



PATIENT ENROLLMENT FORM
PHONE: 844-4-THIOLA (844-484-4652) — FAX: 877-473-3167
For electronic version, visit www.THIOLAECHub.com

STEP 1: PATIENT INFORMATION

Name: (First) (Middle) (Last)

Sex: Male Female DOB: Weight:

Address:

City: State: Zip Code:

Phone: Mobile Phone:

Method of Contact: Phone Mobile Phone E-mail: Best Time to Call:

FOR PATIENTS UNDER 18:

Parent/Guardian Name: (First) (Middle) (Last)

Address:

City: State: Zip Code:

Phone: Mobile Phone:

STEP 2: PRESCRIBER INFORMATION

Prescriber Name: (First) (Last)

Email: State License #:

Prescriber Address:

Prescriber Address #2:

City: State: Zip Code:

Phone: Fax: NPI #:

Physician Office Contact: Phone:

Please complete and return Pages 1 and 2 of this form to THIOLA EC® (tiopronin) Total Care Hub by faxing to (877) 473-3167

Please see accompanying full Prescribing Information on back.

THIOLA EC® is a registered trademark of Mission Pharmacal Company.

STEP 3: PRESCRIPTION INFORMATION

Rx THIOLA EC® (tiopronin) delayed-release tablets Date:

DIAGNOSIS INFORMATION (This medical form is for insurance purposes only, not to suggest approved uses for promotion)

Diagnosis Cystinuria ICD-10-CM Code: E72.01
Other Diagnosis ICD-10-CM Code:

THIOLA EC (tiopronin) Prescription

300 mg EC tablet
tablets taken times a day OR other dose/frequency
Dispense 30 day supply No. of refills

100 mg EC tablet
tablets taken times a day OR other dose/frequency
Dispense 30 day supply No. of refills

Take with food

Recommended Initial Dosage\* - Given in 3 divided doses

Adult Dosage: 800 mg/day Pediatric Dosage(≥ 20 kg): Based on 15 mg/kg/day

Average adult dose was 1000mg/day in a clinical study

Please attach most recent 24-hour urine test results

\*Please see accompanying full Prescribing Information for Indications, complete Dosing Information and Important Safety Information. NY Prescribers please submit prescription on an original NY State prescription blank. For all other states, if not faxed, prescription must be submitted on a state-specific blank, if applicable for your state. If required by your state, please indicate:

PRESCRIBER AUTHORIZATION — Required

Prescriber's full, usual, and actual signature is required-no stamps. This form cannot be processed without the prescriber's signature.

By signing below, I certify that (a) the above therapy is medically necessary and that I will supervise the patient's treatment accordingly; (b) I have received the necessary authorizations, including those required by state law and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), to release the above information and other health and medical information of the patient to Travers Therapeutics, Inc. (Travers), and the company or companies that help Travers administer the THIOLA EC® Total Care Hub services; (c) I am prescribing the drug listed for the patient listed in this application based upon my independent medical judgment. By my signature below, I agree to receive certain reimbursement support services on behalf of the patient. I authorize Travers and Eversana Life Science Services ("Eversana"), acting on behalf of Travers, to use the information contained in the prescription above, my name, and the name, address, and telephone number of my medical practice, and other applicable information, in order to provide me, my practice, and the patient listed in this application with the aforementioned reimbursement support services. I understand that participation in the THIOLA EC® Total Care Hub services described does not constitute a guarantee on the part of Travers or parties acting on its behalf that (1) the drug I have prescribed will be reimbursed by the patient's or any insurance program, or (2) the patient will be eligible for any patient assistance program. I appoint Travers and its agents to convey this prescription—electronically or otherwise—to the dispensing pharmacy.

