# Drug Coverage Policy

**Effective Date.....05/01/2025**
**Coverage Policy Number.....IP0202**
**Policy Title.....Tiopronin**

# Metabolic Disorders - Tiopronin

- Thiola® (tiopronin tablets – Mission Pharmacal, generic)
- Thiola® EC (tiopronin delayed-release tablets – Mission Pharmacal, generic)
- Venxxiva® (tiopronin delayed-release tablets – Torrent [generic only])

***INSTRUCTIONS FOR USE***
*The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.*

**Overview**

Tiopronin products are indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine kidney stone formation in adults and pediatric patients ≥ 20 kg with severe homozygous **cystinuria**, who are not responsive to these measures alone.[1,2,6] Amongst the tiopronin delayed-release formulations, Venxxiva is a branded generic product and is supplied in the same dosage strength as Thiola EC.

**Disease Overview**
Cystinuria is an autosomal recessive disorder of abnormal cystine transport.[3] The estimated prevalence is 1:7,000 to 1:10,000 individuals in the US. Excessive undissolved cystine in the urine leads to formation of stones in the kidney, bladder, and/or ureter. Symptoms typically begin to manifest between 10 and 30 years of age, although elevated cystine excretion may be found in infancy. Diagnosis is made clinically based on quantitative urinary cystine assays; genetic testing is not routine as it does not change medical management.[4] Homozygotes exhibit urinary cystine excretion > 300 to 400 mg/L/day, whereas heterozygotes have intermediate urinary cystine excretion. Treatment is directed at decreasing urinary cystine concentration (generally targeting a urine cystine < 250 mg/L) and enhancing solubility.[4,5,7] Tiopronin products work by binding to cystine and increasing urinary solubility.[4]

**Guidelines**
According to the American Urological Association guideline for medical management of kidney stones (2014, confirmed 2019), all patients with cystine kidney stones should be encouraged to drink large amounts of fluid to maintain low urinary cystine concentrations; often volumes of 4 liters per day are required.[5] Recommended dietary modifications include restriction of sodium and animal proteins. Alkalization of urine is also used to improve cystine solubility. This can be achieved through increased fruit and vegetable intake and/or with medications such as potassium citrate. The guideline recommends tiopronin for patients with cystine kidney stones who are unresponsive to increased fluid intake, dietary modification, and urinary alkalization. Captopril, another thiol agent, has not been shown to be effective for the prevention of recurrent cystine stones. D-penicillamine may be associated with more adverse events and is not preferred.

## Coverage Policy

**Policy Statement**
Prior Authorization is required for prescription benefit coverage of tiopronin products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tiopronin products as well as the monitoring required for adverse events and long-term efficacy, approval requires tiopronin products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Documentation:** Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

**Tiopronin products are considered medically necessary when the following are met:**

**FDA-Approved Indication**

1. **Cystinuria.** Approve for 1 year in the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient weighs ≥ 20 kg; AND
   - **B)** Documentation is provided that the diagnosis of cystinuria has been confirmed based on laboratory testing (e.g., urinary cystine crystals present on microscopy, quantitative urine cystine assay); AND

**C)** According to the prescriber, the patient has had an inadequate response to high fluid intake, dietary modification, and urinary alkalization; AND

**D)** The medication is prescribed by, or in consultation with, a nephrologist, urologist, or physician who specializes in the treatment of cystinuria

**E)** Preferred product criteria is met for the products as listed in the below table(s)

**Employer Plans:**

| Product | Criteria |
|---|---|
| **Thiola** (tiopronin) tablets | The patient has tried **tiopronin tablets** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction |
| **Thiola EC** (tiopronin) delayed-release tablets | Patient has tried tiopronin tablets |

**Individual and Family Plans:**

| Product | Criteria |
|---|---|
| **Thiola** (tiopronin) tablets | Patient has tried **tiopronin tablets** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction |
| **Thiola EC** (tiopronin) delayed-release tablets | Patient has tried tiopronin tablets |
| **Venxxiva** (tiopronin) delayed-release tablets | Patient has tried tiopronin tablets |

**Tiopronin for any other use is considered not medically necessary. Criteria will be updated as new published data are available.**

## References


1. Thiola® tablets [prescribing information]. San Antonio, TX: Mission Pharmacal; June 2019.
2. Thiola® EC delayed-release tablets [prescribing information]. San Antonio, TX: Mission Pharmacal; March 2021.
3. Cystinuria. National Organization for Rare Disorders. Updated 2020. Available at: https://rarediseases.org/rare-diseases/cystinuria/. Accessed on January 31, 2025.
4. Castro Pereira DJ, Schoolwerth AC, Pais VM. Cystinuria: current concepts and future directions. *Clin Nephrology.* 2015;83(3):138-146.

5. Pearle MS, Goldfarb DS, Assimos DG, et al. American Urological Association. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192(2):316-24.
6. Venxxiva® delayed-release tablets [prescribing information]. Cambridge, UK: Torrent; December 2024.
7. Azer SM, Goldfarb DS. A Summary of Current Guidelines and Future Directions for Medical Management and Monitoring of Patients with Cystinuria. Healthcare (Basel). 2023 Feb 24;11(5):674.

## Revision Details

| Type of Revision | Summary of Changes | Date |
|---|---|---|
| Selected Revision | No criteria changes | 01/15/2025 |
| Selected Revision | Individual and Family Plans added to the policy.<br><br>**Policy Title:**<br>**Updated** from "Tiopronin" **to** "Metabolic Disorders – Tiopronin"<br><br>**Added** Venxxiva, a branded generic tiopronin delayed-release product, to the Policy; the same criteria apply for all tiopronin products.<br><br>**Preferred Product Table**:<br>Added Thiola EC and Venxxiva to the Individual and Family Plans table. | 05/01/2025 |

The policy effective date is in force until updated or retired.