming it refers to the Prescribing Information) is intended for healthcare professionals but (b) (4) is to patients, for which this package insert is not intended. If you wish to retain the statement, then please provide your rationale for retaining the statement.
8. The 2D matrix barcode is not present in alignment with the Drug Supply Chain Security Act (DSCSA). We recommend you add a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (e.g. carton labeling) for tracking and tracing purposes. The human readable portion should be located near the 2D data matrix barcode and have the following format^f:

NDC: [insert product’s NDC]
SERIAL: [insert product’s serial number]
LOT: [insert product’s lot number]
EXP: [insert product’s expiration date]

^d Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

^e Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

^f Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Thiola EC received on August 31, 2018 from Mission Pharmacal Company (Mission).

Table 2. Relevant Product Information for Thiola EC	
Initial Approval Date	N/A
Active Ingredient	Tiopronin
Indication	Thiola is indicated for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria with (b) (4) high fluid intake, alkali and diet modification, (b) (4)
Route of Administration	Oral
Dosage Form	Enteric-coated, Delayed-release Tablets
Strength	100 mg and 300 mg
Dose and Frequency	• THIOLA EC may be initiated at a dosage of 800 mg/day in adult patients with cystine stones. In a multiclinic trial, average dose of THIOLA was about 1,000 mg/day. (b) (4) • In children, initial dosage may be based on 15 mg/kg/day. Whenever possible, THIOLA EC should be taken in 3 divided doses with or without food at the same times each day. • (b) (4) • In patients who had shown severe toxicity to D-penicillamine, THIOLA EC might be initiated at a lower dosage. Urinary cystine should be measured at 1 month after THIOLA EC treatment, and every 3 months thereafter. THIOLA EC dosage should be readjusted depending on the urinary cystine value. In vitro dissolution experiments indicate that alcohol may shorten the extended release of Thiola EC.
How Supplied	THIOLA EC is an enteric-coated, delayed release tablet available for oral administration as 100 mg (NDC 0178-0902-01) and 300 mg (NDC 0178-0901-90) tablets. Thiola EC 100 mg tablets are in bottles of 300 tablets. Each 100 mg tablet is imprinted with

	“T1” on one side with red ink and blank on the other side. Thiola EC 300 mg tablets are in bottles of 90 tablets. Each 300 mg tablet is imprinted with “T3” on one side with red ink and blank on the other side.
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	Thiola EC Tablets 100 mg and 300 mg are packaged in a 100 cc, white, high density polyethylene (HDPE) bottle, a (b) (4) closure with an induction inner seal, and a silica gel/carbon desiccant pak.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 2, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Thiola and tiopronin. Our search did not identify any previous labels and labeling review.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On January 2, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin
Search Strategy and Terms	Boolean Query: “Thiola” OR “tiopronin”

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Thiola.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On January 3, 2019, we searched FAERS using the criteria in the table below and identified 279 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[§] We excluded 236 cases because they were coded as “Product Dose Omission” and were not relevant to the label or labeling.

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	Approval to 1/1/19
Product Name:	Thiola
Product Active Ingredient (PAI):	tiopronin
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified 279 cases, of which there were no errors relevant for this review.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

[§] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^h along with postmarket medication error data, we reviewed the following Thiola EC labels and labeling submitted by Mission Pharmacal Company (Mission).

- Container labels received on August 31, 2018.
- Prescribing Information (Image not shown) received on August 31, 2018

G.2 Label and Labeling Images

(b) (4)



^h Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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