When your patient is diagnosed with cystinosis, you should know:

THE EYES HAVE IT[1]

In this booklet:

- A brief overview of cystinosis, including genetic etiology, potential complications, and diagnostic criteria
- An exploration of ocular complications of cystinosis, including corneal crystal accumulation and its consequences, and management strategies for physicians
- Information about CYSTARAN® (CYSTEAMINE OPHTHALMIC SOLUTION) 0.44% for patients with cystinosis

cystaran®

(cysteamine ophthalmic solution) 0.44%

INDICATION

CYSTARAN® (CYSTEAMINE OPHTHALMIC SOLUTION) 0.44% is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Please see complete Important Safety Information on the back of this booklet and accompanying Full Prescribing Information.

INDICATION

CYSTARAN® (CYSTEAMINE OPHTHALMIC SOLUTION) 0.44% STERILE is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

IMPORTANT SAFETY INFORMATION

- 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.
- 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.
- 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.
- CYSTARAN® is for topical ophthalmic use only.
- 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.

About Cystinosis

Cystinosis is a rare but serious multi-system genetic disorder that initially manifests in the kidneys during infancy and early childhood as renal Fanconi syndrome.[2] A defect in the transport protein cystinosin causes free cystine to accumulate in the body, eventually forming crystals within bodily tissues.[3]

Cystinosis is classified as a lysosomal storage disease and involves multiple organ systems.[2] It is potentially sight-threatening.[2]

GENETIC ORIGINS AND DISEASE PHENOTYPES

While the most common form of cystinosis is caused by a deletion on the 57-kb segment of the CTNS gene, other variants exist.[3,4] Severe (infantile) cases have two severe mutations, while other patients may be heterozygous for the severe mutation. This variance is responsible for cystinosis presentations that are milder and/or late-onset.[3]

As with other rare diseases, under-ascertainment of cases of cystinosis is a problem.[4] The full spectrum of clinical variants has not yet been described, but over 100 variations have been identified.[4,5] Three disease phenotypes are currently recognized:

Infantile (classic) nephropathic cystinosis

- **Accounts for 95% of reported cases**[3,4]
- Incidence at 1 per 100,000/200,000 live births worldwide[3]
- Approximately 600 affected children and adults in the U.S.[8]

Juvenile/Late-onset (intermediate) nephropathic cystinosis

- **Precise incidence unknown**
- Same organ system involvement as infantile nephropathic cystinosis, but with a slower progression of disease[4]

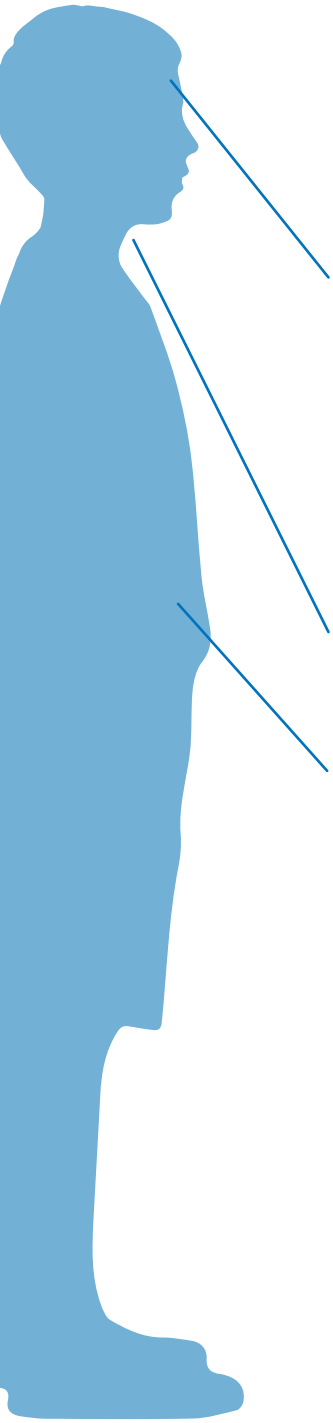
Non-nephropathic/Ocular (benign) cystinosis

