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PHARMACY POLICY – 5.01.612

Pharmacologic Treatment of Cystinosis

Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 24, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Cystinosis is a rare, inherited disease that is caused by a change (mutation) in the CTNS gene. The CTNS gene provides instructions to help move an amino acid called cystine out of cells and into other areas of the body, like the digestive system, immune system, skeletal system, skin, and hair. Cystinosis occurs when cystine doesn't move out of cells and instead builds up and forms crystals that cause cell death. Cystinosis slowly damages and destroys organs, including the kidneys, liver, eyes, muscles, and brain. The kidneys and the eyes are the organs that are most affected. Three types of cystinosis exist based on the age of onset and how severe the symptoms are: nephropathic (infancy), late-onset (teens to adults), and ocular, or "benign" (adults). Treatment of cystinosis is meant to remove cystine from the cells and delay any further damage to organs in the body. This policy describes when drugs used to treat cystinosis may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Cystagon (cysteamine bitartrate) capsules	**Cystagon (cysteamine bitartrate) may be considered medically necessary for the treatment of adult and pediatric individuals with nephropathic cystinosis when the following criteria are met:** • The individual has a confirmed diagnosis of cystinosis by one of the following methods: ○ Elevated cystine content of peripheral blood leukocyte or fibroblasts **OR** ○ Cystine corneal crystals by the slit lamp examination **OR** ○ Confirmed mutation of the CTNS gene
Procysbi (cysteamine bitartrate) delayed-release capsules; delayed-release granules	**Procysbi (cysteamine bitartrate) may be considered medically necessary for the treatment of adult and pediatric individuals with nephropathic cystinosis when the following criteria are met:** • The individual is aged 1 year or older **AND** • Has a confirmed diagnosis of cystinosis by one of the following methods: ○ Elevated cystine content of peripheral blood leukocyte or fibroblasts **OR** ○ Cystine corneal crystals by the slit lamp examination **OR** ○ Confirmed mutation of the CTNS gene **AND** • Has tried Cystagon (cysteamine bitartrate) and has documentation of one of the following: ○ Inadequate response after 6-months of treatment **OR** ○ Had intolerance to use of Cystagon (cysteamine bitartrate)
Cystadrops (cysteamine ophthalmic solution)	**Cystadrops (cysteamine ophthalmic solution) may be considered medically necessary for the treatment of corneal**

Drug	Medical Necessity

	cystine crystal accumulation when the following criteria are met:
	• The individual has a confirmed diagnosis of cystinosis by one of the following methods:
	  ○ Elevated cystine content of peripheral blood leukocyte or fibroblasts
	OR
	  ○ Cystine corneal crystals by the slit lamp examination
	OR
	  ○ Confirmed mutation of the CTNS gene

Cystaran (cysteamine ophthalmic solution)	**Cystaran (cysteamine ophthalmic solution) may be considered medically necessary for the treatment of corneal cystine crystal accumulation when the following criteria are met:**
	• The individual has a confirmed diagnosis of cystinosis by one of the following methods:
	  ○ Elevated cystine content of peripheral blood leukocyte or fibroblasts
	OR
	  ○ Cystine corneal crystals by the slit lamp examination
	OR
	  ○ Confirmed mutation of the CTNS gene

Drug	Investigational
• **Cystagon (cysteamine bitartrate)** • **Procysbi (cysteamine bitartrate)** • **Cystadrops (cysteamine ophthalmic solution)** • **Cystaran (cysteamine ophthalmic solution)**	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of Cystagon (cysteamine bitartrate), Procysbi (cysteamine bitartrate), Cystadrops (cysteamine ophthalmic solution), and Cystaran (cysteamine ophthalmic solution) for conditions not outlined in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for drugs listed in this policy may be approved up to 12 months.** **All other reviews for drugs listed in this policy may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews for drugs listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **All other reviews for drugs listed in this policy may be approved up to 2 years as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

N/A

Related Information

Consideration of Age

The ages stated in this policy for which Cystagon (cysteamine bitartrate), Procysbi (cysteamine bitartrate), Cystadrops (cysteamine ophthalmic solution), and Cystaran (cysteamine ophthalmic solution) are considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

This policy is managed through the pharmacy benefit.

