BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

THIOLA® (tiopronin) immediate release oral
THIOLA® EC (tiopronin delayed release) oral
Tiopronin immediate release oral
Tiopronin DR delayed release oral
VENXXIVA™ (tiopronin delayed release) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Thiola (tiopronin) immediate release, generic tiopronin immediate release, Thiola EC (tiopronin delayed release), generic tiopronin delayed release, and Venxxiva (tiopronin delayed release) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist or Urologist

2. Individual is 9 years of age or older who weigh at least 20 kg or more

3. Individual has a confirmed diagnosis of severe homozygous cystinuria with cystine kidney stone formation with **ONE or more** of the following:
    a. Stone analysis reveals 100% cystine calculi
    b. Presence of pathognomonic hexagonal cystine crystals visualized on urine microscopy
    c. Genetic testing confirming two defects in some combination of the *SLC7A9* and *SLC3A1* genes [**Note**: genetic testing is not required for the diagnosis of cystinuria]

4. There is documentation of an assessment for proteinuria before initiation of treatment and will have continued monitoring as clinically appropriate

5. There is documentation that 24-hour urine collection with urinary cystine greater than 400 mg/day

6. There is documentation individual is resistant to treatment with **ALL** of the following conservative measures:
    a. High fluid intake of at least 2 L/day
    b. Urinary alkalinization with potassium citrate (or other urinary alkalinizing agent) to keep urine above pH 7
    c. Diet modification to restricted sodium and protein intake

7. **For Thiola EC (tiopronin delayed release) or Venxxiva (tiopronin delayed release)**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for tiopronin DR (delayed release)

8. Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic tiopronin immediate release** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
    a. Routine urinalysis
    b. Urinary cystine

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Thiola (tiopronin) immediate release, generic tiopronin immediate release, Thiola EC (tiopronin delayed release), generic tiopronin delayed release, and Venxxiva (tiopronin delayed release) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

PHARMACY COVERAGE GUIDELINE

THIOLA® (tiopronin) immediate release oral
THIOLA® EC (tiopronin delayed release) oral
Tiopronin immediate release oral
Tiopronin DR delayed release oral
VENXXIVA™ (tiopronin delayed release) oral
Generic Equivalent (if available)

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist or Urologist

2. Individual has documentation of positive clinical response to therapy defined as **ALL** of the following:
    a. Urinary cystine concentration is less than 250 mg/L
    b. Urine pH is greater than 7
    c. Reduction in cystine stone production

3. Individual has been adherent with the medication

4. **For Thiola EC (tiopronin delayed release) or Venxxiva (tiopronin delayed release)**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for tiopronin DR (delayed release)

5. **For Thiola (tiopronin) immediate release:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic tiopronin immediate release** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Hypersensitivity reaction
    b. Renal complications of proteinuria or nephrotic syndrome
    c. Membranous nephropathy

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of Non-Cancer Medications**

    2. **Off-Label Use of Cancer Medications**

Description:

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.

PHARMACY COVERAGE GUIDELINE

THIOLA® (tiopronin) immediate release oral
THIOLA® EC (tiopronin delayed release) oral
Tiopronin immediate release oral
Tiopronin DR delayed release oral
VENXXIVA™ (tiopronin delayed release) oral
Generic Equivalent (if available)

Efficacy of tiopronin for cystinuria comes from data from an uncontrolled trial in 66 patients with cystinuria age 9 to 68 years of age and clinical experience.

Tiopronin is a reducing and complexing thiol-glycine compound, it undergoes thiol-disulfide exchange with cysteine 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.

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; and 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. Stone formation is the result of poor aqueous solubility of cystine. Cystine stones form when urinary cystine concentration exceeds the solubility limit. 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. This is 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. It is possible to reduce the likelihood of cystine crystallization by: increasing fluid intake, which decreases the cystine concentration; restricting sodium and protein intake, which modestly reduces cystine excretion and, therefore, cystine concentration; and urinary alkalinization, which increases the solubility of cysteine. Alkalinizers include use of potassium citrate or potassium bicarbonate to obtain a target urine pH of 7 or greater. If conservative measures are unable to adequately reduce the urinary cystine concentration, or stones recur, adding a thiol-containing drugs such as penicillamine or tiopronin is usually tried. In some homozygous patients with severe cystinuria, urinary cystine exceeds 500 mg/day, penicillamine may be used. Like tiopronin, penicillamine undergoes thiol-disulfide exchange with cystine, thereby lowering the amount of sparingly soluble cystine in urine.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

PHARMACY COVERAGE GUIDELINE

THIOLA® (tiopronin) immediate release oral
THIOLA® EC (tiopronin delayed release) oral
Tiopronin immediate release oral
Tiopronin DR delayed release oral
VENXXIVA™ (tiopronin delayed release) oral
Generic Equivalent (if available)

Resources:

Thiola (tiopronin) tablet product information, revised by Mission Pharmacal Company 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Tiopronin tablet product information, revised by Teva Pharmaceuticals USA, Inc. 04-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Thiola EC (tiopronin) delayed release tablet product information, revised by Mission Pharmacal company 03-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Tiopronin delayed release tablet product information, revised by Amneal Pharmaceuticals LLC. 05-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Venxxiva (tiopronin) delayed release tablet product information, revised by Cycle Pharmaceuticals Ltd. 12-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 13, 2025.

Goldfarb DS, Ferraro PM, Sas DJ, Baum MA. Cystinuria and cystine stones. In: UpToDate, Preminger GM, Lam AQ (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through May 2025. Topic last updated June 18, 2025. Accessed June 23, 2025.