BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/18/18
LAST REVIEW DATE: 1/18/18
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

THIOLA® (tiopronin) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

THIOLA® (tiopronin) oral tablet (cont.)

Description:

Thiola (tiopronin) is indicated 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.

Thiola (tiopronin) is a reducing and complexing thiol-glycine compound, it undergoes thiol-disulfide exchange with cysteine to form a mixed disulfide of Thiola-cysteine. From this reaction, a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced.

Background:

- Cystine is a homodimer of the amino acid cysteine
- Patients with cystinuria have impaired renal cystine transport, with decreased proximal tubular reabsorption of filtered cystine resulting in increased urinary cystine excretion and cystine stones
- Cystine stones occur in approximately 10,000 persons in the US who are homozygous for cystinuria
    - These persons excrete abnormal amounts of cystine in urine of > 250 mg/g creatinine
- Almost all cases of cystinuria are accounted for by mutations in two genes specifically, *SLC3A1* and *SLC7A9*
    - People who are heterozygotes for mutations in both *SLC3A1* and *SLC7A9* do not usually form cystine stones
- Cystinuria is diagnosed among patients with nephrolithiasis and one or more of the following findings:
    - Positive family history of cystinuria
    - Stone analysis showing cysteine
    - Identification of pathognomonic hexagonal cystine crystals on urinalysis (seen on initial urinalysis in approximately 25% of patients)
- Stone formation is determined primarily by the urinary supersaturation of cystine
    - Cystine stones form when urinary cystine concentration exceeds the solubility limit
        - Stone formation is the result of poor aqueous solubility of cystine
    - Cystine solubility in urine is pH-dependent, and ranges from 170-300 mg/liter at pH 5, 190-400 mg/liter at pH 7 and 220-500 mg/liter at pH 7.5
- There are no known inhibitors of the crystallization of cystine
- The goal of therapy is to reduce urinary cystine concentration below its solubility limit
    - It may be accomplished by dietary measure aimed at reducing cystine synthesis and by a high fluid intake in order to increase urine volume and thereby lower cystine concentration
- In some homozygous patients with severe cystinuria, urinary cystine exceeds 500 mg/day, d-penicillamine may be used

THIOLA® (tiopronin) oral tablet (cont.)

- Like Thiola, d-penicillamine undergoes thiol-disulfide exchange with cystine, thereby lowering the amount of sparingly soluble cystine in urine.

Thiola (tiopronin)

Medication class:
Urinary Tract Product

FDA-approved indication(s):
- 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 penicillamine

Recommended Dose:
- Adults:
  - Begin at a dosage of 800 mg/day, average dose may be as high as 1000 mg/day, others may require lower dose
  - Doses should be given in divided doses 3 times/day at least 1 hour before or 2 hours after meals
- Children 9 years or age or older:
  - Initial dosage is 15 mg/kg/day
  - Doses should be given in divided doses 3 times/day at least 1 hour before or 2 hours after meals
- Urinary cystine should be measured at 1 month after treatment, and every 3 months thereafter
- Thiola dosage should be readjusted depending on the urinary cystine value
- Dose is based on the amount required to reduce urinary cysteine concentration to below the solubility limit, generally < 250 mg/L

Maximum dosage
- Not stated

Available Dosage Forms:
- 100 mg tablet

Warnings, Precautions, and other Clinical Information:
- Thiola may cause all the same serious adverse effects as reported for d- penicillamine and are more likely to develop during Thiola among patients who had previously shown toxicity to d-penicillamine
- Discontinue Thiola if the WBC is < 3,500/mm^3 or if the platelet count is < 100,000/mm^3
- Discontinue Thiola if Goodpasture syndrome develops
- Discontinue Thiola if myasthenia gravis or myasthenic syndrome develops
- Discontinue Thiola if a pemphigus-type reaction develops

THIOLA® (tiopronin) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Thiola (tiopronin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a Nephrologist or Urologist

  2. Individual is 9 years of age or older

  3. A confirmed diagnosis of severe homozygous cystinuria with **ALL** of the following
     - 24-hour urine collection with urinary cystine > 500 mg/day
     - Individual is resistant to treatment with **ALL** of the following conservative measures
       - High fluid intake of at least 3 L/day
       - Urinary alkalinization with potassium citrate to keep urine above pH 7
       - Diet modification to restricted sodium and protein intake

  4. Individual has failure, contraindication or intolerance to d-penicillamine

  5. There are **NO** contraindications.
     - Contraindications include:
       - Woman of child bearing age who is pregnant, except in those with severe cystinuria where the anticipated benefit of inhibited stone formation clearly outweighs possible hazards of treatment
       - Woman who is breast feeding an infant or child
       - History of agranulocytosis, aplastic anemia, or thrombocytopenia from previous Thiola use

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Thiola (tiopronin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by Nephrologist or Urologist

  2. Individual's condition has responded while on therapy
     - Response is defined as either:
       - Urinary cysteine concentration is < 250 mg/L
       - Reduction in cysteine stone production

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
     - Contraindications as listed in the criteria for initial therapy section
     - Significant adverse effect such as:

THIOLA® (tiopronin) oral tablet (cont.)

- Hypersensitivity
  - Signs and symptoms may include: laryngeal edema, dyspnea, respiratory distress, fever, chills, arthralgia, weakness, fatigue, myalgia, adenopathy
- Agranulocytosis, aplastic anemia, thrombocytopenia
  - Signs and symptoms may include: fever, sore throat, mouth sores, chills, severe shaking or flu-like symptoms, bleeding and easy bruising, unusual bleeding or bruising, nose bleeds, red or purple spots on body
- Renal complications of proteinuria or nephrotic syndrome
  - Signs and symptoms may include: swelling around eyes, swelling of ankles and feet, foamy urine, weight gain, abdominal bloating, protein in urine, low albumin
- Goodpasture syndrome
  - Signs and symptoms may include: fatigue, fever, chills, difficulty breathing, shortness of breath, bloody cough, blood in urine, foamy urine, burning or difficulty when urinating, swelling of legs and hands, back pain
- Myasthenia gravis or myasthenic syndrome
  - Signs and symptoms may include: muscle weakness of arms and legs that worsens with use, drooping of upper eyelid, double vision, difficulty swallowing, fatigue, shortness of breath, speech difficulties, problems chewing
- Pemphigus-type reaction
  - Signs and symptoms may include: painful blistering of skin and mucous membranes, pustules

5. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

Thiola. Package Insert. Revised by manufacturer 11/2012. Accessed 01-06-18.

UpToDate: Cystine stones. Current through Dec 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/cystine-stones?search=cystinuria&source=search_result&selectedTitle=1~30&usage_type=default&display_rank=1

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.