- **Precise incidence unknown**
- Characterized only by corneal crystal accumulation with no renal component or organ involvement whatsoever[3]

Ocular involvement in the form of corneal crystal accumulation is the only commonality between **all three forms** of cystinosis.[2]

Nonrenal Complications of Cystinosis[1]

Complications may include[1]:



(entire body)

- Vacuolar myopathy
- Male hypogonadism
- Vascular calcifications

- Photophobia (due to corneal involvement)
- Retinal blindness
- Benign intracranial hypertension
- Central nervous system involvement
- Cerebral calcifications
- Hypercholesterolemia
- Corneal crystals

- Swallowing dysfunction
- Hypothyroidism

- Pulmonary dysfunction
- Diabetes mellitus – requiring insulin therapy
- Pancreatic exocrine insufficiency
- Nodular regenerating hyperplasia of the liver

DIAGNOSTIC CRITERIA

Systemic Diagnosis

Diagnosis of nephropathic cystinosis (whether infantile or juvenile) can be made by measuring leukocyte cystine content (LCC)[4]

- In unaffected persons, concentration is less than 0.2 nmol of half-cystine per mg of protein
- In nephropathic cystinosis patients, values exceed 2.0 nmol per mg of protein

Ocular Diagnosis

Imaging of the corneas may show crystal accumulation in affected patients and is a suitable diagnostic indicator for ocular cystinosis[8]

- Slit-lamp photography is often used, although this is not reliable in infants younger than one year[4]
- Other ophthalmologic diagnostic tools are available

Molecular Diagnosis

Molecular diagnosis can be done in affected individuals to confirm the presence of the defective CTNS gene. This can be accomplished through prenatal chorionic villi sampling or DNA testing on cultured fibroblasts obtained from a skin biopsy[5]

- Compound heterozygous or homozygous mutations should be found
- Genetic testing of both the patient and the patient's family is recommended

Ocular Complications of Cystinosis and Clinical Management Implications

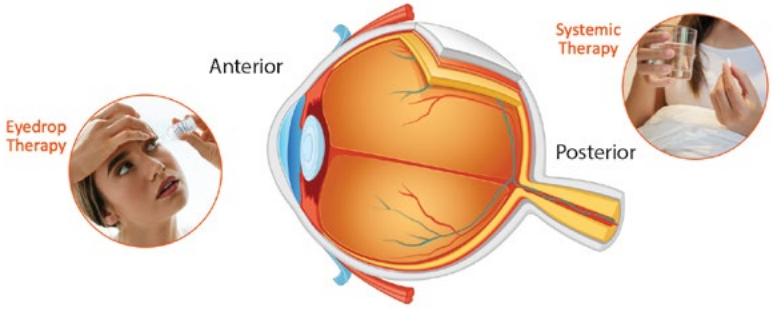
ANTERIOR SEGMENT COMPLICATIONS

While a cystinosis patient's systemic therapy can help prevent crystal accumulation in the eye's posterior segment and prevent complications there, including retinal damage, there is no vascular supply to the cornea to deliver the drug. [6-8]

The anterior segment is left vulnerable to accumulating crystals, necessitating the use of a topical therapy.[6-8] In severe untreated or undertreated cases, anterior segment complications can be severe[7]:

- Band keratopathy
- Corneal scarring
- Peripheral corneal neovascularization
- Posterior synechiae
- Pupillary block with secondary glaucoma

The need for a **"whole-eye"** approach to cystinosis that encompasses adherence to both **systemic** and **topical** medication is clear.



