THE THREAT OF RECURRING CYSTINE STONES

THE POWER OF PREVENTION

Take in 3 divided doses per day, the same times each day.
Dose to effect based on the results of a 24-hour urine test.

Thiola EC® (tiopronin)
Delayed-Release Tablets 100mg|300mg

Indications and usage

THIOLA EC® (tiopronin) delayed-release tablets 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 with severe homozygous cystinuria, who are not responsive to these measures alone.

Important Safety Information

Contraindications

THIOLA EC is contraindicated in patients with hypersensitivity to tiopronin or any other components of THIOLA EC.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

71% OF PATIENTS ACHIEVED STONE PREVENTION WITH TIOPRONIN IN A MULTI-CENTER CLINICAL TRIAL[1]

THIOLA® (tiopronin) tablets can help manage recurring cystine stones[1]

Efficacy results in patients with cystinuria	Naïve to d-penicillamine (n=14)
Stopped new stone formation	71%
Reduced rate of new stone formation	94%

In patients previously treated with d-penicillamine (n=43):

- **62%** stopped forming new stones
- **81%** reduced the rate of new stone formation

THIOLA may help prevent stones by reducing urinary cystine levels below the solubility limit (generally <250 mg/L)[1]

Study design: Sixty-six cystine stone-formers (mean age 32.0±13.3 years), with 1 or more stone episodes (spontaneous passage, surgical removal, or appearance on X-ray) in the prior 2 years, were enrolled at 12 study sites. Forty-nine patients had been previously treated with d-penicillamine (at a mean dosage of 1125±640 mg/day for a mean of 2.81±3.94 years) and 17 patients had no prior d-penicillamine therapy. All patients maintained ongoing dietary and fluid regimens, and 45/66 patients continued ongoing alkali therapy. Patients received tiopronin for between 4 months and 4 years at a mean dosage of 1193±450 mg/day, in 3 to 4 divided doses ≥1 hour before or 2 hours after meals.[1]

Important Safety Information (cont.)

Warnings and precautions

- **Proteinuria:** Proteinuria, including nephrotic syndrome, and membranous nephropathy, has been reported with tiopronin use. Pediatric patients receiving >50 mg/kg of tiopronin per day may be at increased risk for proteinuria. Monitor patients for the development of proteinuria and discontinue therapy in patients who develop proteinuria.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (drug fever, rash, fever, arthralgia and lymphadenopathy) have been reported.

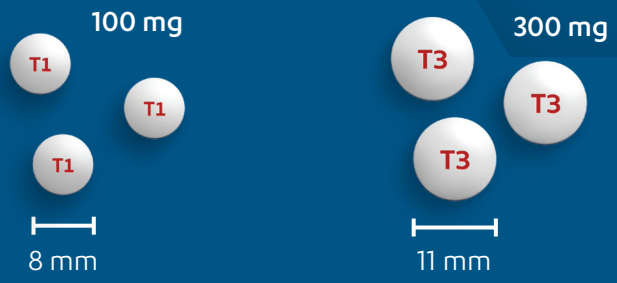
ThiolaEC® (tiopronin) Delayed-Release Tablets 100mg/300mg

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

THIOLA EC IS FORMULATED TO HELP PATIENT COMPLIANCE[2]

THIOLA EC offers patients flexible dosing options[3]

- Larger dosage strength—300 mg—may help reduce pill burden.
- Available in 2 dosage strengths—100 mg and 300 mg.
- Patients have the freedom to take their dose with or without food.



Pills are shown in actual sizes.

Dosing guidance[3]

- Taking THIOLA EC with food may decrease the levels of tiopronin in the blood by approximately 25%.
- THIOLA EC should be taken in 3 divided doses per day, the same times each day.
- Patients should also maintain a routine pattern with regard to meals.
- THIOLA EC tablets must be swallowed whole.
- THIOLA EC should be dosed to effect based on the results of a 24-hour urine test.

Important Safety Information (cont.)

