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

THE EYES HAVE IT[1]

cystaran®

(cysteamine ophthalmic solution) 0.44%

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 for patients with cystinosis

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 page 2 of this booklet or click here for full Prescribing Information.

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- 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 multisystem 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.[3] It is potentially sight-threatening.

GENETIC ORIGINS AND DISEASE PHENOTYPES

The most common form of cystinosis is caused by a deletion on the 57-kb segment of the *CTNS* gene, but over 100 molecular variants exist. Severe (infantile) cases have severe mutations on both copies of the *CTNS* gene, while other patients may be heterozygous for the severe mutation. This variance is responsible for cystinosis presentations that are milder and/or late onset.[4]

As with other rare diseases, the complete diagnosis and detection of cystinosis is under-ascertained, leading to a delay in recognition.[4] Three disease phenotypes are currently recognized:

Infantile (classic) nephropathic cystinosis

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

Juvenile/late-onset (intermediate) nephropathic cystinosis

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

Non-nephropathic/ocular (benign) cystinosis

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

Ocular involvement in the form of corneal crystal accumulation is the only commonality between **all three forms** of cystinosis.[3]

Nonrenal Complications of Cystinosis[1]

Complications may include:

(System-wide)

- Vacuolar myopathy
- Male hypogonadism
- Vascular calcifications
- Hypercholesterolemia

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

- Swallowing dysfunction
- Hypothyroidism

- Pulmonary dysfunction
- Diabetes mellitus (requires 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)

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

- Slit lamp photography is often used, although this is not reliable in infants younger than one year of age
- 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

- 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

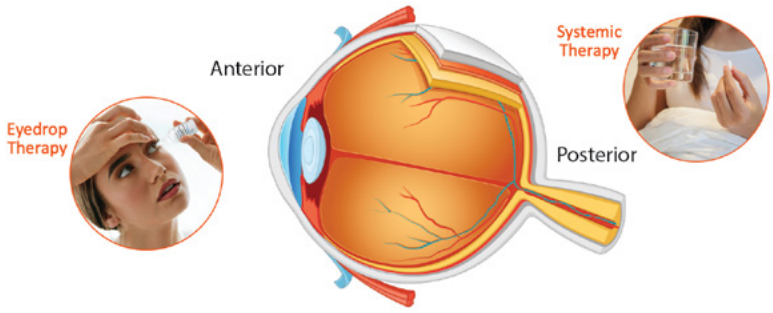
ANTERIOR SEGMENT COMPLICATIONS[6]

While systemic therapy for a patient with cystinosis 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.

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

- 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[8]

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

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

fyo

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

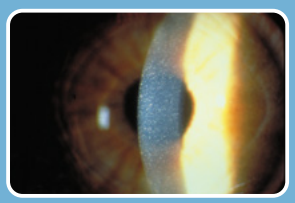
DETERMINING THE EXTENT OF CRYSTAL ACCUMULATION

Corneal Cystine Crystal Score (CCCS)

The extent of crystal accumulation can be estimated using slit lamp photography.[11] Patients are assigned a CCCS, which uses a scale from 0 (no crystals) to 3 (densely packed with crystals) in increments of .25. This method is widely available to ophthalmologists, as slit lamp photography is part of a routine eye exam.


CCCS = 0.00


CCCS = 1.00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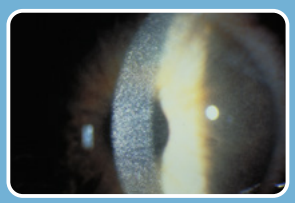
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CORNEAL MANAGEMENT FOR PEDIATRIC PATIENTS

Upon cystinosis diagnosis an ophthalmologist should be involved in patient care as soon as possible.[11]

- Any treatment plan should encompass the entire body.
- When ocular crystals are first diagnosed, eyedrops should be initiated without delay.
- Levels of crystal accumulation can vary widely, even early on. Crystals have been seen as early as 6 months in some patients with cystinosis, with all patients showing crystal accumulation after 16 months.
- Even young children with cystinosis can start to show signs of severe photophobia, including eye pain and difficulty opening the eyes in daylight.