SYMPTOMS OF CORNEAL CRYSTAL ACCUMULATION

Ask your cystinosis patients if they're experiencing these symptoms:

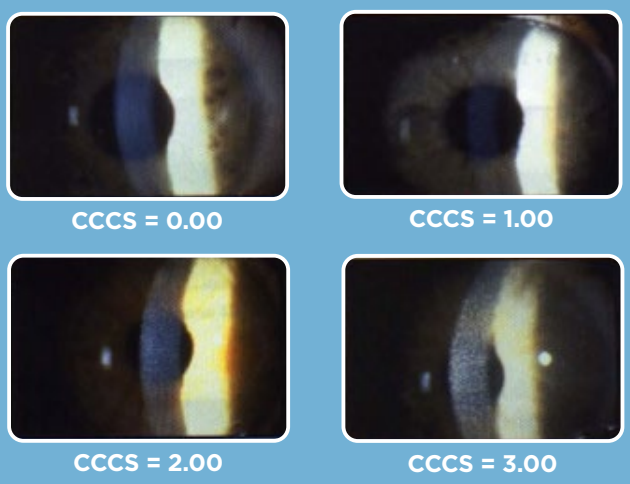
- Photophobia (typically the first and most commonly reported)[6,9]
- Blepharospasm (as a result of chronic squinting due to photophobia)[9,10]
- Chronic red eye[9]
- Foreign body sensation[9]
- Pain (which may be caused by recurrent corneal erosions or corneal scarring)[7,10]

Ocular complications are common causes of **discomfort** and **disability** in patients with nephropathic cystinosis if left untreated.[7]

DETERMINING THE EXTENT OF CRYSTAL ACCUMULATION

Corneal Cystine Crystal Score (CCCS)

The extent of crystal accumulation can be estimated using slit lamp photography.[10] Patients are assigned a CCCS, which uses a scale from 0 (no crystals) to 3 (densely packed with crystals) with .25 increments. This method is widely available to ophthalmologists, as slit lamp photography is part of a routine eye exam.



CORNEAL MANAGEMENT FOR PEDIATRIC PATIENTS

Upon cystinosis diagnosis an ophthalmologist should be involved in patient care as soon as possible.[6]

- Any treatment plan should encompass the entire body.[5]
- When ocular crystals are first diagnosed, eyedrops should be initiated without delay.[7]
- Levels of crystal accumulation can vary widely, even early on.[10] Crystals have been seen in patients as young as 16 months.[10]
- Even young children with cystinosis can start to show signs of severe photophobia, including eye pain and difficulty opening the eyes in daylight.[11]

CORNEAL MANAGEMENT FOR ADULT PATIENTS

Topical therapy can reduce crystal density in patients of all ages, regardless of initial density.[10]

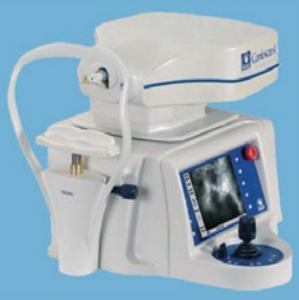
- Older cystinosis patients are more likely to report superficial punctuate keratopathy, foreign body sensation, and pain.[1,7]

ADOPTING A MULTIDISCIPLINARY APPROACH IS KEY

A multidisciplinary approach to the management of cystinosis patients may be key in achieving optimal clinical outcomes.[5,6] For most cystinosis patients, that means regular follow-ups from both **nephrologists** and **ophthalmologists** to assess disease progress and treatment efficacy.

Coordination of care is important and requires the inclusion of the primary care provider in a multidisciplinary plan of care. Other specialists may need to be involved based on complications in other organ systems as well, notably[5]:

- Endocrinologists
- Cardiologists
- Neurologists
- Gastroenterologists



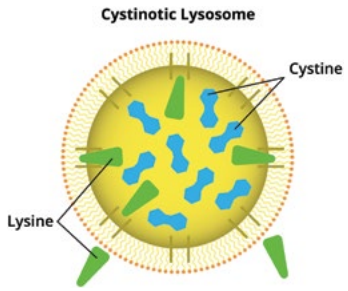
In Vivo Confocal Microscopy (IVCM)

While assigning patients a CCCS based on slit lamp imaging is a well-established method, an examination with an IVCM machine can provide comparatively enhanced accuracy at identifying and quantifying corneal cystine crystals.[6] IVCM is useful for follow up for patients with established ocular/corneal crystals from cystinosis and under an ophthalmologist's direction.