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

Drug interactions
Avoid alcohol consumption 2 hours before and 3 hours after taking THIOLA EC as THIOLA EC is released faster in the presence of alcohol.

References: 1. Pak et al. *J Urol*. 1986;136(5):1003-1008. **2.** Data on file. Retrophin, Inc. **3.** THIOLA EC [package insert]. San Antonio, TX: Mission Pharmacal Company.

RARE, LIFELONG, GENETIC DISORDER: CYSTINURIA REQUIRES ONGOING MANAGEMENT[1,2]

Failure to prevent cystine stones has been demonstrated approximately 55% of the time[3]

- High fluid intake, alkali, and diet modification alone may not be enough to control cystine.[3,4]
- In a clinical trial of 27 patients with cystinuria managed by high fluid intake and alkalization, 15 patients failed to manage their condition on these methods alone.[3]

If your patients are still experiencing cystine stone events even with these modifications, THIOLA EC® (tiopronin) tablets may help

STONE PREVENTION BEGINS WITH EARLY RECOGNITION OF CYSTINE BUILDUP

Regular monitoring enables early detection

Take action at the first sign of cystine buildup; the following are indicators that you may need to modify your patients' management plans:

- Sand/gravel in urine[1]
- 24-hour urine test results showing elevated cystine levels[5,6]
- Imaging showing presence of stones[7]
- Kidney stone-related pain[6]

ThiolaEC® (tiopronin) Delayed-Release Tablets 100mg/300mg

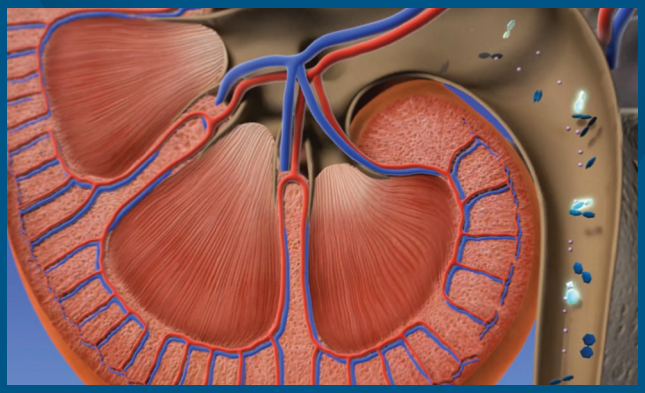
Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

THIOLA EC MAY HELP PREVENT STONES BY BINDING TO CYSTINE[4]

Prevention of stones requires removal of excess cystine

Tiopronin increases solubility of cystine

Tiopronin undergoes thiol-disulfide exchange with cystine, forming a more soluble complex.



Tiopronin-cysteine complex is excreted in the urine, reducing the possibility of stone formation.

The American Urological Association recommends using cystine-binding thiol drugs such as tiopronin as the next line of therapy when fluids, alkali and diet modifications fail to prevent stones from forming[5]

Important Safety Information (cont.)

Specific populations

- **Lactation:** Breastfeeding is not recommended during treatment with THIOLA EC.
- **Geriatric Use:** 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.

You may report negative side effects to Retrophin® Medical Information at 1-877-659-5518, or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. Biyani et al. *EAU-EBU Update Series*. 2006;4(5):175-183. **2.** Parr et al. *BJU Int*. 2015;116(suppl 3):31-35. **3.** Barbey et al. *J Urol*. 2000;163(5):1419-1423. **4.** THIOLA EC [package insert]. San Antonio, TX: Mission Pharmacal Company. **5.** Pearle et al. *J Urol*. 2014;192(2):316-324. **6.** What are cystine stones? The National Kidney Foundation website. https://www.kidney.org/atoz/content/what-are-cystine-stones. Published March 8, 2016. Accessed September 26, 2019. **7.** Claes et al. *Pediatr Nephrol*. 2012;27(11):2031-2038.