Prescriber Signature: (No stamps permitted; prescription will be dispensed as written unless otherwise noted)

Date:

Complete Information on following page ->

➔ Patient Name: \_\_\_\_\_  
(First) (Middle) (Last)

Patient DOB: \_\_\_\_\_

**PRIMARY INSURANCE — Please attach a copy of both sides of the patient’s insurance card**

Insurance Carrier: \_\_\_\_\_ Phone: \_\_\_\_\_

Subscriber Name: \_\_\_\_\_

Subscriber Date of Birth: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Relationship to Subscriber:  Self  Spouse  Child  Other: \_\_\_\_\_

Employer Name: \_\_\_\_\_ ID Number: \_\_\_\_\_

Policy #: \_\_\_\_\_ Group ID #: \_\_\_\_\_

**PHARMACY BENEFITS-PRESCRIPTION DRUG CARD**

Insurance Carrier: \_\_\_\_\_ Phone: \_\_\_\_\_

Rx BIN: \_\_\_\_\_ Rx PCN: \_\_\_\_\_

Rx ID #: \_\_\_\_\_ Group #: \_\_\_\_\_

(Pharmacy Benefits) section: \_\_\_\_\_

**PATIENT AUTHORIZATION—HIPAA Release**

[Before signing, the patient and/or patient’s authorized representative should review and understand the terms of this Authorization and Release (“Authorization”) before signing. *If an authorized representative signs for the patient, please indicate the relationship to the patient.*]

I understand that the collection, use, and disclosure of the patient’s health information are protected under law. Information contained in this Patient Enrollment Form, such as the patient’s name, address, insurance, prescription, and medical information, is “protected health information” (“PHI”). By signing this Authorization, the patient agrees to the collection, use, and disclosure of the patient’s PHI as described below.

**I understand that I may decline to sign this Authorization, and that doing so will not affect the patient’s ability to receive THIOLA EC® (tiopronin) or obtain insurance or insurance coverage.**

I understand that once PHI about the patient is released based on this Authorization, federal privacy laws may not prevent Travers Therapeutics, Inc. (“Travers”) and company or companies who administer the THIOLA EC Total Care Hub Support Services (“Services”) from further disclosing my information. However, I understand that such entities have agreed to use or disclose PHI they receive only for the purposes described in this Authorization or as required by law.

I also understand that I may revoke (withdraw) this Authorization at any time by sending a signed, written statement to the THIOLA EC Total Care Hub by faxing it to (877) 473-3167.

Revoking this Authorization will prohibit PHI disclosures after the date written revocation is received by the THIOLA EC Total Care Hub, except to the extent that action has been taken already on this Authorization. After I revoke this Authorization, the patient’s PHI may be disclosed among Travers and the company or companies that help Travers administer the Services in order to maintain records of the patient’s participation, but it will not be otherwise disclosed or used. Further information on Travers’s privacy practices can be found at <https://travers.com/privacy/>.

I understand that the pharmacy who may administer some of the Services may receive payment from Travers in exchange for securely sharing the patient’s PHI with companies who administer the Services.

By signing below, I authorize Travers Therapeutics, Inc. (“Travers”) and the company or companies that help Travers administer the Services, to do the following:

1. Request and receive information from the patient’s treating physician, healthcare provider, health insurer, or pharmacist necessary to investigate and resolve the patient’s insurance coverage, coding, or reimbursement inquiry or to provide the reimbursement support service that I have requested. Information may include the patient’s medical diagnosis, condition, and treatment (including prescription information), the patient’s health insurance, name, address and telephone number;
2. Collect, use, and disclose to each other any patient information including patient name, contact information, date of birth, information related to disease, diagnosis, and treatment, medical insurance information, some of which may be considered PHI or consumer health data as defined by applicable law, for the purpose of investigating and resolving the patient’s insurance coverage, coding, or reimbursement inquiry or to administer the Services, including entering and maintaining the patients in a database;
3. Disclose patient information as described above with Travers’s service providers, contractors, analytics service providers and business partners, including our business partners who support our research, surveys, focus groups, or interviews related to cystinuria and the effectiveness of the THIOLA EC Total Care Hub program;
4. Disclose patient information as described above to the patient’s treating physician, healthcare professional, health insurer or pharmacist as necessary to resolve the patient’s insurance coverage, coding, or reimbursement inquiry. The patient authorizes their health insurer, treating physician, healthcare provider, or pharmacist to release PHI about the patient’s prescribed medications and medical condition requested by Travers and the company or companies that help Travers administer the Services;
5. Contact me by mail, email, telephone or alternative communication to discuss and receive marketing communications, invitations to participate in research, educational materials, treatment support services and patient engagement initiatives designed for people taking THIOLA EC, including nutritional support and counseling;
6. Provide financial assistance resources, including copay assistance or free drug programs if I meet program eligibility;
7. Communicate with my healthcare providers and health plans about my insurance benefit and coverage status and product administration (e.g., prescription, dosing, refills) and;
8. Contact the patient’s insurer, other potential funding sources, social workers, patient advocacy organizations, or patient assistance programs (e.g., the THIOLA EC Total Care Hub) on the patient’s behalf to determine if the patient may be eligible for health insurance coverage or other funds, and disclose to them PHI about the patient’s prescribed medications and medical condition that has been provided by the patient or patient’s authorized representative or physician, healthcare provider, or pharmacist.

