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

CYSTADROPS® (cysteamine ophthalmic solution) 0.37%, for topical ophthalmic use
Initial U.S. Approval: 1994

----------INDICATIONS AND USAGE----------
CYSTADROPS is a cystine-depleting agent indicated for the treatment of corneal cystine crystal deposits in adults and children with cystinosis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop of CYSTADROPS in each eye, 4 times a day during waking hours. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 3.8 mg/mL of cysteamine (0.37%). (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 (≥ 10%) are eye pain, vision blurred, eye irritation, ocular hyperaemia, instillation site discomfort, eye pruritus, lacrimation increased, and ocular deposits. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CYSTADROPS is a cystine-depleting agent indicated for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

Instill one drop of CYSTADROPS in each eye, 4 times a day during waking hours.

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

In case of concomitant therapy with other topical ocular products, an interval of 10 minutes should be allowed between successive applications. Eye ointments should be administered last.

If the patient misses an instillation, the patient should be told to administer a dose as soon as feasible and then continue the treatment with the next scheduled instillation. Discard bottle 7 days after first opening.

2.2 Preparation for Administration

1. Patients should be advised to store new unopened CYSTADROPS bottles in the refrigerator in the original carton between 36°F to 46°F (2°C to 8°C).
2. Each week, one new bottle should be removed from the refrigerator. Patients are to write the date the bottle was opened in the space on the carton. After first opening, store opened CYSTADROPS at room temperature between 68°F to 77°F (20°C to 25°C). **Do not** refrigerate after opening.
3. Patients are to wash their hands carefully in order to avoid microbiological contamination of the content in the bottle.
4. Remove the green protective cap (see Figure A).
5. Remove the metal seal (see Figure B).
6. Remove the gray stopper (see Figure C) from the bottle.
7. Do not touch the opening of the bottle after removing the gray stopper.

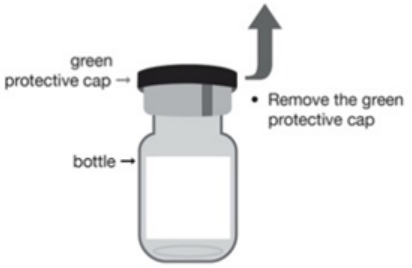


Figure A.

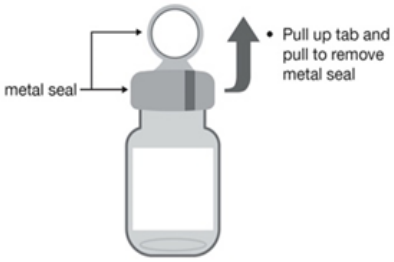


Figure B.

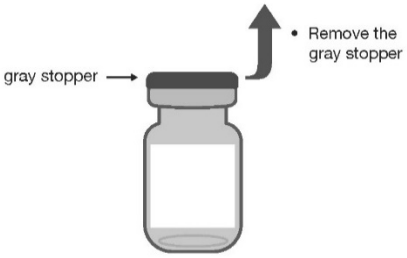


Figure C.

1. Take the dropper out of its packaging, without touching the end intended to be attached to the bottle, attach it (see Figure D) to the bottle and do not remove it.
2. Patients should be advised not to lose the small white cap that comes on the top of the dropper (see Figure E). Keep the small white cap tightly closed when not in use.

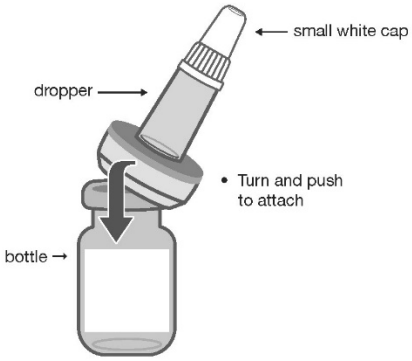


Figure D.

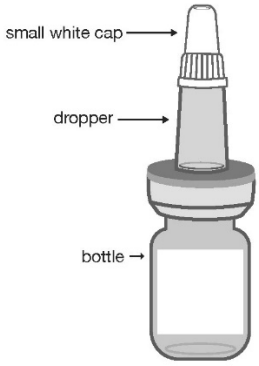


Figure E.

3. Instill one drop of CYSTADROPS in each eye, 4 times a day during waking hours.
4. At the end of 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 7 days after first opening.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 3.8 mg/mL of cysteamine (0.37%).