THIOLA EC® (tiopronin) TABLETS, ALONG WITH THERAPEUTIC LIFESTYLE CHANGES, MAY HELP PREVENT CYSTINE STONE FORMATION[1]

Maximize cystine stone prevention with a multifaceted approach

Increasing water intake helps dilute cystine in the urine.[2]

TARGET: A minimum urine output of 2.5 L/day on a consistent basis[3]
HOW TO ACHIEVE: Talk to your patients about targeting a daily fluid intake of 4 L[3]

Reducing sodium and animal protein in the diet reduces the amount of cystine in the urine.[2]

TARGET: A diet low in sodium and animal protein[2]
HOW TO ACHIEVE: A reasonable goal for sodium intake is ≤100 mEq (2300 mg/day)[3]

Important Safety Information (cont.)

Warnings and precautions

- **Proteinuria:** Proteinuria, including nephrotic syndrome, and membranous nephropathy, has been reported with tiopronin use. Pediatric patients receiving >50 mg/kg of tiopronin per day may be at increased risk for proteinuria. Monitor patients for the development of proteinuria and discontinue therapy in patients who develop proteinuria.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (drug fever, rash, fever, arthralgia and lymphadenopathy) have been reported.

Thiola EC® (tiopronin) Delayed-Release Tablets 100mg/300mg

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ADJUST THESE MEASURES TO OPTIMIZE TREATMENT PLANS FOR EACH PATIENT

Maintaining a urinary pH level of 7.0 increases the solubility of cystine in the urine.[3]

TARGET: A urine pH level of 7.0
HOW TO ACHIEVE: This is often made possible by taking potassium alkali

Taking THIOLA EC at the right dosage increases the solubility of cystine in urine.[1]

TARGET: The optimal THIOLA EC dosage needed to reduce cystine below its solubility limit, generally <250 mg/L

- In adults, the recommended starting dosage is 800 mg/day.
- In children ≥20 kg, the recommended starting dose is 15 mg/kg/day.

THIOLA EC dosage may need to be adjusted to reduce cystine below its solubility limit. Use the THIOLA EC adult dosing calculator at **THIOLAECDosingGuide.com**.

Measure urinary cystine 1 month after starting THIOLA EC, and every 3 months thereafter.

References: 1. THIOLA EC [package insert]. San Antonio, TX: Mission Pharmacal Company. **2.** Knoll et al. *Pediatr Nephrol*. 2005;20(1):19-24. **3.** Pearle et al. *J Urol*. 2014;192(2):316-324.

START WITH THE RIGHT DOSE AND MONITOR REGULARLY TO HELP MAXIMIZE TREATMENT OUTCOMES

Recommended starting dosage of THIOLA EC® (tiopronin) tablets[1]

Adults	Children ≥20 kg
	
May begin at **800 mg/day**	May begin at **15 mg/kg/day**

In clinical studies, the average adult dosage was about 1000 mg/day.[1]

- Patients with a history of severe toxicity to d-penicillamine may start at a lower dosage.
- Avoid dosages >50 mg/kg per day in pediatric patients.
- 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. The potential reduction in urinary cystine is:
  - 250 to 350 mg/day for a 1 g/day adult dosage
  - 500 mg/day for a 2 g/day adult dosage
- THIOLA EC should be used in combination with high fluid intake, alkali, and diet modification.
- 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.

Important Safety Information

Adverse reactions

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

Drug interactions

Avoid alcohol consumption 2 hours before and 3 hours after taking THIOLA EC as THIOLA EC is released faster in the presence of alcohol.

ThiolaEC® (tiopronin) Delayed-Release Tablets 100mg|300mg

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

OPTIMIZE DOSAGE OF THIOLA EC WITH THE ONLINE DOSING CALCULATOR

The dosing calculator is a guide for determining THIOLA EC dosage

Snapshot of the THIOLA EC adult dosing calculator
Factors including urinary pH, urinary output, and urinary cystine concentration can help determine the appropriate dose of THIOLA EC. It is important to consider these factors as you adjust a patient's THIOLA EC dosage.[1]

