

THIOLA[®] (tiopronin)

Dosing and Administration in Patients With Cystinuria

Summary

Prescribing Information

- THIOLA (tiopronin) immediate-release tablets are a reducing and cystine-binding thiol drug¹
- The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine 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 reduced¹
- In an uncontrolled study of 66 patients with cystinuria age 9 to 68 years, adverse events (AE) with an occurrence rate $\geq 5\%$ included anemia, nausea, proteinuria, and rash¹

Background

- Cystinuria is a genetic disorder that results in the formation of kidney stones and affects ~1 in 7,000 to ~1 in 10,000 people in the United States²
- The American Urological Association (AUA) has established evidence-based guidelines for the diagnosis, prevention, and follow-up of adults with kidney stones, based on systematic review of published studies³
- To decrease incidence of stone formation, urinary cystine concentration should be reduced to <250 mg/L⁴
- A study of 31 pediatric and adult patients with cystinuria assessed the effect of tiopronin on management of cystine levels and cystine stone formation⁵

Study Data

- Systematic review resulted in 27 guideline statements to inform clinicians on the use of a screening evaluation for stone formers, appropriate initiation of metabolic evaluation, and recommendations for treatment³
- Several recommendations within these guidelines directly address monitoring of patients undergoing treatment for formation of kidney stones³
- In patients with cystinuria (N=31), treatment with tiopronin resulted in significantly reduced cystine levels in the urine and decreased cystine stone formation⁵
- In this clinical study, doses of tiopronin as high as 3000 mg/day were used⁵

Prescribing Information

- THIOLA (tiopronin) immediate-release tablets are a reducing and cystine-binding thiol drug for oral use. THIOLA is indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are not responsive to these measures alone¹
- The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine 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 reduced¹
- AEs occurring at an incidence of $\geq 5\%$ in an uncontrolled trial in 66 patients with cystinuria age 9 to 68 years are shown in **Table 1**. Patients in group 1 had previously been treated with d-penicillamine; those in group 2 had not. Of those patients who had stopped taking d-penicillamine due to toxicity (34 out of 49 patients in group 1), 22 were able to continue treatment with THIOLA. In those without prior history of d-penicillamine treatment, 6% developed reactions of sufficient severity to require THIOLA withdrawal¹

Table 1. Adverse Reactions Occurring in One or More Patients

System Organ Class	Adverse Reaction	Group 1 Previously Treated With d-penicillamine (n=49)	Group 2 Naive to d-penicillamine (n=17)
Blood and Lymphatic System Disorders			
	anemia	1 (2%)	1 (6%)
Gastrointestinal Disorders			
	nausea	12 (25%)	2 (12%)
	emesis	5 (10%)	-
	diarrhea/soft stools	9 (18%)	1 (6%)
	abdominal pain	-	1 (6%)
	oral ulcers	6 (12%)	3 (18%)
General Disorders and Administration Site Conditions			
	fever	4 (8%)	-
	weakness	2 (4%)	2 (12%)
	fatigue	7 (14%)	-
	peripheral (edema)	3 (6%)	1 (6%)
	chest pain	-	1 (6%)
Metabolism and Nutrition Disorders			
	anorexia	4 (8%)	-
Musculoskeletal and Connective Tissue Disorders			
	arthralgia	-	2 (12%)
Renal and Urinary Disorders			
	proteinuria	5 (10%)	1 (6%)
	impotence	-	1 (6%)
Respiratory, Thoracic and Mediastinal Disorders			
	cough	-	1 (6%)
Skin and Subcutaneous Tissue Disorders			
	rash	7 (14%)	2 (12%)
	ecchymosis	3 (6%)	-
	pruritus	2 (4%)	1 (6%)
	urticaria	4 (8%)	-
	skin wrinkling	3 (6%)	1 (6%)

Summary	PI	Background	Study Data	References
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- AEs have also been reported during post-approval use of THIOLA (**Table 2**). Because post-approval reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to THIOLA exposure.¹

Table 2. Adverse Reactions Reported for THIOLA Pharmacovigilance by System Organ Class and Preferred Term

System Organ Class	Preferred Term
Cardiac Disorders	congestive heart failure
Ear and Labyrinth Disorder	vertigo
Gastrointestinal Disorders	abdominal discomfort; abdominal distension; abdominal pain; chapped lips; diarrhea; dry mouth; dyspepsia; eructation; flatulence; gastrointestinal disorder; gastroesophageal reflux disease; nausea; vomiting; jaundice; liver transaminitis
General Disorders and Administration Site Conditions	asthenia; chest pain; fatigue; malaise; pain; peripheral swelling; pyrexia; swelling
Investigations	glomerular filtration rate decreased; weight increased
Metabolism and Nutrition Disorders	decreased appetite; dehydration; hypophagia
Musculoskeletal and Connective Tissue Disorders	arthralgia; back pain; flank pain; joint swelling; limb discomfort; musculoskeletal discomfort; myalgia; neck pain; pain in extremity
Nervous System Disorders	ageusia; burning sensation; dizziness; dysgeusia; headache; hypoesthesia
Renal and Urinary Disorders	nephrotic syndrome; proteinuria; renal failure
Skin and Subcutaneous Tissue Disorders	dry skin; hyperhidrosis; pemphigus foliaceus; pruritus; rash; rash pruritic; skin irritation; skin texture abnormal; skin wrinkling; urticaria