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 Contact Lens Use

CYSTADROPS contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact with soft contact lenses should be avoided. Contact lenses should be removed prior to application of solution and may be reinserted 15 minutes following its administration *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 most common adverse reactions (≥ 10%) reported during clinical trials were eye pain, vision blurred, eye irritation, ocular hyperaemia, instillation site discomfort, eye pruritus, lacrimation increased, and ocular deposits.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ophthalmic cysteamine in pregnant women to inform any drug associated risks. Oral administration of cysteamine to pregnant rats throughout the period of organogenesis was teratogenic at doses 240 to 960 times the recommended human ophthalmic dose (based on body surface area) *[see Data]*. CYSTADROPS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

Teratology studies have been performed in rats at oral doses in the range of 37.5 mg/kg/day to 150 mg/kg/day (240 to 960 times the recommended human ophthalmic dose based on body surface area) and have shown cysteamine bitartrate to be teratogenic. Observed teratogenic findings were intrauterine death, cleft palate, kyphosis, heart ventricular septal defects, microcephaly, exencephaly, and growth deficits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cysteamine in human milk, the effects on the breastfed infants, or the effects on milk production. Cysteamine administered orally is present in milk of lactating rats. It is not known whether measurable levels of cysteamine would be present in maternal milk following topical ocular administration of CYSTADROPS. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CYSTADROPS and any potential adverse effects on the breastfed child from CYSTADROPS or from the underlying maternal conditions.

8.4 Pediatric Use

The safety and effectiveness of CYSTADROPS has been established in pediatric patients. Use of CYSTADROPS is supported by adequate and well controlled trials in pediatric patients and additional experience supporting the safety of CYSTADROPS.

8.5 Geriatric Use

Clinical studies of CYSTADROPS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

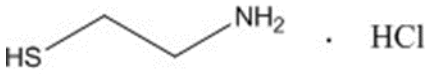
8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of cysteamine following ophthalmic administration of cysteamine ophthalmic solution has not been evaluated. Clearance of cysteamine from the conjunctival sac of the eye is not dependent on renal function and the total systemic dose is negligible, so impaired renal function is unlikely to affect total body clearance.

The total daily ophthalmic dose is less than 4% 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

CYSTADROPS is a sterile, viscous, ophthalmic solution containing 3.8 mg/mL of cysteamine (0.37%) equivalent to 5.6 mg/mL of cysteamine hydrochloride (0.55%). 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 CYSTADROPS contains: Active: cysteamine 3.8 mg (equivalent to cysteamine hydrochloride 5.6 mg); Preservative: benzalkonium chloride 0.1 mg; Inactive Ingredients: carmellose sodium, citric acid monohydrate, disodium edetate dihydrate, hydrochloric acid and sodium hydroxide (to adjust pH to 4.6-5.4), and water for injection.

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, because all patients concomitantly received oral cysteamine and the total daily ophthalmic dose is less than 4% of the recommended oral daily dose of cysteamine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.

Mutagenesis
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.

Impairment of Fertility
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 (480 times the recommended human ophthalmic dose based on body surface area). At an oral dose of 375 mg/kg/day (2,400 times the recommended human ophthalmic dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.

14 CLINICAL STUDIES

Clinical safety and efficacy of CYSTADROPS were assessed in two studies: a single-arm study conducted for 5 years (OCT-1) and a randomized controlled study conducted for 90 days (CHOC).

In the OCT-1 study, 8 patients with cystinosis (2 males and 6 females) with a mean age of 12.1 ± 4.6 (range: 7.0 – 21.0) were enrolled and received a median of 4 drops/eye/day of CYSTADROPS. In CHOC study, 32 patients with cystinosis (15 males and 17 females) with a mean age of 17.1 ± 13.0 (range: 2.9 – 62.6) were enrolled and received a median of 4 drops/eye/day. Fifteen patients were exposed to CYSTADROPS and 16 were exposed to cysteamine hydrochloride 0.1% (control arm).

Efficacy was assessed with In-Vivo Confocal Microscopy total score (IVCM score) by quantifying the cystine crystals in the cornea. A decrease in IVCM total score from baseline indicated a reduction in corneal crystals.

In the CHOC study, after 30 and 90 days of treatment with CYSTADROPS, 12% and 40% reduction in the total IVCM total score across all corneal layers was observed from baseline, respectively. CYSTADROPS demonstrated greater reduction compared to the control arm at 90 days. The average reduction in IVCM total score was 4.6 in the CYSTADROPS arm and 0.5 in the control arm, mean difference 3.8 (95% CI: (2.1, 5.6)).