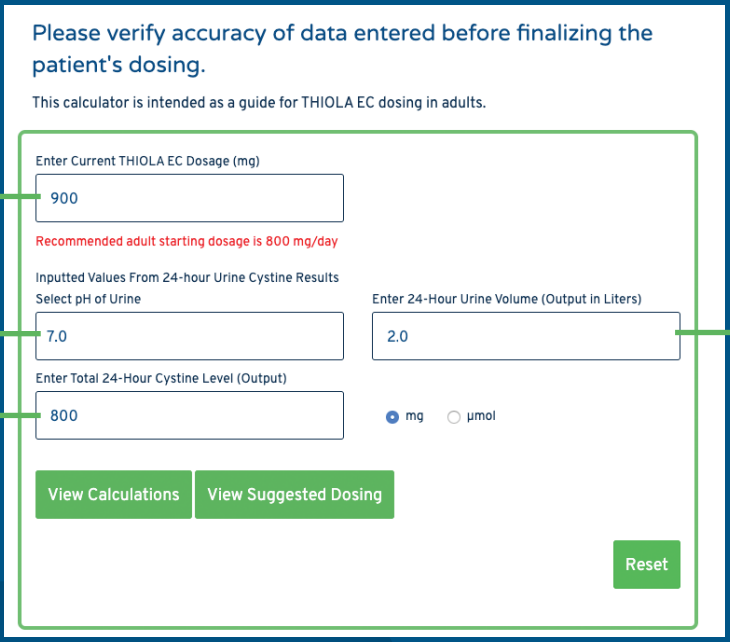
Start by conducting a 24-hour urine test and using the results to populate the fields of the online dosing calculator

Note: This dosing calculator is for THIOLA EC only.

STEP 1
Enter current dose of THIOLA EC. Enter "0" if patient is not currently on THIOLA EC.

STEP 2
Enter the patient's pH value from 24-hour urine test results.

STEP 3
Enter the total 24-hour cystine level output.



STEP 4
Enter the 24-hour urine volume.

Routine monitoring of patients' cystine levels is critically important to ensuring they are on the right dosage of THIOLA EC. As patients' 24-hour cystine and urinary output may fluctuate over time, adjust THIOLA EC dosage to maintain urinary cystine concentration <250 mg/L.[1]

Calculate your adult cystinuria patient's dosage at THIOLAECDosingGuide.com

Reference: 1. Goldstein et al. *Urol Nurs*. 2017;37(2):81-89,102.

ADVERSE REACTIONS (≥5%) OCCURRING IN A MULTI-CLINIC TRIAL OF 66 CYSTINE STONE-FORMERS TREATED WITH THIOLA® (tiopronin) TABLETS[1,2]

System Organ Class	Adverse Reaction	Group 1 Previously treated with d-penicillamine (N = 49)	Group 2 Naïve to d-penicillamine (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%)
Respiratory, thoracic, and mediastinal disorders	Cough	–	1 (6%)
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%)

Thiola EC® (tiopronin) Delayed-Release Tablets 100mg|300mg

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

POSTMARKETING ADVERSE REACTIONS REPORTED[1]

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

Important Safety Information (cont.)

Adverse reactions

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

References: 1. THIOLA EC [package insert]. San Antonio, TX: Mission Pharmacal Company. **2.** Pak et al. *J Urol*. 1986;136(5):1003-1008.

YOUR GOAL IS STONE PREVENTION — THE TOTAL CARE HUB® HELPS WITH THE REST

THIOLA EC Total Care Hub provides personalized support to help patients access and manage their treatment

ACCESS HUB:
Financial support and reimbursement options

- Dedicated Hub Counselors will assist with benefit verification, prior authorizations, and appeals.
- Reimbursement support and patient assistance programs are available.

$0 copay
for eligible, commercially insured patients.*

DELIVERY HUB:
Convenient home delivery and prescription refills

- Your patients' THIOLA EC® (tiopronin) tablets will be delivered directly to their doorsteps–avoiding trips to the pharmacy.
- Your patients will be contacted when prescriptions need to be refilled to promote adherence and help ensure they never run out.

*Go to THIOLAEChcp.com for full Copay Terms and Conditions.