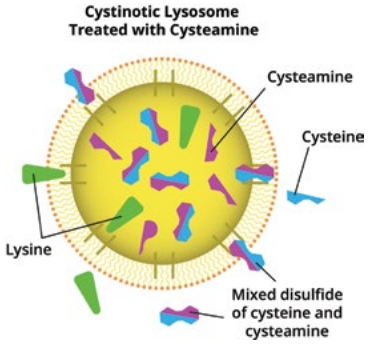
IVCM allows for high resolution imagery in a specific tissue plane or depth and can be used to quantify crystal density in all corneal layers at the cellular level.[12] The capabilities of IVCM that allow for monitoring of the progression of corneal crystal disease as patients age are exciting, but IVCM is not available in all hospitals and community physicians may not have easy access to the technology.[6,9] It may also be difficult to administer an IVCM examination to children.[6]

Cysteamine, the active ingredient in CYSTARAN, is an aminothiol that depletes lysosomal cystine, preventing accumulation of cystine crystals in bodily tissues.[1]

CYSTARAN MECHANISM OF ACTION



Within lysosomes, cysteamine interacts with cystine to form cysteine and cysteine–cysteamine mixed disulfide[1,13]



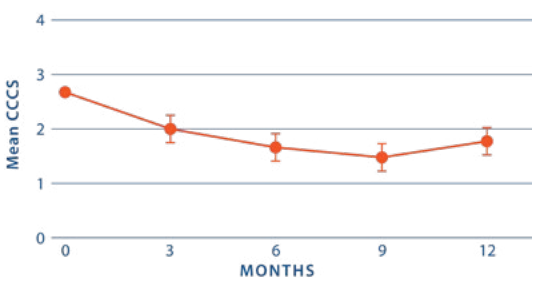
These substances can pass through the lysosomal membrane and be eliminated from the cell[1,13]

CYSTARAN CLINICAL STUDIES

In a prospective study*, 67% of eyes showed CCCS† reductions of ≥ 1 unit[13,14]

***STUDY DESIGN:** Multicenter, randomized, double-blind efficacy trial of CYSTARAN in 15 treatment-naïve patients with a baseline CCCS [0 units (clear at the center) to 3 units (highest crystal density)] of ≥ 1.25. The primary end point was the estimated proportion of eyes with a CCCS reduction ≥1 relative to baseline (where baseline CCCS was ≥1) anytime during the treatment period and at Months 3, 6, 9, and 12. Slit-lamp photography was used to assess CCCS changes from baseline.[13,14]

Rapid CCCS Reductions as Early as 3 Months and Sustained Through 1 Year[14]



† CCCS = Corneal Cystine Crystal Score

In the combined analysis of 3 clinical studies‡, sustained CCCS reductions and improvement in ocular complications[14]

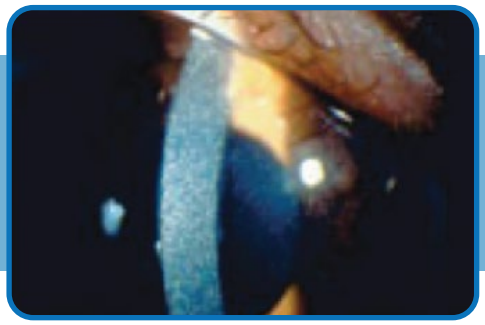
- Overall, 30.5% of eyes treated with CYSTARAN had a CCCS response
  - The greatest response—32%—was seen in eyes with CCCS ≥ 1 unit at baseline