➔ Patient/Guardian Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Relationship to Patient: \_\_\_\_\_ Date: \_\_\_\_\_

Patient/Guardian Address: \_\_\_\_\_

Phone: \_\_\_\_\_ Cell Phone: \_\_\_\_\_

**Please complete and return Pages 1 and 2 of this form to THIOLA EC® (tiopronin) Total Care Hub by faxing to (877) 473-3167**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use THIOLA EC<sup>®</sup> safely and effectively. See full prescribing information for THIOLA EC.

THIOLA EC (tiopronin) delayed-release tablets, for oral use  
Initial U.S. Approval: 1988

-----RECENT MAJOR CHANGES-----  
Dosage and Administration (2.2) 03/2021

-----INDICATIONS AND USAGE-----  
THIOLA EC is a reducing and complexing thiol 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. (1)

-----DOSAGE AND ADMINISTRATION-----  
• The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dosage was about 1,000 mg/day. (2.1)  
• The recommended initial dosage in pediatric patients 20 kg and greater is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients. (5.1, 8.4)  
• Measure urinary cystine 1 month after initiation of THIOLA EC and every 3 months thereafter. (2.3)  
• 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. (2.1)  
• THIOLA EC can be crushed and mixed with applesauce. For preparation and administration instructions, see the full prescribing information. (2.2)

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

**Adults:** The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dosage 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 [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].

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.

Consider starting THIOLA EC at a lower dosage in patients with history of severe toxicity to d-penicillamine.

#### 2.2 Preparation and Administration Instructions

For patients who cannot swallow the tablet whole, THIOLA EC can be crushed and mixed with applesauce. Administration of THIOLA EC with other liquids or foods has not been studied and is not recommended.

#### Preparation and Administration of THIOLA EC Mixed in Applesauce

For patients who can swallow semi-solid food, THIOLA EC can be crushed and mixed with applesauce:

1. Crush the THIOLA EC tablet in a clean pill crusher or mortar and pestle. Always crush one tablet at a time.
2. Measure approximately one tablespoon of applesauce and transfer it into a container with the crushed THIOLA EC tablet.
3. Mix the crushed THIOLA EC tablet in the applesauce until the powder is well dispersed.
4. Administer the entire THIOLA EC-applesauce mixture to the patient's mouth immediately. (However, if this is not possible, the mixture can be stored in a refrigerator for up to 2 hours after adding the crushed tablet to the applesauce. Discard any mixture that has not been given within 2 hours.)
5. To assure that any leftover applesauce mixture from the container is recovered, add tap water to the same container, mix, and have the patient drink the water.

#### 2.3 Monitoring

Measure urinary cystine 1 month after starting THIOLA EC and every 3 months thereafter. Adjust THIOLA EC dosage to maintain urinary cystine concentration less than 250 mg/L.

Assess for proteinuria before treatment and every 3 to 6 months during treatment [see Warnings and Precautions (5.1)].

Discontinue THIOLA EC in patients who develop proteinuria, and monitor urinary protein and renal function. Consider restarting THIOLA EC treatment at a lower dosage after resolution of proteinuria.