In the OCT-1 study, a mean decrease in corneal cystine crystal deposits of 30%, in comparison with baseline, was maintained over the 60 month period of the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

CYSTADROPS (cysteamine ophthalmic solution) 0.37% is supplied as a 5 mL sterile viscous solution in a 10 mL amber glass bottle closed by a bromobutyl stopper and sealed with an aluminum tear-off cap. A PVC dropper applicator with HDPE closure is packed separately and included in each carton box.

Each carton box (NDC 55292-410-05) contains 1 bottle (NDC 55292-410-05) and 1 dropper applicator individually wrapped.

Before First Opening: Before opening, store new, unopened CYSTADROPS in the refrigerator between 36°F to 46°F (2°C to 8°C). Keep the bottle in the outer carton in order to protect from light.

After First Opening: After opening, store opened CYSTADROPS at room temperature between 68°F to 77°F (20°C to 25°C). **Do not** refrigerate after opening. Keep the dropper bottle tightly closed in the outer carton in order to protect from light. Discard 7 days after first opening.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Preparation for Administration and Storage of Bottles

1. Advise patients to store new unopened bottles in the refrigerator in the original carton.
2. Each week, one new bottle should be removed from the refrigerator. Advise patients to write the date the bottle was opened in the space on the carton. After first opening, keep the bottle tightly closed and store at room temperature in the original carton.
3. Patients are to wash their hands carefully in order to avoid microbiological contamination of the content in the bottle.
4. Remove the green protective cap (see Figure A).
5. Remove the metal seal (see Figure B).
6. Remove the gray stopper (see Figure C) from the bottle.
7. Do not touch the opening of the bottle after removing the gray stopper.

Figure A.

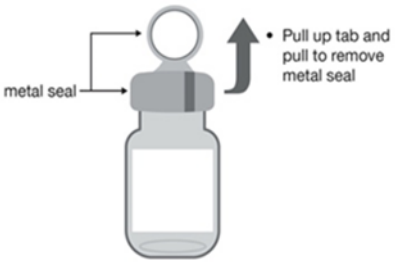


Figure B.

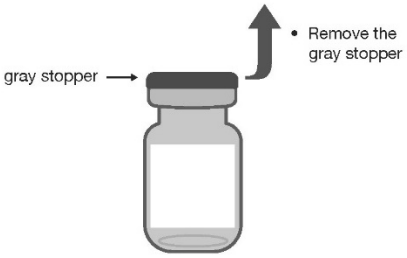


Figure C.

1. Take the dropper out of its packaging, without touching the end intended to be attached to the bottle, attach it (see Figure D) to the bottle and do not remove it.
2. Patients should be advised not to lose the small white cap (see Figure E) that comes on the top of the dropper. Keep the small white cap tightly closed when not in use.

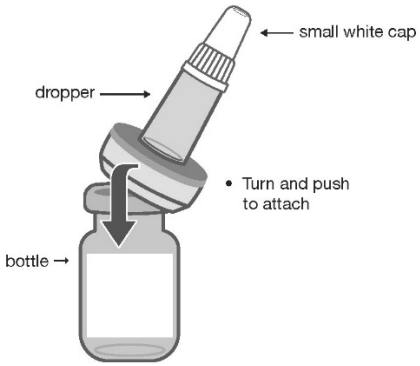


Figure D.

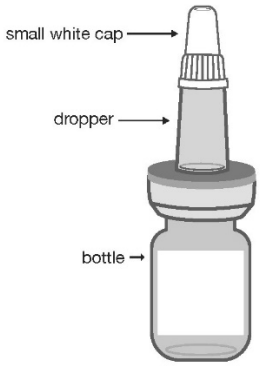


Figure E.

3. Instill one drop of CYSTADROPS in each eye, 4 times a day during waking hours.
4. Instruct patients to discard the bottle at the end of 7 days. There may be medication left in the bottle; however, the bottle must be discarded by the patient because the medication is only stable for 7 days after first opening.

Risk of Contamination

Advise patients 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.

Contact Lens Use

Advise patients that contact lenses should be removed prior to application of CYSTADROPS. Contact lenses may be reinserted 15 minutes following CYSTADROPS administration *[see Warnings and Precautions (5.3)]*.

Topical Ophthalmic Use

Advise patients that CYSTADROPS is for topical ophthalmic use.

Missed Dose

If the patient misses an instillation, instruct the patient to administer a dose as soon as feasible and then to continue the treatment with the next scheduled instillation.

Manufactured by: Baccinex SA, 2822 Courroux, Switzerland

Manufactured for: Recordati Rare Diseases Inc., Lebanon, NJ 08833, U.S.A.

RECORDATI RARE DISEASES GROUP

This product label may have been updated. For the most recent prescribing information, please visit www.recordatirarediseases.com/us.