THIOLA® (tiopronin)

Effects on Cystine (Kidney) Stones in Patients With Cystinuria

Summary

Prescribing Information

- THIOLA (tiopronin) immediate-release tablets are a reducing and cystine-binding thiol drug[1]
- 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 reduced[1]
- In an uncontrolled study of 66 patients with cystinuria age 9 to 68 years, adverse events (AE) with an occurrence rate ≥5% included anemia, nausea, proteinuria, and rash[1]

Background

- Cystinuria is a genetic disorder that results in the formation of kidney stones and affects ~1 in 7000 to ~1 in 10,000 people in the United States[2]
- 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 studies[3]
- A pivotal multicentric study evaluated long-term treatment with tiopronin (mean±SD dose of 1193±450 mg/day) in 66 patients with cystinuria with ongoing alkali therapy and dietary and maintained fluid regimens[4]
- The safety and efficacy of tiopronin were also evaluated in several open-label studies in patients with cystinuria[5-13]

Study Data

- In a pivotal trial, tiopronin appeared to be effective with a tolerable safety profile[4]:
    - New stone formation rate was significantly decreased during treatment with tiopronin for patients with or without prior d-penicillamine therapy
    - In treatment-naïve patients (n=14) who received tiopronin for 4 months to 4 years (mean, 1.59 years), 71.4% of patients achieved remission and reduced stone formation was achieved in 94.1% of patients
    - Tiopronin was equally as effective as d-penicillamine in reducing cystine excretion. During long term treatment with tiopronin (at 1000 mg/day), urinary cystine was maintained at 350 to 560 mg/day and urinary saturation of cystine was kept undersaturated

  - Among 49 patients with prior d-penicillamine therapy, 41 reported AEs with d-penicillamine and 37 reported AEs with tiopronin. Among the 17 patients without prior d-penicillamine therapy, 11 reported AEs with tiopronin

- In open-label studies, effects of tiopronin on stone remission and reduction in stone formation in patients with cystinuria were consistent with results from the pivotal study[5-13]

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 alone[1]
- 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 reduced[1]
- AEs occurring at an incidence of ≥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 withdrawal[1]

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%)

- 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

- Monitoring of patients taking THIOLA includes[1]:
  - 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.[2,14] 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.[2,14] 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.[2,14]
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 patients[3]:

- 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]

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]

Recommended treatment guidelines include both dietary and pharmacologic therapies:

- Clinicians should counsel patients with cystine stones to limit sodium and protein intake (Expert Opinion)[3]
    - Dietary therapy should be offered in combination with pharmacological treatment
    - Cystine concentration is greatly involved in stone formation; therefore, high fluid intake is an important therapy
    - ≥4 liters/day is often required to meet a target urinary cystine concentration <250 mg/L
    - Sodium restriction aids in reducing cystine excretion; target goal is ≤100 mEq (2300 mg) per day
    - Limiting animal protein is recommended, as it can increase cystine substrate load

- 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 alkalization, or have large recurrent stone burdens (Expert Opinion)[3]
    - First-line therapy includes increased fluid intake, restriction of sodium and protein intake, and urinary alkalization
    - Cystine-binding thiol drugs should be added when dietary therapy is insufficient
    - Tiopronin is potentially more effective and associated with fewer adverse events than d-penicillamine
- Clinicians should obtain periodic blood testing to assess for adverse effects in patients on pharmacological therapy (Standard; Evidence Strength: Grade: A)[3]
    - Blood testing can detect some adverse events associated with medications prescribed for stone prevention
    - Tiopronin may cause an increase in liver enzymes and induce anemia and other hematologic abnormalities

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]

Pivotal Study

A multicenter study was conducted to determine the safety and efficacy of long-term treatment with tiopronin in 66 patients (ages 9 to 68 years; mean±SD, 32.0±13.3 years) with cystine nephrolithiasis. Cystine nephrolithiasis was documented by the presence of cystine on stone analysis and cystine excretion >400 mg/day. Prior to receiving treatment with tiopronin, patients were required to have had ≥1 stone episodes (spontaneous passage, surgical removal, or appearance on abdominal X-ray) during the previous 2 years. Patients did not have severe renal failure (endogenous creatinine clearance <25 mL/minute), congenital abnormalities of the urinary tract, or persistent urinary tract infection with urea-splitting organisms.[4]

Participants were enrolled in one of two groups: patients who had taken d-penicillamine prior to tiopronin (Group 1; n=49*)* and patients who did not have prior d-penicillamine therapy (Group 2; n=17). The primary objective of the study was to determine the safety and efficacy of tiopronin in patients with known toxicity to d-penicillamine. A secondary objective was to determine if the biochemical responses to treatment with tiopronin were similar to those of d-penicillamine.[4]