Dosage and Administration

- Adults: The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dose was about 1000 mg/day¹
- Pediatrics: The recommended initial dosage in pediatric patients weighing 20 kg and greater is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients¹
- Administer THIOLA in 3 divided doses at the same times each day at least 1 hour before or 2 hours after meals¹
- Consider starting THIOLA at a lower dosage in patients with history of severe toxicity to d-penicillamine¹
- There is no information on overdosage with tiopronin¹

Monitoring

- Monitoring of patients taking THIOLA includes¹:
 - Measurement of urinary cystine 1 month after starting THIOLA and every 3 months after. THIOLA dosage should be adjusted to maintain urinary cystine concentration <250 mg/L

- Assessment for proteinuria before treatment and every 3 to 6 months during treatment
- Discontinuation of THIOLA in patients who develop proteinuria and monitoring of urinary protein and urinary function. After resolution of proteinuria, restarting THIOLA at a lower dose can be considered

Background

Cystinuria Disease State

Cystinuria is a genetic metabolic disorder that disrupts transport of dibasic amino acids in the proximal tubules of the kidney.^{2,4} Cystinuria is characterized by excessive urine levels of cystine, arginine, lysine, and ornithine. Concentrations of cystine in excess of 250 mg/L in the urine can lead to formation of crystals and calculi (stones) in the kidney, bladder, and ureters. Due to the low solubility of cystine in urine, patients may develop hundreds of stones per year; severe cases bring about an increased risk of developing hypertension, chronic kidney disease, and end-stage kidney disease.^{2,4} Cystinuria occurs in both adults and children and affects males and females in equal numbers. Symptoms typically begin between ages 10 and 30 years, with mean age of first presentation of 12 to 13 years.^{2,4}

The primary objective of treatment for cystinuria is the reduction of urinary cystine. A multifaceted approach to treatment may decrease urinary cystine and prevent cystine stone formation.²

This includes daily consumption of large amounts of fluid to increase urine volume and decrease cystine levels, alkalization of urine with potassium citrate and acetazolamide to increase dissolution of cystine, and further alkalization by modifications in dietary salt and animal protein intake.² Specifically, it is recommended that patients³:

- maintain a daily fluid intake of 4 L in order to dilute urinary cystine and achieve a targeted minimum urine output of 2.5 L/day
- maintain a urine pH level of 7.0 by taking potassium alkali
- maintain a diet low in animal protein and restrict sodium intake to ≤ 2300 mg/day

Treatment Guidelines

In 2014, the AUA published guidelines for the medical management of kidney stones. The objective was to provide a clinical framework for the diagnosis, prevention, and follow-up of adults with kidney stones based on published studies meeting prespecified qualifications. Development of guidelines was largely based on a systematic review conducted by the Agency for Healthcare Research and Quality on recurrent nephrolithiasis in adults. These data were supplemented with additional searches of PubMed and EMBASE for relevant studies (January 2007 to November 2012) and further systematic review. A total of 46 studies were identified and utilized to develop evidence-based guidelines.³

Publications identified within the search period were systematically reviewed within an extensive peer review process composed of 40 reviewers of various backgrounds. Comments from peer reviewers were discussed and reviewed by the AUA panel and ultimately revised as needed. The AUA nomenclature system links each statement type to strength of the evidence and the panel's judgment of the balance between benefits and risks/burdens. In areas lacking sufficient evidence, additional statements were noted as Clinical Principles and Expert Opinions.³

Clinical Research

The impact of tiopronin on urine cystine levels and formation of cystine stones was assessed in 31 adult and pediatric patients with confirmed cystinuria who started long-term treatment of tiopronin between 1979 and 1992. Conditions for beginning tiopronin treatment were urinary concentration of cystine >1200 µmol/L in a 24-h urine sample, or active stone formation despite standard of care including administration of sodium bicarbonate and a high fluid intake or both. Tiopronin doses ranged from 500 to 3000 mg/day (mean, 1540 mg/day). The primary objective of tiopronin treatment was the prevention of cystine stone formation. Frequency of stone formation was estimated from patient records. Noted symptoms of renal colic, stone passage and formation were identified as renal stone episodes. The number of newly formed urinary tract stones was assessed by radiogram and reported stone passages. Urinary excretion of cystine was measured by ion-exchange chromatography at least every 6 months; the total number of cystine measurements was 709. Urinary cystine concentrations >1200 µmol/L in repeated 24-h urine collections or continuous formation of stones prompted an increased dose of tiopronin.⁵