### 3 DOSAGE FORMS AND STRENGTHS

Tablets for oral use:

100 mg tablets: round, white to off-white and imprinted in red with "T1" on one side  
300 mg tablets: round, white to off-white and imprinted in red with "T3" on one side

### 4 CONTRAINDICATIONS

THIOLA EC is contraindicated in patients with hypersensitivity to tiopronin or any other components of THIOLA EC [see Warnings and Precautions (5.2)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Proteinuria

Proteinuria, including nephrotic syndrome, and membranous nephropathy, have been reported with tiopronin use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria. [see Dosage and Administration (2.3), Adverse Reactions (6.1, 6.2) Use in Specific Populations (8.4)]. Monitor patients for the development of proteinuria and discontinue therapy in patients who develop proteinuria [see Dosage and Administration (2.3)].

## -----DOSAGE FORMS AND STRENGTHS-----

Tablets: 100 mg and 300 mg (3)

## -----CONTRAINDICATIONS-----

- Hypersensitivity to tiopronin or any component of THIOLA EC (4)

## -----WARNINGS AND PRECAUTIONS-----

- Proteinuria, including nephrotic syndrome, and membranous nephropathy, has been reported with tiopronin use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria. (2.1, 5.1, 8.4)
- Hypersensitivity reactions have been reported during tiopronin treatment. (4, 5.2)

## -----ADVERSE REACTIONS-----

Most common adverse reactions (≥10%) are nausea, diarrhea or soft stools, oral ulcers, rash, fatigue, fever, arthralgia, proteinuria, and emesis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mission Pharmacal Company at toll-free phone # 1-800-298-1087 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Lactation: Breastfeeding is not recommended. (8.2)
- Geriatric: Choose dose carefully and monitor renal function in the elderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2021

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\* Sections or subsections omitted from the full prescribing information are not listed.

### 5.2 Hypersensitivity Reactions

Hypersensitivity reactions (drug fever, rash, fever, arthralgia and lymphadenopathy) have been reported [see Contraindications (4)].

### 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Proteinuria [see Warnings and Precautions (5.1)]
- Hypersensitivity [see Warnings and Precautions (5.2)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of the drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions occurring at an incidence of ≥5% in an uncontrolled trial in 66 patients with cystinuria age 9 to 68 years are shown in the table below. Patients in group 1 had previously been treated with d-penicillamine; those in group 2 had not. Of those patients who had stopped taking d-penicillamine due to toxicity (34 out of 49 patients in group 1), 22 were able to continue treatment with THIOLA. In those without prior history of d-penicillamine treatment, 6% developed reactions of sufficient severity to require THIOLA withdrawal.

Table 1 presents adverse reactions ≥5% in either treatment group occurring in this trial.

Table 1: Adverse Reactions Occurring in One or More Patients

| System Organ Class                                   | Adverse Reaction     | Group 1<br>Previously treated<br>with d-penicillamine<br>(N = 49) | Group 2<br>Naïve to<br>d-penicillamine<br>(N = 17) |
|--|----------------------|---|--|
| Blood and Lymphatic System Disorders                 | anemia               | 1 (2%)  | 1 (6%)   |
| Gastrointestinal Disorders                           | nausea               | 12 (25%)  | 2 (12%)  |
|  | emesis               | 5 (10%)   | –  |
|  | diarrhea/soft stools | 9 (18%)   | 1 (6%)   |
|  | abdominal pain       | –   | 1 (6%)   |
|  | oral ulcers          | 6 (12%)   | 3 (18%)  |
| General Disorders and Administration Site Conditions | fever                | 4 (8%)  | –  |
|  | weakness             | 2 (4%)  | 2 (12%)  |
|  | fatigue              | 7 (14%)   | –  |
|  | peripheral (edema)   | 3 (6%)  | 1 (6%)   |
|  | chest pain           | –   | 1 (6%)   |
| Metabolism and Nutrition Disorders                   | anorexia             | 4 (8%)  | –  |
| Musculoskeletal and Connective Tissue Disorders      | arthralgia           | –   | 2 (12%)  |
| Renal and Urinary Disorders                          | proteinuria          | 5 (10%)   | 1 (6%)   |
|  | impotence            | –   | 1 (6%)   |
|  | cough                | –   | 1 (6%)   |
| Respiratory, Thoracic and Mediastinal Disorders      |                      |   |  |
| Skin and Subcutaneous Tissue Disorders               | rash                 | 7 (14%)   | 2 (12%)  |
|  | ecchymosis           | 3 (6%)  | –  |
|  | pruritus             | 2 (4%)  | 1 (6%)   |
|  | urticaria            | 4 (8%)  | –  |
|  | skin wrinkling       | 3 (6%)  | 1 (6%)   |

## Taste Disturbance

A reduction in taste perception may develop. It is believed to be the result of chelation of trace metals by tiopronin. Hypogeusia is often self-limited.

