HIGHLIGHTS OF PRESCRIBING INFORMATION

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

THIOLA (tiopronin) tablets, for oral use

Initial U.S. Approval: 1988

INDICATIONS AND USAGE

THIOLA 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

1. 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)
2. 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)
3. Monitor proteinuria every 3 months. (2.2)
4. Monitor urinary cystine every 3 months. (2.1)

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)

Measure urinary cystine 1 month after initiation of THIOLA and every 3 months thereafter. (2.1)

Dosage Modification

Pediatric: 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. (2.1, 5.1, 8.4)

Pediatric Use (8.4)

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

Avoid dosages greater than 50 mg/kg per day in pediatric patients. (2.1, 5.1, 8.4)

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. (4, 5.2)

Proteinuria has been reported during tiopronin treatment. (4, 5.2)

Dosage and Administration for Pediatric Patients

Pediatric patients: 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. (2.1, 5.1, 8.4)

Pediatric use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria. (4, 5.2)

Proteinuria has been reported during tiopronin treatment. (4, 5.2)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse reactions (>10%) in clinical trials were nausea, diarrhea or soft stools, oral ulcers, rash, fatigue, fever, arthralgia, proteinuria, and emesis. (6)

See 17 for PATIENT COUNSELING INFORMATION.

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8.2 Lactation

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13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

17 PATIENT COUNSELING INFORMATION

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

1 INDICATIONS AND USAGE

THIOLA 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. (1)

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. (2.1)

Pediatric: 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. (2.1, 5.1, 8.4)

Pediatric Use (8.4)

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

Avoid dosages greater than 50 mg/kg per day in pediatric patients. (2.1, 5.1, 8.4)

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. (4, 5.2)

Proteinuria has been reported during tiopronin treatment. (4, 5.2)

)|(N = 49) | (N = 17) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>anemia 1 (2%) 1 (6%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>nausea 12 (25%) 2 (12%)</td>
</tr>
<tr>
<td></td>
<td>ameis 5 (10%) –</td>
</tr>
<tr>
<td></td>
<td>diarrhea/soft stools 9 (18%) 1 (6%)</td>
</tr>
<tr>
<td></td>
<td>abdominal pain – 1 (6%)</td>
</tr>
<tr>
<td></td>
<td>oral ulcers 6 (12%) 3 (18%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>fever 4 (8%) –</td>
</tr>
<tr>
<td></td>
<td>weakness 2 (4%) 2 (12%)</td>
</tr>
<tr>
<td></td>
<td>fatigue 7 (14%) –</td>
</tr>
<tr>
<td></td>
<td>peripheral (edema) 3 (6%) 1 (6%)</td>
</tr>
<tr>
<td></td>
<td>chest pain – 1 (6%)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>anorexia 4 (8%) –</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>arthralgia – 2 (12%)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>proteinuria 5 (10%) 1 (6%)</td>
</tr>
<tr>
<td></td>
<td>impotence – 1 (6%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>cough – 1 (6%)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>rash 7 (14%) 2 (12%)</td>
</tr>
<tr>
<td></td>
<td>ecchymosis 3 (6%) –</td>
</tr>
<tr>
<td></td>
<td>prunus 2 (4%) 1 (6%)</td>
</tr>
<tr>
<td></td>
<td>urticaria 4 (8%) –</td>
</tr>
<tr>
<td></td>
<td>skin wrinkling 3 (6%) 1 (6%)</td>
</tr>
</tbody>
</table>

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

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 human dose (based on mg/m²). The estimated background risk of major developmental outcomes with oral administration of tiopronin to pregnant mice and rats during organogenesis 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 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

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/m²).

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 breastfeeding 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.

8.4 Pediatric Use

THIOLA 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 63 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 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)].