Study Data

Treatment Guidelines

The AUA developed 27 guideline statements informing clinicians on the use of a screening evaluation for first-time and recurrent kidney stone formers, appropriate use of a metabolic evaluation in recurrent stone formers and high-risk first-time formers, and follow-up of medication and/or dietary therapies in select patients.³

Within the guidelines, several recommendations specifically address diet, pharmacologic therapies, and monitoring:

- Clinicians should counsel patients with cystine stones to limit sodium and protein intake (Expert Opinion)³
 - Uric acid crystal formation and growth are more frequent in more acidic urine. It should be recommended to patients to increase alkali load and decrease acid load in their diet
- Clinicians should offer cystine-binding thiol drugs, such as alpha-mercaptopropionylglycine (tiopronin), to patients with cystine stones who are unresponsive to dietary modifications and urinary alkalinization, or have large recurrent stone burdens (Expert Opinion)³
 - Standard of care for cystine stones is not always effective in all patients. In these cases, cystine-binding thiol drugs are the next step in therapy
- Clinicians should obtain periodic blood testing to assess for adverse effects in patients on pharmacological therapy (Standard; Evidence Strength: Grade: A)³
 - Medications carry risk of AEs, some of which are identifiable by blood testing
- Clinicians should obtain a repeat stone analysis, when available, especially in patients not responding to therapy (Expert Opinion)³

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- Changes in stone composition may reflect a lack of efficacy of current treatment approaches
- Clinicians should periodically obtain follow-up imaging studies to assess for stone growth or new stone formation based on stone activity (plain abdominal imaging, renal ultrasonography or low dose computerized tomography) (Expert Opinion)³
 - Imaging provides a sensitive way to monitor stone activity, including growth of existing stones or formation of new stones
- As part of patient follow-up, clinicians should obtain a single 24-hour urine specimen for stone risk factors within 6 months of the initiation of treatment to assess response to dietary and/or medical therapy (Expert Opinion)³
 - The aim of treatment is to promote changes in the urinary environment, including the reduction of cystine, to reduce stone recurrence or growth
- After the initial follow-up, clinicians should obtain a single 24-hour urine specimen annually or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response (Expert Opinion)³
 - Long-term and repeated assessment provides information on patient adherence and response to treatment and can identify the need for changes in treatment approach

Clinical Study Data

In a study of long-term use of tiopronin, patient age at the time of first renal stone disease symptoms was 23 years (range, 3 to 48 years); mean age at the start of tiopronin treatment was 42 years (range, 17 to 70 years). Average time between first signs of symptoms and beginning treatment with tiopronin was 15 years (range, 0.9 to 41 years). Average time of treatment was 7.8 years (range, 0.4 to 12).⁵

During tiopronin treatment, 13 of 31 patients were free of new cystine stone formation and stone growth. No staghorn stones, described as large kidney stones that fill the renal pelvis and at least 1 renal calyces, were formed.^{5,6} Five cases of partial stone dissolution were observed; 19 surgeries were performed on 9 patients. Six surgical patients were treated with extracorporeal shock wave lithotripsy. At final dose of tiopronin, 19 patients showed no signs of stone activity. Assessment of annual rates of renal stone episodes showed a 69% decrease in episodes, a 60% decrease in the frequency of new stone formation, and 72% decrease in required surgical procedures.⁵

In addition to effect on kidney stone activity, treatment with tiopronin combined with fluid intake resulted in significantly decreased mean urinary cystine. Measured levels were lower at time of final dose of tiopronin ($862 \pm 228 \mu\text{mol}$) compared to levels at baseline ($1382 \pm 526 \mu\text{mol}$), $P < 0.001$. Urinary cystine excretion was also significantly reduced, with $1619 \pm 524 \mu\text{mol}$ at final tiopronin dose vs $2355 \pm 917 \mu\text{mol}$ at baseline. Concentrations of cystine $< 1200 \mu\text{mol/L}$ were achieved in 28 of the 31 patients at time of last tiopronin dose.⁵

Safety

AUA guidelines noted that tiopronin may cause elevations in liver enzymes and induce anemia and other hematologic abnormalities, and recommended that clinicians obtain periodic blood tests to assess for adverse reactions.³

In a study of 31 adult and pediatric patients with cystinuria, 5 patients withdrew from study drug; 4 patients experienced proteinuria and 1 patient showed systemic lupus erthematosus-like

syndrome without renal involvement. In all 5 cases, symptoms were reversed upon termination of tiopronin.⁵

References

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