## 6.2 Postmarketing Experience

Adverse reactions have been reported from the literature, as well as during post-approval use of THIOLA. Because the post-approval reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to THIOLA exposure.

Adverse reactions reported during the postmarketing use of THIOLA are listed by body system in **Table 2**.

**Table 2: Adverse Reactions Reported for THIOLA Pharmacovigilance by System Organ Class and Preferred Term**

| System Organ Class                                   | Preferred Term  |
|--|---|
| Cardiac Disorders                                    | congestive heart failure  |
| Ear and Labyrinth Disorder                           | vertigo   |
| Gastrointestinal Disorders                           | abdominal discomfort; abdominal distension; abdominal pain; chapped lips; diarrhea; dry mouth; dyspepsia; eructation; flatulence; gastrointestinal disorder; gastroesophageal reflux disease; nausea; vomiting; jaundice; liver transaminitis |
| General Disorders and Administration Site Conditions | asthenia; chest pain; fatigue; malaise; pain; peripheral swelling; pyrexia; swelling  |
| Investigations                                       | glomerular filtration rate decreased; weight increased  |
| Metabolism and Nutrition Disorders                   | decreased appetite; dehydration; hypophagia   |
| Musculoskeletal and Connective Tissue Disorders      | arthralgia; back pain; flank pain; joint swelling; limb discomfort; musculoskeletal discomfort; myalgia; neck pain; pain in extremity   |
| Nervous System Disorders                             | ageusia; burning sensation; dizziness; dysgeusia; headache; hypoesthesia  |
| Renal and Urinary Disorders                          | nephrotic syndrome; proteinuria; renal failure  |
| Skin and Subcutaneous Tissue Disorders               | dry skin; hyperhidrosis; pemphigus foliaceus; pruritus; rash; rash pruritic; skin irritation; skin texture abnormal; skin wrinkling; urticaria  |

## 7 DRUG INTERACTIONS

### 7.1 Alcohol

Tiopronin is released faster from THIOLA EC in the presence of alcohol and the risk for adverse events associated with THIOLA EC when taken with alcohol is unknown. Avoid alcohol consumption 2 hours before and 3 hours after taking THIOLA EC [see *Clinical Pharmacology* (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available published case report data with tiopronin 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 up to 2 times a 2 grams/day human dose (based on mg/m<sup>2</sup>). 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 are 2% to 4% and 15% to 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

No findings of fetal malformations could be attributed to the drug in reproduction studies in mice and rats at doses up to 2 times the highest recommended human dose of 2 grams/day (based on mg/m<sup>2</sup>).

### 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. A published study suggests that tiopronin may suppress milk production. Because of the potential for serious adverse reactions, including nephrotic syndrome, advise patients that breastfeeding is not recommended during treatment with THIOLA EC.

### 8.4 Pediatric Use

THIOLA EC is indicated in pediatric patients weighing 20 kg or more with severe homozygous cystinuria, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation who are not responsive to these measures alone. This indication is based on safety and efficacy data from a trial in patients 9 years to 68 years of age and clinical experience. Proteinuria, including nephrotic syndrome, has been reported in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day may be at greater risk [see *Dosage and Administration* (2.1, 2.3), *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

THIOLA EC tablets are not approved for use in pediatric patients weighing less than 20 kg [see *Dosage and Administration* (2.1)].

### 8.5 Geriatric Use

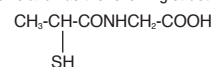
This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

## 10 OVERDOSAGE

There is no information on overdosage with tiopronin.

## 11 DESCRIPTION

THIOLA EC (tiopronin) delayed-release tablets are a reducing and cystine-binding thiol drug (CBTD) for oral use. Tiopronin is N-(2-Mercaptopropionyl) glycine and has the following structure:



Tiopronin has the empirical formula C<sub>5</sub>H<sub>9</sub>NO<sub>3</sub>S and a molecular weight of 163.20. In this drug product tiopronin exists as a dl racemic mixture.