‡**STUDY DESIGN:** In the Combined Analysis of Patients Treated with Ophthalmic Cysteamine (CAPTOC) study, 247 patients were enrolled. Of these, 161 patients were the mITT population (defined as patients with CCCS values at baseline and post baseline timepoints). The primary end point was reduction of CCCS in eyes with high (≥1) CCCS at baseline and lack of increase in CCCS in eyes with low (<1) CCCS at baseline. End points were based on photo-rated CCCS (slit-lamp photography in conjunction with a photography-based scoring system) to quantify and document corneal cystine crystal accumulation over time.[14]

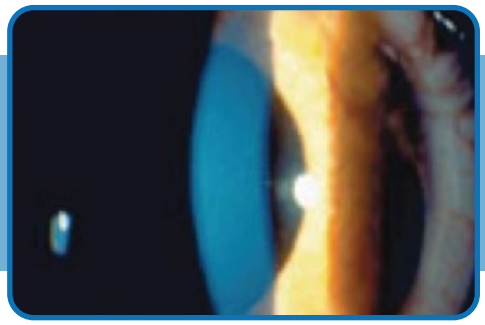
See examples of treatment with CYSTARAN®10*

5-year-old patient

BEFORE

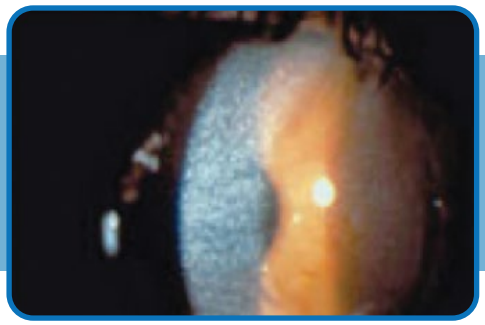


After 15 Months of Treatment

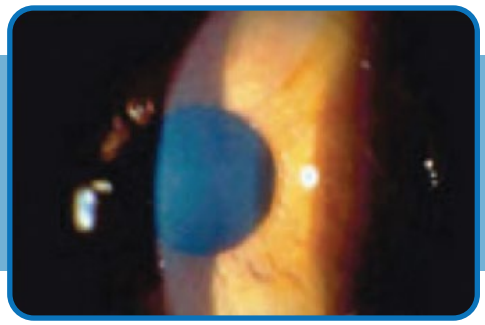


25-year-old patient

BEFORE



After 12 Months of Treatment



* Corneal slit-lamp photographs of patients treated with CYSTARAN.[10] Study represents patients who responded to treatment and in subsequent follow up appointments. Duration of therapy varied from 8 – 41 months.

DOSING AND ADMINISTRATION

- CYSTARAN is supplied in a 15-mL bottle of sterile ophthalmic solution. Each mL contains 6.5 mg cysteamine hydrochloride equivalent to 4.4 mg of cysteamine (0.44%)
- 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
- 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

STORING CYSTARAN

- Patients should be advised to store bottles in the freezer in the original carton
- Each week, one new bottle should be removed from the freezer
- Patients should be advised to allow the bottle to thaw completely (approximately 24 hours) prior to use
- 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
- 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

Visit **www.cystaran.com** for more information about treatment with **CYSTARAN®**

Alliance Rx Walgreens Prime is the **sole dispensing pharmacy** for CYSTARAN

You and your patients can call **1-877-534-9627** to speak directly with an Alliance Rx Walgreens Prime Cystaran team member Monday-Friday 8:00AM-7:00PM EST

INDICATION

CYSTARAN® (CYSTEAMINE OPHTHALMIC SOLUTION) 0.44% STERILE is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

IMPORTANT SAFETY INFORMATION

- 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.
- 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.
- 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.
- CYSTARAN® is for topical ophthalmic use only.
- 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.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088, or call Leadiant Biosciences, Inc. at 1-800-447-0169.

