HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CYSTARAN™ safely and effectively. See full prescribing information for CYSTARAN.

CYSTARAN (cysteamine ophthalmic solution) 0.44%.
Initial U.S. Approval: 1994

----------INDICATIONS AND USAGE----------
CYSTARAN is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop of CYSTARAN in each eye, every waking hour. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Sterile ophthalmic solution containing 6.5 mg/mL of cysteamine hydrochloride equivalent to 4.4 mg/mL of cysteamine (0.44%). (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
To minimize the risk of contamination, do not touch the dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence approximately 10% or greater) are sensitivity to light, redness, eye pain/irritation, headache and visual field defects. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sigma-Tau Pharmaceuticals, Inc. at 1-888-393-4584 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CYSTARAN is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

2 DOSAGE AND ADMINISTRATION

Instill one drop of CYSTARAN in each eye, every waking hour.

Do not touch dropper tip to any surface, as this may contaminate the solution.

Discard after 1 week of use.

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic solution containing 6.5 mg/mL of cysteamine hydrochloride equivalent to 4.4 mg/mL of cysteamine (0.44%).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution

To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Benign Intracranial Hypertension

There have been reports of benign intracranial hypertension (or pseudotumor cerebri) associated with oral cysteamine treatment that has resolved with the addition of diuretic therapy.

There have also been reports associated with ophthalmic use of cysteamine; however, all of these patients were on concurrent oral cysteamine.

5.3 Use with Contact Lenses

CYSTARAN contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of solution and may be reinserted 15 minutes following its administration *[see Patient Counseling Information (17.3)]*.

5.4 Topical Ophthalmic Use Only

CYSTARAN is for topical ophthalmic use only.

6 ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure in controlled clinical trials of six months to 19 years duration in approximately 300 patients.

The most frequently reported ocular adverse reactions occurring in ≥10% of patients were sensitivity to light, redness, and eye pain/irritation, headache and visual field defects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies of ophthalmic cysteamine in pregnant women. CYSTARAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Pregnancy Category C.
Teratology studies have been performed in rats at oral doses in a range of 37.5 mg/kg/day to 150 mg/kg/day (about 0.2 to 0.7 times the recommended human maintenance dose on a body surface basis) and have revealed cysteamine bitartrate to be teratogenic. Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly, and exencephaly.

Nonteratogenic Effects: Cysteamine was fetotoxic, resulting in intrauterine death and growth retardation in rats at oral doses of 0.2 to 0.7 times the recommended human maintenance dose on a body surface basis.

8.3 Nursing Mothers

It is not known whether oral cysteamine is excreted in human milk. Because many drugs are excreted in human milk and because of the manifested potential of cysteamine for developmental toxicity in suckling rat pups when it was administered to their lactating mothers at an oral dose of 375 mg/kg/day (2,250 mg/m^2/day, 1.7 times the recommended human dose based on body surface area), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The incremental increase in systemic cysteamine levels derived from drug applied topically to the eye in patients treated with oral cysteamine is negligible.

8.4 Pediatric Use

The safety and effectiveness of CYSTARAN (cysteamine ophthalmic solution) 0.44% have been established.

8.5 Geriatric Use

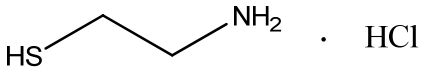
When the clinical studies with CYSTARAN were conducted, the reduced life expectancy from cystinosis did not make it possible to include patients in the geriatric age range.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of cysteamine following ophthalmic administration of cysteamine ophthalmic solution has not been evaluated because ophthalmic exposure compared to systemic exposure is negligible. The majority of the patients in the ophthalmic clinical studies are assumed to have had some degree of renal impairment due to their underlying systemic disease. The total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine; thus, the systemic exposure following ophthalmic administration is expected to be negligible compared to oral administration.

11 DESCRIPTION

CYSTARAN is a sterile ophthalmic solution containing 6.5 mg/mL of cysteamine hydrochloride, equivalent to 4.4 mg/mL of cysteamine (0.44%) as the active ingredient. Cysteamine is a cystine-depleting agent which lowers the cystine content of cells in patients with cystinosis.



