**Tiopronin**

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**Related Coverage Resources**

**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. 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**

This policy supports medical necessity review for the following tiopronin products:

- **Thiola®** (tiopronin tablets)
- **Thiola® EC** (tiopronin delayed-release tablets)

**Medical Necessity Criteria**

Tiopronin products (Thiola, Thiola EC) are considered medically necessary when the following are met:

1. **Cystinuria.** Individual meets **ALL** of the following criteria:
   A. Documented diagnosis of homozygous cystinuria confirmed based on laboratory testing (for example, urinary cystine crystals present on microscopy, quantitative urine cystine assay)
   B. Individual weighs 20 kg or more
   C. Documented failure/inadequate response to high fluid intake, dietary modification, and urinary alkalization
D. Prescribed by, or in consultation with, a nephrologist, urologist, or physician who specializes in the treatment of cystinuria

Coverage for Tiopronin products (Thiola, Thiola EC) varies across plans and may require the use of preferred products in addition to the medical necessity criteria listed above. Refer to the customer’s benefit plan document for coverage details.

When coverage requires the use of preferred products, there is documentation of ONE of the following:

A. The individual has had inadequate efficacy to the number of covered alternatives according to the table below

OR

B. The individual has a contraindication according to FDA label, significant intolerance, or is not a candidate* for the covered alternatives according to the table below

*Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], other attributes/conditions, or is unable to administer and requires this dosage formulation

Employer Group Non-Covered Products and Preferred Covered Alternatives by Drug List:

<table>
<thead>
<tr>
<th>Non-Covered Product</th>
<th>Standard / Performance</th>
<th>Value / Advantage</th>
<th>Cigna Total Savings</th>
<th>Legacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiola (tiopronin) tablets</td>
<td>• tiopronin tablet (generic for Thiola)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiola EC (tiopronin) delayed-release tablets</td>
<td>• tiopronin tablet (generic for Thiola)</td>
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*Documentation that individual has tried the bioequivalent generic product AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Tiopronin products (Thiola, Thiola EC) are considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up to 12 months.

Reauthorization approval duration is up to 12 months.
Conditions Not Covered

Tiopronin products (Thiola, Thiola EC) are considered experimental, investigational or unproven for ANY other use.

Background

OVERVIEW
Thiola and Thiola EC 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

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 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), 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.

References