Effective Date **4/1/2024**
Next Review Date… **4/1/2025**
Coverage Policy Number **IP0202**

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)

Coverage for the following tiopronin products (Thiola, Thiola ES) varies across plans and requires the use of preferred products in addition to the criteria listed below. Refer to the customer's benefit plan document for coverage details.

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

Medical Necessity Criteria

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

Cystinuria. Individual meets **ALL** of the following criteria:

A. Documented diagnosis of homozygous cystinuria confirmed based on laboratory testing
B. Weighs 20 kg or more
C. Documented failure to high fluid intake, dietary modification, and urinary alkalization
D. Medication is prescribed by, or in consultation with, a nephrologist, urologist, or physician who specializes in the treatment of cystinuria
E. Non-Covered Product Criteria is met, refer to below table(s)

Employer Group Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Thiola (tiopronin) tablets	Trial of **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	Documentation of failure, contraindication, or intolerance to tiopronin tablets

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.

Reauthorization Criteria

Continuation of tiopronin products (Thiola, Thiola EC) are considered medically necessary for the treatment of cystinuria when the above medical necessity criteria are met AND beneficial response is demonstrated.

Authorization Duration

Initial approval duration: up to 12 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven

Background

OVERVIEW
Tiopronin tablets (Thiola, generic) 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, 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.

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 October 10, 2023.
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.