Evidence Review

Background

Cystinosis is a metabolic disease that results from mutations in the *CTNS* gene located at 17p13a. These mutations cause a defect in the transporter for cystine resulting in intracellular accumulation of cystine, which crystallizes and causes cell death. Cystinosis slowly destroys the organs in the body including the kidneys, liver, eyes, muscles and the brain. There are three types of cystinosis:

1. Infantile (nephropathic)
2. Late-onset (juvenile)
3. Adult (benign)

Cystinosis is an "orphan" disease that affects approximately 1 in 100,000 to 200,000. Cystinosis is an autosomal recessive genetic disease meaning both parents are carriers of the abnormal gene that leads to this condition but they themselves do not exhibit any of the symptoms of cystinosis.

Nephropathic cystinosis in untreated children is characterized by renal tubular Fanconi syndrome, poor growth, impaired glomerular function, and accumulation of cystine crystals leading to tissue destruction. Cysteamine therapy should be started as soon as the diagnosis of cystinosis is confirmed as it preserves renal function and improves growth in affected children. The administration of cysteamine directly treats the disease by reducing the intracellular cystine

content. Cysteamine is an aminothiol that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in individuals with cystinosis.

Summary of Evidence

Cystagon (cysteamine bitartrate)

The National Collaborative Cysteamine Study (NCCS) treated 94 children (mainly from the United States) with nephropathic cystinosis with increasing doses of cysteamine HCl (mean dose 54 mg/kg/day) to attain white cell cystine levels of less than 2 nmol/½ cystine/mg protein 5 to 6 hours post-dose, and compared their outcome with an historical control group of 17 children who had been in the placebo group of a randomized placebo-controlled trial of ascorbic acid. Cysteamine treated individuals had been diagnosed at a mean age of 22 months and were a mean age of 46 months old at study entry; placebo patients had been diagnosed at about 29 months and were a mean age of about 52 months old at study entry. The principal measures of effectiveness were serum creatinine and calculated creatinine clearance and growth (height).

The average median white cell cystine level attained during treatment in the NCCS was 1.7 ± 0.2 nmol/½ cystine/mg protein. There were 70 cysteamine individuals with baseline serum creatinine less than 2 mg/dL who were followed for at least a year and 17 placebo patients. Twelve of the 94 cysteamine treated individuals required early dialysis or renal transplant. Median follow-up of cysteamine individuals was over 32 months and 20% were followed more than 5 years. For the placebo group median follow-up was 20 months and only one was followed more than 24 months. Among cysteamine individuals glomerular function was maintained over time despite the longer period of treatment and follow-up. Placebo treated individuals, in contrast, experienced a gradual rise in serum creatinine. Height, corrected for age, was compared for treated individuals with the height, at the various ages individuals appeared, of the 143 individuals initially screened for inclusion in the NCCS. Individuals on treatment maintained growth (did not show increasing growth failure compared to normal) although growth velocity did not increase enough to allow individuals to catch up to age norms. Renal tubular function was not affected by treatment.

Calculated creatinine clearances were evaluated for two groups of children, one with poor white cell cystine depletion and one with good white cell cystine depletion. The final mean creatinine clearance of the good depletion group was 20.8 ml/min/1.73 m^2 greater than the mean for the poor depletion group, despite the older mean age of the good depletion group.

The Long Term Study, initiated in 1988, utilized both cysteamine HCl and phosphocysteamine (patient's choice) in 46 individuals who had completed the NCCS (averaging 6.5 years of treatment) and 93 new individuals. Individuals had cystinosis diagnosed by elevated white cell cystine (mean 3.63 nmol/½ cystine/mg). New patients and 46 continuing patients were required to have serum creatinine less than 3.0 mg/dL and 4.0 mg/dL, respectively. Individuals were randomized to doses of 1.3 or 1.95 g/m^2/day and stratified according to whether the serum creatinine was above 1.2 mg/dL or not. Doses could be raised if white cell cystine levels were approximately 2 nmol/½ cystine/mg protein and lowered due to intolerance.