Tiopronin is a white crystalline powder, which is freely soluble in water.

Each THIOLA EC tablet contains 100 or 300 mg of tiopronin. The inactive ingredients in THIOLA EC tablets include lactose monohydrate, hydroxypropyl cellulose, hydroxypropyl cellulose (low substitute), magnesium stearate, hydroxypropyl methylcellulose E5, methacrylic acid: ethyl acrylate copolymer (Eudragit L 100-55), talc, triethyl citrate.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of tiopronin-cystine. From this reaction, a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced.

### 12.2 Pharmacodynamics

The decrement in urinary cystine produced by tiopronin is generally proportional to the dose. A reduction in urinary cystine of 250-350 mg/day at tiopronin dosage of 1 g/day, and a decline of approximately 500 mg/day at a dosage of 2 g/day, might be expected. Tiopronin has a rapid onset and offset of action, showing a fall in cystine excretion on the first day of administration and a rise on the first day of drug withdrawal.

### 12.3 Pharmacokinetics

#### Absorption

##### THIOLA EC Tablets

When THIOLA IR and THIOLA EC single doses were given to fasted healthy subjects, the median time to peak plasma levels (T<sub>max</sub>) was 1 (range: 0.5 to 2.1) and 3 (range: 1.0 to 6.0) hours, respectively. The peak exposure (C<sub>max</sub>) and total exposure (AUC<sub>0-∞</sub>) of tiopronin from THIOLA EC tablets were decreased by 22% and 7% respectively compared to THIOLA IR tablets.

When THIOLA EC tablets were administered crushed in applesauce, the median time to peak plasma levels of tiopronin (T<sub>max</sub>) was 1 hour (range: 0.5 to 2.0) compared to 3.1 hours (range: 1.5 to 4.0) when administered as intact EC tablets.

When THIOLA EC tablets were administered crushed in applesauce, the maximum concentration (C<sub>max</sub>) and exposure (AUC<sub>0-∞</sub>) to tiopronin were increased by 38% and 14%, respectively, compared to THIOLA EC tablets administered intact.

#### Food Effects

Administration of the THIOLA EC tablet with food decreases C<sub>max</sub> of tiopronin by 13% and AUC<sub>0-4</sub> by 25% compared to THIOLA EC administered in a fasted state.

Since the drug is dosed to effect, the study results support administration of THIOLA EC tablets with or without food; administer at the same time each day with a routine pattern with regard to meals.

#### Elimination

##### Excretion

When tiopronin is given orally, up to 48% of dose appears in urine during the first 4 hours and up to 78% by 72 hours.

#### Drug Interactions

##### Alcohol

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40%) on the dose dumping of THIOLA EC tablets. The study results showed that the addition of alcohol to the dissolution media increases the dissolution rate of THIOLA EC tablets in the acidic media of 0.1N HCl [see *Drug Interactions* (7.1)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

Long-term carcinogenicity studies in animals have not been performed.

#### Mutagenesis

Tiopronin was not genotoxic in the chromosomal aberration, sister chromatid exchange, and *in vivo* micronucleus assays.

#### Impairment of Fertility

High doses of tiopronin in experimental animals have been shown to interfere with maintenance of pregnancy and viability of the fetus. In 2 published male fertility studies in rats, tiopronin at 20 mg/kg/day intramuscular (IM) for 60 days induced reductions in testis, epididymis, vas deferens, and accessory sex glands weights and in the count and motility of cauda epididymal sperm.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

100 mg delayed-release, round, white to off-white tablet imprinted with "T1" on one side with red ink and blank on the other side: Bottles of 300 NDC 0178-0902-01.

300 mg delayed-release, round, white to off-white tablet imprinted with "T3" on one side with red ink and blank on the other side: Bottles of 90 NDC 0178-0901-90.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see *USP Controlled Room Temperature*].

## 17 PATIENT COUNSELING INFORMATION

#### Administration Instructions

For patients who cannot swallow the tablet whole, the THIOLA EC tablets can be crushed and mixed with applesauce. See *Dosage and Administration* (2.2) for preparation and administration instructions.

#### Lactation

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



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