CORNEAL MANAGEMENT FOR ADULT PATIENTS

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

- Older patients with cystinosis are more likely to report superficial punctuate keratopathy, foreign body sensation, and pain.

ADOPTING A MULTIDISCIPLINARY APPROACH IS KEY

A multidisciplinary approach to the management of patients with cystinosis s may be key in achieving optimal clinical outcomes.[8] For most patients with cystinosis, 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:

- Endocrinologists
- Cardiologists
- Neurologists
- Gastroenterologists

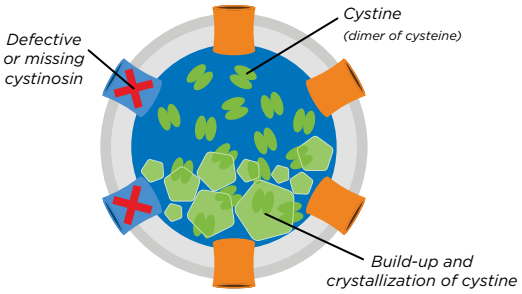
Slit Lamp Photography

Due to widespread availability and ease of use, **slit lamp photography remains the standard of care** for diagnosing corneal crystals.

Cysteamine, the active ingredient in CYSTARAN® (cysteamine ophthalmic solution) 0.44%, is an aminothiol that depletes lysosomal cystine, preventing accumulation of cystine crystals in bodily tissues.[1]

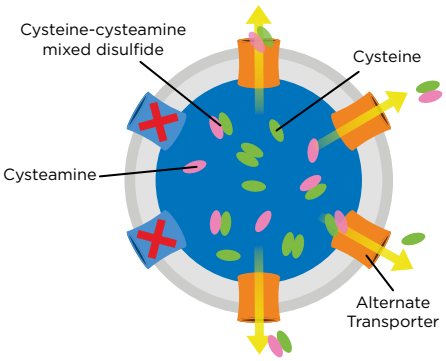
CYSTARAN MECHANISM OF ACTION

Cystinotic Lysosome



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

Cystinotic Lysosome Treated With Cysteamine



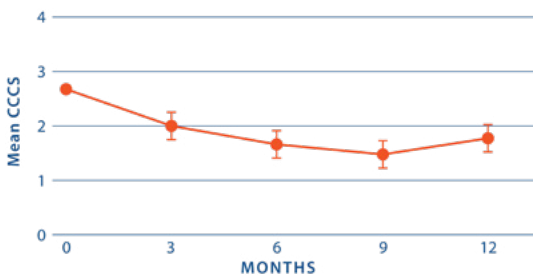
These substances can pass through the lysosomal membrane and be eliminated from the cell[1,13]

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 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.

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



†CCCS = Corneal cystine crystal score, a measure of crystal density assessed using slit lamp photography. CCCS ranges from 0 units (clear at the center) to 3 units (highest crystal density).

In the combined analysis of 3 clinical studies,‡ patients treated with CYSTARAN showed sustained CCCS reductions and improvement in ocular complications

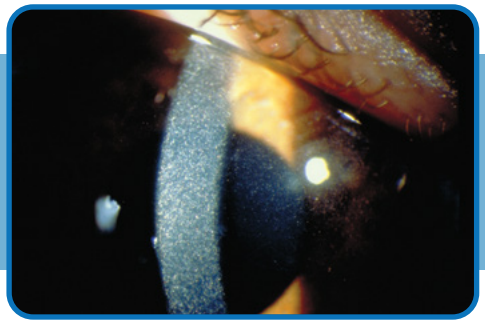
- Overall, 30.5% of eyes treated with CYSTARAN had a CCCS response
  - The greatest response—32%—was seen in eyes with CCCS ≥ 1 unit at baseline

‡**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.