Mean doses were 1.27 g/m^2/day and 1.87 g/m^2/day in the two groups and white cell cystine levels averaged 1.72 ± 1.65 nmol/½ cystine/mg protein and 1.86 ± 0.92 nmol/½ cystine/mg protein in the 1.3 and 1.95 g/m^2/day groups, respectively. In new patients, a group similar in age to the NCCS group, serum creatinine was essentially unchanged over the period of follow-up (about half of the individuals were followed for 24 months) and phosphocysteamine and cysteamine HCl had similar effects. The long-term follow-up group, about nine years old on average at entry, stayed in the study (almost 80% were followed at least 2 years) and had essentially no change in renal function. In four studies of untreated cystinosis, renal death (need for transplant or dialysis) occurred at median age of less than 10 years. Both groups maintained height (although they did not catch up from baseline). There was no apparent difference between the two doses.

Safety

In three clinical trials, cysteamine or phosphocysteamine have been administered to 246 children with cystinosis. Causality of side effects is sometimes difficult to determine because adverse effects may result from the underlying disease.

The most frequent adverse reactions seen involve the gastrointestinal and central nervous systems. These are especially prominent at the initiation of cysteamine therapy. Temporarily suspending treatment, then gradual re-introduction may be effective in improving tolerance.

Adverse reactions were not collected systematically in the NCCS, but were often listed by investigators. The following rates may therefore be underestimated. The most common events (> 5%) were vomiting 35%, anorexia 31%, fever 22%, diarrhea 16%, lethargy 11%, and rash 7%.

Procysbi (cysteamine bitartrate)

Procysbi is a delayed-release oral formulation of cysteamine bitartrate. Results demonstrated that at steady state, delayed-release cysteamine administered every 12 hours was noninferior to immediate-release cysteamine administered every 6 hours in depleting WBC cystine levels. As per the FDA per protocol analysis of 39 individuals, the least-square-mean value of WBC cystine was 0.52 ± 0.06 nmol ½ cystine/mg protein after 12 hours under delayed-release cysteamine and 0.44 ± 0.06 nmol ½ cystine/mg protein after 6 hours under immediate-release cysteamine. Absolute difference of 0.08 ± 0.03 (95.8% CI: 0.01 to 0.15). This confidence interval did not include the non-inferiority margin of 0.30 nmol ½ cystine/mg protein. The analysis by the sponsor reported in the published paper included 38 individuals in the per-protocol analysis and 41 individuals in the ITT analysis. The results were not materially different in the sponsor analysis. The outcome of non-inferior WBC cystine levels was achieved at a lower average daily dose of delayed-release cysteamine (1513±477 mg/d) compared with immediate-release cysteamine (1801±511 mg/d).

Pharmacokinetic results shows that Cmax of a larger, single 12-hourly dose of delayed-release cysteamine compared with 2 consecutive 6-hourly doses of immediate-release cysteamine were not very different. As expected, the half-life of delayed-release cysteamine was longer than immediate-release cysteamine.

Results published as an abstract include 20-month data from 40 individuals from the pivotal trial who enrolled into the extension phase. This study demonstrated that there was no change in the mean values for WBC cystine in the individuals from study onset to the end of 20 months. After 20 months of treatment, the total daily dose of delayed-release cysteamine needed to achieve optimal WBC cystine levels was on average 72% of the initial immediate-release cysteamine dose. Kidney function was well preserved over the length of the study, as indicated by steady eGFR levels. The QOL outcomes measured using a generic instrument PedsQLTM version 4.08 improved significantly. From the study onset, the PedsQLTM scores improved significantly in all individuals, including the Total Functioning Score ($p < 0.001$) and the Social Performance ($p < 0.001$).

Safety

The most commonly reported AEs were vomiting, abdominal pain/discomfort, headaches, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash. The number of GI related AEs was 3-fold higher during the delayed-release cysteamine treatment period compared to the immediate-release cysteamine treatment period. PPI therapy

was allowed as per the discretion of the patient and/or the physician during the immediate-release cysteamine treatment period, but was discontinued initially during the delayed-release cysteamine treatment period to maintain an optimal gastric pH environment for kinetics of the delayed-release formulation. Patient or study physician were given the option to restart PPI therapy. The use of PPI therapy was reduced by 87% during the delayed-release cysteamine treatment period, which could have potentially increased the incidence of GI related AEs.