Tiopronin was initiated at a dose of 100 to 2000 mg/day (mean±SD, 1193±450 mg/day) while ongoing alkali therapy and dietary and fluid regimens were maintained. Patients were instructed to take tiopronin in 3 to 4 divided doses ≥1 hour before or 2 hours after meals. Prior to taking tiopronin, patients in Group 1 received d-penicillamine at a mean±SD dose of 1125±640 mg/day for a mean±SD of 2.81±3.94 years and stopped d-penicillamine at least 1 month prior to starting tiopronin.[4]

Effect on Stone Formation

A total of 57 patients (Group 1, n=43; Group 2, n=14) received tiopronin for ≥4 months (6 patients in Group 1 and 3 patients in Group 2 did not because of AEs or recent entry). In Group 1, 43 patients received tiopronin for 4 months to 3.7 years (mean, 1.81 years). More than 2 years prior to treatment with tiopronin, 17 patients had taken d-penicillamine, while 26 patients had

received d-penicillamine for ≥6 months (mean, 1.55 years). In these 26 patients, new stone formation rate was 9.1±22.0 stones per patient-year while on d-penicillamine, with only 1 (3.8%) patient achieving remission. Pre-existing stones were present in 60.4% of patients when treatment with tiopronin was initiated. The new stone formation rate was 5.8±16.8 stones per patient-year during treatment with tiopronin (*P*<0.001 by Chi-square test), 61.5% of patients achieved remission, and 73.1% had reduced stone formation. In Group 2, 14 patients received tiopronin for 4 months to 4 years (mean, 1.59 years). Pre-existing stones were present in 71.4% of patients when treatment with tiopronin was initiated. Stone formation data before and during treatment with tiopronin in Groups 1 and 2 are summarized in **Table 3**.[4]

Table 3. Stone Formation Before and During Treatment With THIOLA

	Group 1 (n=43)	Group 2 (n=14)
Previous stone formation rate (stones per patient-year) 2 years prior to THIOLA	8.5±22.3	5.3±13.0
New stone formation rate (stones per patient-year) during THIOLA treatment	3.7±13.2*	1.83±1.29*
Remission (cessation of stone formation) with THIOLA (% patients)	62.8%	71.4%
Reduction in stone formation with THIOLA (% patients)	81.4%	94.1%

**P*<0.001 by Chi-square test.
Adapted from Pak et al. *J Urol*. 1986;136(5):1003-1008.

Effect on Urinary Cystine

The mean urinary cystine concentration was 778±290 mg/day at baseline. During treatment with tiopronin, the mean urinary cystine concentration decreased significantly (range, 353-553 mg/per day for Months 4-36; *P*<0.05).[4]

Safety

Among the 49 patients in Group 1 who had taken both drugs, 41 reported AEs with d-penicillamine and 37 with tiopronin. The most common AEs in Group 1 are listed in **Table 4**. Among the 41 patients who reported AEs with d-penicillamine, 32 also experienced AEs with tiopronin. Among the 34 patients who discontinued d-penicillamine due to AEs, 22 were able to continue treatment with tiopronin.[4]

Table 4. Adverse Reactions in Group 1

	THIOLA n (%)	d-penicillamine n (%)
Nausea	12 (24.5)	18 (36.7)
Emesis	5 (10.2)*	14 (28.6)
Diarrhea/soft stools	9 (18.4)	4 (8.2)
Anorexia	4 (8.2)	9 (18.4)
Impaired taste	2 (4.1)	4 (8.2)
Oral ulcers	6 (12.2)	2 (4.1)
Rash	7 (14.3)*	17 (34.7)
Ecchymosis	3 (6.1)	3 (6.1)
Urticaria	4 (8.2)	2 (4.1)
Skin wrinkling	3 (6.1)	2 (4.1)
Dyspnea	1 (2.0)	4 (8.2)
Fever	4 (8.2)	6 (12.2)
Weakness	2 (4.1)	3 (6.1)
Fatigue	7 (14.3)	8 (16.3)
Proteinuria	5 (10.2)	6 (12.2)
Peripheral edema	3 (6.1)	5 (10.2)
Multiple symptoms	21 (42.9)*	33 (67.3)
≥1 symptoms	37 (75.5)	41 (83.7)
Discontinued treatment due to adverse events	15 (30.6)	34 (69.4)

*Significant difference ($P<0.05$) by Chi-square test.
Adapted from Pak et al. *J Urol*. 1986;136(5):1003-1008.

