BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/18/19**
SECTION: DRUGS	**LAST REVIEW DATE: 8/15/19**
	LAST CRITERIA REVISION DATE: 8/15/19
	ARCHIVE DATE:

THIOLA® (tiopronin) oral tablet
THIOLA® EC (tiopronin delayed-release) 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)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Criteria:

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

1. Prescriber is a physician specializing in kidney disorders or is in consultation with 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 penicillamine tablet

5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Complete blood count
   - Serum albumin
   - Liver function tests
   - 24-hour urinary protein
   - Routine urinalysis
   - Urinary cysteine
   - KUB

6. 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

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

1. Individual continues to be seen by a physician specializing in kidney disorders or is in consultation with Nephrologist or Urologist

2. Individual's condition has responded while on therapy
   - Response is defined as either:
     - Urinary cystine concentration is < 250 mg/L
     - Reduction in cystine 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:
     - Hypersensitivity reaction
     - Agranulocytosis, aplastic anemia, thrombocytopenia
     - Renal complications of proteinuria or nephrotic syndrome
     - Goodpasture syndrome
     - Myasthenia gravis or myasthenic syndrome
     - Pemphigus-type reaction

5. There are no significant interacting drugs

Renewal duration: 12 months

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

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

Resources:

Thiola (tiopronin) product information accessed 01-14-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=494a714e-923c-cd57-df6c-12886afb265a

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

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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