THIOLA® and THIOLA EC® (tiopronin) Drug Formulations

Summary

Prescribing Information

- THIOLA (tiopronin) immediate-release and THIOLA EC delayed-release tablets are reducing and cystine-binding thiol drugs[1,2]
- 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[1,2]
- THIOLA is supplied as a round, white, 100 mg immediate-release tablet imprinted in red with "M" on one side and blank on the other side[1]
- THIOLA EC is available in 2 dosages[2]:
    - 100 mg delayed-release, supplied as a round, white to off-white tablet imprinted with "T1" on one side with red ink and blank on the other side
    - 300 mg delayed-release, supplied as a round, white to off-white tablet imprinted with "T3" on one side with red ink and blank on the other side
- For patients who cannot swallow the tablet whole, THIOLA EC can be crushed and mixed with applesauce. Administration of THIOLA EC with other liquids or foods has not been studied and is not recommended[2]

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 States[3]
- To decrease incidence of stone formation, urinary cystine concentration should be reduced to <250 mg/L[4]

Study Data

- A switching study between THIOLA and THIOLA EC has not been conducted. Therefore, the dose of THIOLA EC cannot be extrapolated from the dose of THIOLA[5]

Prescribing Information

- THIOLA (tiopronin) immediate-release and THIOLA EC (tiopronin) delayed-release tablets are reducing and cystine-binding thiol drugs for oral use. THIOLA and THIOLA EC are 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[1,2]
- 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[1,2]

Dosage and Administration

THIOLA Immediate-Release and THIOLA EC Delayed-Release

- Adults: The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dose was about 1000 mg/day[1,2]
- 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 patients[1,2]
- Administer THIOLA or THIOLA EC in 3 divided doses at the same times each day at least 1 hour before or 2 hours after meals[1,2]
- Consider starting THIOLA or THIOLA EC at a lower dosage in patients with history of severe toxicity to d-penicillamine[1,2]
- There is no information on overdosage with tiopronin[1,2]

Monitoring

- Monitoring of patients taking THIOLA or THIOLA EC includes[1,2]:
  - Measurement of urinary cystine 1 month after starting THIOLA or THIOLA EC and every 3 months after. 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 or THIOLA EC in patients who develop proteinuria and monitoring of urinary protein and urinary function. After resolution of proteinuria, restarting THIOLA or THIOLA EC at a lower dose can be considered

Pharmacodynamics[1,2]

- The decrement in urinary cystine produced by tiopronin is generally proportional to the dose
- A reduction in urinary cystine of 250-350 mg/day at tiopronin dosage of 1 g/day, and a decline of approximately 500 mg/day at a dosage of 2 g/day, might be expected
- Tiopronin has a rapid onset and offset of action, showing a fall in cystine excretion on the first day of administration and a rise on the first day of drug withdrawal

Pharmacokinetics[1,2]

Absorption

- When THIOLA immediate-release and THIOLA EC single doses were given to fasted healthy subjects (n=39), the median time to peak plasma levels (T_{max}) was 1 (range: 0.5 to 2.1) and 3 (range: 1.0 to 6.0) hours, respectively
- The peak exposure (C_{max}) and total exposure (AUC_{0-t}) of tiopronin from THIOLA EC tablets were decreased by 22% and 7% respectively compared to THIOLA immediate-release tablets
- When THIOLA EC tablets were administered crushed in applesauce, the median time to peak plasma levels of tiopronin (T_{max}) was 1 hour (range: 0.5 to 2.0) compared to 3.1 hours (range: 1.5 to 4.0) when administered as intact tablets
- When THIOLA EC tablets were administered crushed in applesauce, the maximum concentration (C_{max}) and exposure (AUC_{0-t}) to tiopronin were increased by 38% and 14%, respectively, compared to THIOLA EC tablets administered intact
- Administration of the THIOLA EC tablet with food decreases C_{max} of tiopronin by 13% and AUC_{0-t} by 25% compared to THIOLA EC administered in a fasted state
- Since the drug is dosed to effect, THIOLA EC tablets can be administered with or without food; administer at the same time each day with a routine pattern with regard to meals

Excretion

- When tiopronin is given orally, up to 48% of dose appears in urine during the first 4 hours and up to 78% by 72 hours

Drug Interactions[2]

- Tiopronin is released faster from THIOLA EC in the presence of alcohol and the risk for adverse events associated with THIOLA EC when taken with alcohol is unknown. Avoid alcohol consumption 2 hours before and 3 hours after taking THIOLA EC

Background

Cystinuria Disease State

Cystinuria is a genetic metabolic disorder that disrupts transport of dibasic amino acids in the proximal tubules of the kidney.[3,4] 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.[3,4] 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.[3,4]

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 patients[6]:

- 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

References

1. THIOLA. Prescribing information. Mission Pharmacal; January 2021.
2. THIOLA EC. Prescribing information. Mission Pharmacal; March 2021.
3. Cystinuria - symptoms, causes and treatment. National Organization for Rare Disorders. Accessed June 29, 2023. https://rarediseases.org/rare-diseases/cystinuria/
4. 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
5. Data on file. Mission Pharmacal; 2023.
6. 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