Molecular Formula: C_2H_7NS HCl
Molecular Weight: 113.61

Each milliliter of CYSTARAN contains: Active: cysteamine 4.4 mg (equivalent to cysteamine hydrochloride 6.5 mg); Preservative: benzalkonium chloride 0.1 mg; Inactive Ingredients: sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH to 4.1-4.5), and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cysteamine acts as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides and reduces corneal cystine crystal accumulation.

12.3 Pharmacokinetics

The peak plasma concentration of cysteamine following ocular administration of cysteamine ophthalmic solution in humans is unknown, but it is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine bitartrate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.
Cysteamine was not mutagenic in the Ames test. It produced a negative response in an *in vitro* sister chromatid exchange assay in human lymphocytes but a positive response in a similar assay in hamster ovarian cells.

Repeat breeding reproduction studies were conducted in male and female rats. Cysteamine was found to have no effect on fertility and reproductive performance at an oral dose of 75 mg/kg/day (450 mg/m^2/day, 0.4 times the recommended human dose based on body surface area). At an oral dose of 375 mg/kg/day (2,250 mg/m^2/day, 1.7 times the recommended human dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.

14 CLINICAL STUDIES

Clinical efficacy was evaluated in controlled clinical trials in approximately 300 patients. The primary efficacy end point was the response rate of eyes that had a reduction of at least 1 unit in the photo-rated Corneal Cystine Crystal Score (CCCS) at some time point during the study when baseline CCCS ≥1, or a lack of an increase of more than 1 unit in CCCS throughout the study when baseline CCCS <1.

Study 1 combined the data from three smaller studies. For eyes with a lower baseline of CCCS <1, the response rate was 13% (4/30) [95% CI: (4, 32)]. For eyes with a higher baseline of CCCS ≥1, the response rate was 32% (94/291) [95% CI: (27, 38)].

Study 2 evaluated ocular cystinosis patients who had a baseline of CCCS ≥1. The response rate was 67% (10/15) [95% CI: (38, 88)].

Study 3 also evaluated ocular cystinosis patients; for eyes with a baseline of CCCS ≥1, the response rate was 33% (3/9) [95% CI: (8, 70)].

Corneal crystals accumulate if CYSTARAN is discontinued.

16 HOW SUPPLIED/STORAGE AND HANDLING

CYSTARAN (cysteamine ophthalmic solution) 0.44% is supplied in a 15 mL, opaque, white, low-density polyethylene (LDPE) bottle with a 15 mm white, LDPE controlled dropper tip and closed with a white, polypropylene screw cap.

Storage: Store in freezer at -25°C to -15°C (-13°F to 5°F). Thaw for approximately 24 hours before use. Store thawed bottle at 2°C to 25°C (36°F to 77°F) for up to 1 week. Do not refreeze. Discard after 1 week of use.

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17 PATIENT COUNSELING INFORMATION

17.1 Storage of Bottles

1. Patients should be advised to store bottles in the freezer in the original carton.
2. Each week, one new bottle should be removed from the freezer.
3. Patients should be advised to allow the bottle to thaw completely (approximately 24 hours) prior to use.
4. After the bottle is completely thawed, the patient should record the discard date on the bottle label. The discard date is seven (7) days from the day the bottle is thawed.
5. Patients should be advised to store thawed bottle at 2°C to 25°C (36°F to 77°F) for up to 1 week. The thawed bottles should not be refrozen.
6. At the end of 1 week (7 days), patients should discard the bottle. There may be medication left in the bottle; however, the bottle must be discarded by the patient because the medication is only stable for 1 week after thawing.

17.2 Risk of Contamination

Patients should be advised not to touch the eyelid or surrounding areas with the dropper tip of the bottle. The cap should remain on the bottle when not in use.

17.3 Use with Contact Lenses

Patients should be advised that contact lenses should be removed prior to application of CYSTARAN. Contact lenses may be reinserted 15 minutes following CYSTARAN administration.

17.4 Topical Ophthalmic Use Only

Patients should be advised that CYSTARAN is for topical ophthalmic use only.

Manufactured by:

Hi-Tech Pharmacal, Co., Inc., Amityville, NY 11701 for

sigma-tau
PHARMACEUTICALS, INC.
GAITHERSBURG, MD 20878

Place Rev Code Here

cyspi-5-ht 10/2012