Thiola EC® (tiopronin) Delayed-Release Tablets 100mg|300mg

ThiolaEC®
(tiopronin)
Delayed-Release Tablets 100mg|300mg

TOTAL CARE HUB

SUPPORT HUB:
Your patients receive live, on-demand support

- ***Hub Counselors:*** Dedicated counselors available to answer questions about THIOLA EC and set up prescription refill reminders to help your patients stay organized and on track.
- ***Pharmacists:*** 24/7 access to THIOLA EC Total Care Hub pharmacists is available for any questions about THIOLA EC prescription or dosing administration.
- ***Clinical Nurse Coordinators:*** Your patients will receive calls directly from specialized nurses trained to help support their treatment and provide disease education.

EDUCATION HUB:
Patients will learn more about cystinuria

- Optional patient emails and brochures with updates and information about cystinuria.
- Monthly educational materials and tools.
- Information about live patient events.

Visit THIOLAEChub.com or call 844-4-THIOLA (844-484-4652) to access information about prescribing THIOLA EC

For patients with cystinuria managing recurring cystine stone events

Thiola EC® (tiopronin) Delayed-Release Tablets 100mg|300mg

A DELAYED-RELEASE FORMULATION[1]

- Larger dosage strength—300 mg—may **help reduce pill burden**.
- Available in **2 dosage strengths**—100 mg and 300 mg.
- Can be **taken with or without food** to give your patients more flexibility.

$0 copay for eligible, commercially insured patients.*

Download and complete the enrollment form at THIOLAEChcp.com

*Go to THIOLAEChcp.com for full Copay Terms and Conditions.

Important Safety Information (cont.)

Specific populations

- **Lactation:** Breastfeeding is not recommended during treatment with THIOLA EC.
- **Geriatric Use:** 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.

You may report negative side effects to Retrophin® Medical Information at 1-877-659-5518, or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information and additional Important Safety Information.

Reference: 1. THIOLA EC [package insert]. San Antonio, TX: Mission Pharmacal Company.

Retrophin®

Thiola EC® (tiopronin) Delayed-Release Tablets 100mg|300mg

HHIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

----------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. (2.1, 5.1, 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. (2.1)
- Swallow THIOLA EC tablets whole. (2.1)
- Measure urinary cystine 1 month after initiation of THIOLA EC and every 3 months thereafter. (2.1)

----------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: 06/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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), Pediatric Use (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. Swallow THIOLA EC tablets whole.

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

2.2 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 (2.2), Adverse Reactions (6.1, 6.2) Pediatric Use (8.4)]*. Monitor patients for the development of proteinuria and discontinue therapy in patients who develop proteinuria *[see Dosage and Administration (2.2)]*.

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 Previously treated with d-penicillamine (N = 49)	Group 2 Naïve to d-penicillamine (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%)
Respiratory, Thoracic and Mediastinal Disorders	cough	–	1 (6%)
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^2). 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^2).

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, 2.2), 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 or in pediatric patients unable to swallow tablets *[see Recommended Dosage (2.1)]*.

8.5 Geriatric Use

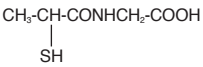
This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful 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 $C_5H_9NO_3S$ 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 E 100), 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-cysteine. 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 (n = 39) in a crossover study, the median time to peak plasma levels (T_{max}) were 1 (range: 0.5 to 2.1) and 3 (range: 1.0 to 6.0) hours, respectively. The peak exposure (C_{max}) and total exposure (AUC_{0-t}) of tiopronin from THIOLA EC tablets were decreased by 22% and 7% respectively compared to THIOLA IR tablets.

Food Effects

Administration of the THIOLA EC tablet with food decreases C_{max} of tiopronin by 13% and AUC_{0-t} 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

Advise patients to swallow THIOLA EC tablets intact and not to chew, crush, or split the tablets.

Lactation

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

Mission® PHARMACAL

Manufactured and packaged by Mission Pharmacal Company, San Antonio, TX 78230 1355
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