References: 1. Gahl WA, Balog JZ, Kleta R. Nephropathic Cystinosis in Adults: Natural History and Effects of Oral Cysteamine Therapy. *Ann Intern Med*. 2007;147:242-250. 2. Radojkovic, B. Cysteamine eye drops in the treatment of cystinosis – an Australian perspective. *J Pharm Practice and Research* 2015;45:440-445. 3. Nesterova G, Gahl WA. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol* 2008;23:863-878. 4. Gahl, W, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med*. 2002;347(2):111-121 5. Ariceta G, Camacho JA, Fernandez-Obsipo M, Fernandez-Polo A, et al. Cystinosis in adult and adolescent patients: Recommendations for the comprehensive care of cystinosis. *Nefrologia.* 2015;35(3):304-321. 6. Pinxten A-M, Hua M-T, Simpson J, Hohenfellner K, et al. Clinical Practice: A Proposed Standardized Ophthalmological Assessment for Patients with Cystinosis. *Ophthalmol Ther.* 2017;6:93-104. 7. Bishop, R. Ocular Complications of Infantile Nephropathic Cystinosis. *J Peds.* 2017;183S:S19-S21. 8. Huynh, N, Gahl WA, Bishop RJ. Cysteamine ophthalmic solution 0.44% for the treatment of corneal cystine crystals in cystinosis. Expert Rev. *Ophthalmol.* 2013;8(4): 341-345. 9. Liang H, Baudouin C, Hassani RTJ, Brignole-Baudouin F, Labbe A. Photophobia and Corneal Crystal Density in Nephropathic Cystinosis: An In Vivo Confocal Microscopy and Anterior-Segment Optical Coherence Tomography Study. *IOVS*. 2015;56(5): 3218-3225. 10. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Corneal Crystals in Nephropathic Cystinosis: Natural History and Treatment with Cysteamine Eyedrops. *Molec Genet Metab.* 2000;71:100-120. 11. Tsilou E, Zhou M, Gahl WG, Sieving PC, Chan C-C. Ophthalmic Manifestations and Histopathology of Infantile Nephropathic Cystinosis: Report of a Case and Review of the Literature. *Surv Ophthalmol*. 2007;52(1):97-105. 12. Jalbert I, Stapleton F, Papas E, Sweeney DF, Coroneo M. In vivo confocal microscopy of the human cornea. *Br J Ophthalmol*. 2003;87:225-236. 13. CYSTARAN [prescribing information]. Gaithersburg, MD: Leadiant Biosciences, Inc.; 2018. 14. Data on File. Leadiant Biosciences, Inc.

Please see accompanying full **Prescribing Information**.

Leadiant Biosciences

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%, for topical ophthalmic use

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----------

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 Leadiant Biosciences, 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: 4/2020

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

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 Contact Lenses Use

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)]*.

5.4 Topical Ophthalmic Use

CYSTARAN is for topical ophthalmic use.

6 ADVERSE REACTIONS

6.1 Clinical Trials 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

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 86 to 345 times the recommended human ophthalmic dose (based on body surface area) [*see Data*]. CYSTARAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 (86 to 345 times the recommended human ophthalmic dose based on a body surface area) and have revealed 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 CYSTARAN.

8.4 Pediatric Use

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

8.5 Geriatric Use

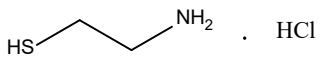
When the clinical studies with CYSTARAN were conducted, the reduced life expectancy from cystinosis did not make it possible to include patients in the geriatric age range.

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

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 (173 times the recommended human ophthalmic dose based on body surface area). At an oral dose of 375 mg/kg/day (864 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 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) in the original carton. 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 the thawed medication. Discard after 1 week of use.

NDC 54482-020-01

17 PATIENT COUNSELING INFORMATION

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.

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.

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.

Topical Ophthalmic Use

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

Manufactured by Hi Tech Pharmacal Co., Inc., Amityville, NY 11701 for Leadiant Biosciences, Inc., Gaithersburg, MD 20878.

cyspi-8-ht 04/2020

Leadiant Biosciences