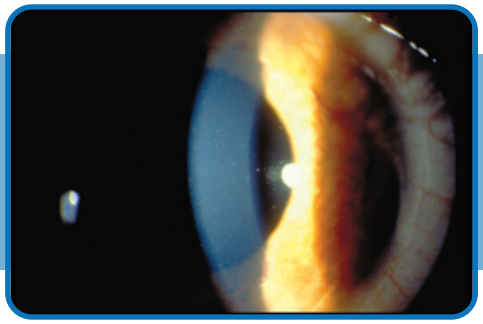
See examples of treatment with CYSTARAN® (cysteamine ophthalmic solution) 0.44%[11]*:

5-year-old patient

Before

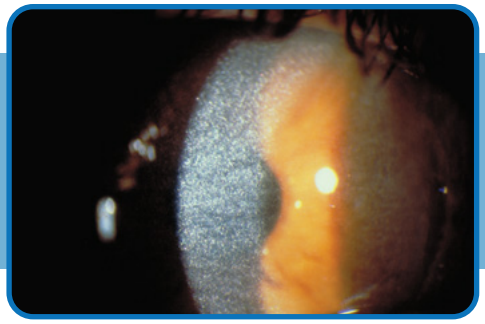


After 15 Months of Treatment

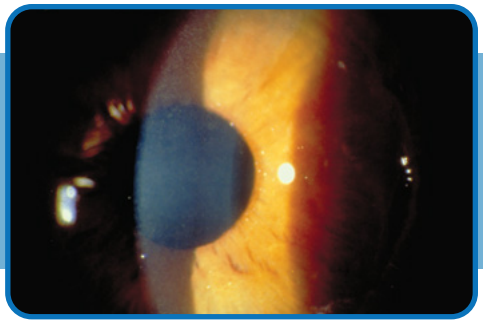


25-year-old patient

Before



After 12 Months of Treatment



*Corneal slit lamp photographs of patients treated with CYSTARAN.[11] Study represents patients who responded to treatment and in subsequent follow-up appointments. Duration of therapy varied from 8 to 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 opening.

STORING CYSTARAN

Before Opening CYSTARAN:

- Patients should be advised to store unopened bottles in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton and foil wrapping.

Opening CYSTARAN:

- Patients should be advised to open the carton and the foil only when starting a new bottle.
- The patient should record the discard date on the bottle, which is one week from the day the foil and bottle were opened.

After Opening CYSTARAN:

- During the week of use, patients should be advised to store the bottle at room temperature, 20°C to 25°C (68°F to 77°F).
- Patients should be advised to discard the bottle one week after the foil and bottle were opened, even if there is medication left inside.

Visit **www.cystaran.com** for more information about treatment with **CYSTARAN® (cysteamine ophthalmic solution) 0.44%**

Walgreens Specialty Pharmacy is the **sole dispensing pharmacy** for CYSTARAN

You and your patients can call **1-877-534-9627** to speak directly with a Walgreens Specialty Pharmacy CYSTARAN team member Monday-Friday 8:00AM-8:00PM EST and Saturday-Sunday 8:00AM-6:00PM EST

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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. Bäumner S, Weber LT. Nephropathic Cystinosis: Symptoms, Treatment, and Perspectives of a Systemic Disease. *Front Pediatr*. 2018;6:58. 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. Elmonem MA, Veys KR, Soliman NA, Van Duyk M, Van Den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet J Rare Dis*. 2016;11(47):1-17. 6. 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 7. Ariceta G, Camacho JA, Fernandez-Obispo 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. 8. 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. 9. Bishop, R. Ocular Complications of Infantile Nephropathic Cystinosis. *J Peds*. 2017;183S:S19-S21. 10. 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. 11. 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. 12. 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. 13. CYSTARAN [prescribing information]. Gaithersburg, MD: Leadiant Biosciences, Inc.; Current approved PI. 14. Data on File. Leadiant Biosciences, Inc.

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