Among the 17 patients in Group 2 without prior d-penicillamine therapy, 11 reported AEs with tiopronin. The AEs in Group 2 are listed in **Table 5**. One patient discontinued tiopronin due to proteinuria.[4]

Table 5. Adverse Reactions to THIOLA in Group 2

	n (%)
Nausea	2 (11.8)
Soft stools	1 (5.9)
Abdominal pain	1 (5.9)
Oral ulcers	3 (17.6)
Rash	2 (11.8)
Pruritus	1 (5.9)
Skin wrinkling	1 (5.9)
Arthralgia	2 (11.8)
Weakness	2 (11.8)
Anemia	1 (5.9)
Proteinuria	1 (5.9)
Peripheral edema	1 (5.9)
Impotence	1 (5.9)
Chest pain	1 (5.9)
Cough	1 (5.9)
Multiple symptoms	4 (23.5)
≥1 symptoms	11 (64.7)
Discontinued treatment due to adverse events	1 (5.9)

Adapted from Pak et al. *J Urol*. 1986;136(5):1003-1008.

Open-Label Studies

The safety and efficacy of tiopronin in reducing urinary cystine and kidney stone formation were also evaluated in several open-label studies in patients with cystinuria.[5-13]

In open-label studies, effects of tiopronin on stone remission and reduction in stone formation in patients with cystinuria were consistent with results from the pivotal study.[5-13] In one study, 13 of 31 patients experienced no new stone formation; at final dose of tiopronin 19 patients showed no stone activity.[5] Across additional studies, some patients showed no recurrent stone formation, complete or partial stone dissolution, and reduced urinary cystine levels.[7-13] Tiopronin appeared to be tolerable across dosages, with an acceptable safety profile.[5,7-12]

References

1. THIOLA. Prescribing information. Mission Pharmacal; January 2021.
2. Cystinuria - symptoms, causes and treatment. National Organization for Rare Disorders. Accessed June 29, 2023. https://rarediseases.org/rare-diseases/cystinuria/
3. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol*. 2014;192(2):316-324. doi:10.1016/j.juro.2014.05.006
4. Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol*. 1986;136(5):1003-1008. doi:10.1016/s0022-5347(17)45188-3
5. Lindell A, Denneberg T, Hellgren E, Jeppsson JO, Tiselius HG. Clinical course and cystine stone formation during tiopronin treatment. *Urol Res*. 1995;23(2):111-117. doi:10.1007/BF00307941
6. Lindell A, Denneberg T, Jeppsson JO. Urinary excretion of free cystine and the tiopronin-cysteine-mixed disulfide during long-term tiopronin treatment of cystinuria. *Nephron*. 1995;71(3):328-342. doi:10.1159/000188740
7. Hautman RE. Cystine stone—therapy with alpha-mercapto-propionylglycine—ten years of experience with forty-two patients. In: Smith LH, Robertson WG, Finlayson B, eds. *Urolithiasis: Clinical and basic research*. Springer; 1983:139-143.
8. Koide T, Kinoshita K, Takemoto M, Yachiku S, Sonoda T. Conservative treatment of cystine calculi: Effect of oral alpha-mercaptopropionylglycine on cystine stone dissolution and on prevention of stone recurrence. *J Urol*. 1982;128(3):513-516. doi:10.1016/s0022-5347(17)53023-2
9. Miano L, Gallucci M, Petta S. Results of medical treatment of cystine lithiasis. *Eur Urol*. 1979;5(4):265-272. doi:10.1159/000473127
10. Remien A, Kallistratos G, Burchardt P. Treatment of cystinuria with THIOLA (alpha-mercaptopropionyl glycine). *Eur Urol*. 1975;1(5):227-228.
11. Tekin A, Tekgul S, Atsu N, Sahin A, Bakkaloglu M. Cystine calculi in children: The results of a metabolic evaluation and response to medical therapy. *J Urol*. 2001;165(6 Pt 2):2328-2330.
12. Pavanello L, Rizzoni G, Dussini N, et al. Cystinuria in children. *Eur Urol*. 1981;7:139-143.

13. Dello Strologo L, Laurenzi C, Legato A, Pastore A. Cystinuria in children and young adults: Success of monitoring free-cystine urine levels. *Pediatr Nephrol*. 2007;22(11):1869-1873. doi:10.1007/s00467-007-0575-2

14. Eisner BH, Goldfarb DS, Baum MA, et al. Evaluation and medical management of patients with cystine nephrolithiasis: A consensus statement. *J Endourol*. 2020;34(11):1103-1110. doi:10.1089/end.2019.0703