More individuals experienced an SAE with delayed-release cysteamine compared to immediate-release cysteamine (6 and 1 respectively). The investigators considered only 1 SAE as possibly related to delayed-release cysteamine treatment. SAEs were cervical femoral fracture from a fall, 1 elective knee surgery, 5 GI-related SAEs, and all SAEs were resolved by site investigator. No unexpected SAEs were reported in the Phase III trial or the extension phase of the study.

Serious adverse events such as skin and bone lesions that resemble clinical findings for Ehlers-Danlos syndrome, severe skin rashes such as erythema multiforme bullosa or toxic epidermal necrolysis, benign intracranial hypertension and neurological complications have been described with use of immediate-release cysteamine. Therefore, caution about the possibility of such adverse reaction should be exercised with delayed-release cysteamine.

Cystaran (cysteamine ophthalmic solution)

Clinical efficacy was evaluated in controlled clinical trials in approximately 300 individuals. 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 individuals 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)].

Safety

The safety data described reflects exposure in controlled clinical trials of six months to 19 years duration in approximately 300 individuals. The most frequently reported ocular adverse reactions occurring in ≥10% of individuals were sensitivity to light, redness, and eye pain/irritation, headache and visual field defects.

Cystadrops (cysteamine ophthalmic solution)

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 individuals 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 individuals 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 individuals 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.

Safety

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.

2020 Update

Reviewed prescribing information for all drugs in policy and performed a review on the management of cystinosis. Added a new dosage form of Procysbi to policy which are delayed-release granules. Added a new product called Cystadrops (cysteamine ophthalmic solution) 0.37%, which requires less frequent administration of 4 times a day during waking hours than Cystaran (cysteamine ophthalmic solution) 0.44%, which requires administration every waking hour.

2021 Update

Reviewed prescribing information for all drugs in policy and performed a review on the management of cystinosis. No new evidence found that would change this policy.

2022 Update

Reviewed prescribing information for all drugs in policy and performed a review on the management of cystinosis. No new evidence found that would change this policy.

2023 Update

Reviewed prescribing information for all drugs in policy and performed a review on the management of cystinosis. No new evidence found that would change this policy.

2024 Update

Reviewed prescribing information for all drugs in policy and performed a review on the management of cystinosis. No new evidence found that would change this policy.

2025 Update

Reviewed prescribing information for all drugs in policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

References

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2. Cystagon (cysteamine bitartrate) Prescribing Information. Mylan Pharmaceuticals Inc., Morgantown, WV. Revised August 2021.
3. Cystadrops (cysteamine ophthalmic solution) Prescribing Information. Recordati Rare Diseases Inc., Lebanon, NJ. Revised August 2020.
4. Cystaran (cysteamine ophthalmic solution) Prescribing Information. Leadiant Biosciences, Inc., Gaithersburg, MD. Revised May 2023.
5. Cystinosis. UpToDate. Lexicomp, 2024. Last updated March 2024. Accessed February 11, 2025.
6. McDowell GA, Town MM, van't Hoff W, Gahl WA. Clinical and molecular aspects of nephropathic cystinosis. J Mol Med (Berl) 1998;76(5):295-302.
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9. Langman CB, Greenbaum LA, Sarwal M, et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine level and comparison of safety. Clin J Am Soc Nephrol: 2012(7):1112-1120.

History

Date	Comments
10/01/19	New policy, approved September 10, 2019. Add to Prescription Drug section. Criteria added for Cystagon (cysteamine bitartrate), Procysbi (cysteamine bitartrate) and Cystaran (cysteamine ophthalmic solution).
10/01/20	Annual Review, approved September 17, 2020. Added coverage criteria for Cystadrops (cysteamine ophthalmic solution) for the treatment of corneal cystine crystal accumulation. Added Procysbi (cysteamine bitartrate) delayed-release granules to policy.
11/01/21	Annual Review, approved October 21, 2021. No changes to policy statements.

Date	Comments
11/01/22	Annual Review, approved October 24, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
12/01/23	Annual Review, approved November 20, 2023. No changes to policy statements.
08/01/24	Annual Review, approved July 8, 2024. No changes to policy statements.
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.