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Prior Authorization Review: Cysteamine Delayed-release Capsule (PROCYSBI®)

Background:
Cysteamine is a medication used to deplete cystine from the cells of patients with nephropathic cystinosis. Cystinosis is a rare, autosomal recessive error in the metabolic transport of cystine out of lysosomes.[1] The accumulation of cystine and subsequent formation of crystals can damage various organs.[2] The kidneys are severely affected by cystine accumulation and cystinosis can lead to progressive renal failure by 10 years of age.[1] Infants with this syndrome present between 3 and 6 months of age with failure to thrive, vomiting, constipation, polyuria, excessive thirst, rickets, and dehydration.[1] The estimated incidence is 1 case per 100,000 to 200,000 live births with a prevalence of 1.6 cases per million people.[3] Diagnosis is confirmed by measuring cystine levels in white blood cells (WBC).[1] Patients with newly diagnosed cystinosis will have WBC cystine levels in the range of 3 to 20 nmol ½ cystine/mg protein.[1] The usual range for WBC cystine levels in patients without cystinosis is less than 0.2 nmol ½ cystine/mg protein.[1] The most frequent form of this disease is infantile nephropathic cystinosis; however, 2 other variations of cystine accumulation have also been described.[1] The intermediate form is usually diagnosed during childhood or adolescence and presents with less severe renal symptoms and ocular discomfort. In adults, a third form has been identified that is characterized by photophobia and cystine accumulation in the corneas. For ocular cystinosis, a topical eye drop product is available that must be administered every waking hour and, due to limited stability, should be discarded after one week.[4]

Lifelong oral cysteamine therapy is indicated for all patients with nephropathic cystinosis. Early treatment is imperative and can delay progression to end stage renal disease by 6 to 10 years.[1] Cysteamine is available as an immediate-release (IR) formulation (Cystagon®) and a delayed-release (DR) formulation (Procysbi®). The IR formulation must be administered every 6 hours around-the-clock to prevent cysteine accumulation. The DR formulation can be administered every 12 hours. The dose is titrated to a WBC cystine trough concentration of less than 1 nmol ½ cystine/mg protein. The most frequently reported adverse effect with both IR and DR formulations is gastrointestinal (GI) such as nausea, dyspepsia, and epigastric pain.[5,6] More GI adverse reactions have been reported with the DR formulation compared to the IR formulation.[6] Reducing the dose and gradually titrating back up to the target dose is recommended to minimize GI adverse effects. The DR formulation is approved in adults and children over 2 years of age. The IR formulation does not have any age restrictions so it can be administered to infants by opening the capsule and sprinkling the contents directly onto food.[5] The DR formulation should be swallowed whole, although the prescribing information has instructions for opening the capsule to disperse the DR granules into 4 ounces of applesauce or berry jam for patients that cannot swallow capsules.[6]

An 8-week crossover study demonstrated DR cysteamine was not inferior to IR cysteamine controlling WBC cystine levels in 43 patients with nephropathic cystinosis.[7] The mean WBC cystine level with IR cysteamine was 0.54 nmol ½ cystine/mg protein compared to a mean WBC level of 0.62 nmol ½ cystine/mg protein with DR cysteamine.[7] The difference between the two formulations was 0.08 nmol ½ cystine/mg protein (95.8 % Confidence Interval, 0-0.16).[7] There were 3-fold more adverse GI effects with the IR product than the DR product. The same investigators extended this first crossover study into a 24-month, open-label, single arm study to evaluate the long term efficacy of DR cysteamine as assessed by WBC cystine levels. [8] Other metrics evaluated in the study included kidney function, growth, and quality of life.[8] Forty of the 41 patients that completed the initial study participated in the 2-year extension trial. Laboratory assessments, physical examination, and BMI were obtained for the first six months of the study followed by quarterly visits. The average age of the participants

was 11.5 years. Over 24 months, administration of DR cysteamine maintained WBC cystine levels under optimal control which was defined as less than 1 nmol ½ cystine/mg protein.[8] The baseline WBC cystine level was 0.43 ± 0.15 nmol ½ cystine/mg protein and at 24 months the median WBC cystine level was 0.55 ± 0.34 nmol ½ cystine/mg protein (p = 0.38).[7] Changes in patient body mass index (BMI) did not change significantly over the study period (baseline BMI = 18.2 kg/m^2, compared to 24 month BMI = 18.3 kg/m^2 p=0.27).[8] Kidney function, as evaluated by the estimated glomerular filtration rate (eGFR), was preserved in 39 patients (baseline eGFR = 63±25 ml/min/1.73m^2, compared to 24 month eGFR of 57 ±25 ml/min/1.73m^2, p=0.32).[8] One patient proceeded to renal transplantation at 17 months and another patient was placed on maintenance dialysis at 21 months of the study. Emesis was experienced by 28 (70.0%) subjects, followed by headache in 14 (35.0%) subjects, upper respiratory tract symptoms in 9 (22.5%) subjects, and diarrhea in 8 (20.0%) subjects.[8] The authors concluded administration of DR cysteamine over 24 months did not significantly impact WBC cystine levels, kidney function, or patient growth; however, there were substantial GI adverse effects. This extension of the original non-inferiority study did not directly compare the 2 different formulations of cysteamine but it does provide some long-term safety and efficacy data for DR cysteamine.

Another exploratory study evaluated conversion from the IR to the DR product in 11 pediatric patients with an average age of 12 years.[9] The primary reason for switching products was difficulty adhering to the night time administration of the IR formulation. Eight patients successfully transitioned to the DR formulation without any complications or additional side effects. Three patients had difficulties switching from IR to DR cysteamine due to vomiting, weight loss, and difficulty swallowing the DR capsules. Median follow-up in this study was 14 months (range, 3 to 18 months). No significant changes in WBC cystine values were noted after the transition to DR therapy (median 1 nmol ½ cystine/mg protein before [range 0.2-5.7 nmol ½ cystine /mg protein] and 1 nmol ½ cystine/mg protein after [range 0-2.5 nmol ½ cystine /mg protein]; p = 0.64).[9]

Prior Authorization (PA) requests for the DR cysteamine product in the Oregon Health Plan Fee-for-Service population has averaged between 1-3 per month for the past year and all requests have been approved.

Recommendations:
No changes to the current PA criteria are recommended. No further review or research needed at this time.

References:

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3. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med*. 2002;347(2):111-121. doi:10.1056/NEJMra020552.

4. Cysteamine Opthalmic Solution (Cystaran) Prescribing Information. Amityville, NY: Sigma-Tau Pharmaceuticals ; 10/2012.

5. Cysteamine bitartre (Cystagon) Prescribing Information. Morganton, WV: Mylan Pharmaceuticals, Inc.; July 2007.

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6. Cysteamine bitartrate (Proscybi) Prescribing Information. Novato, CA: Raptor Pharmaceuticals Inc.; 8/2015.

7. 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 levels and comparison of safety. *Clin J Am Soc Nephrol*. 2012;7(7):1112-1120. doi:10.2215/CJN.12321211.

8. Langman CB, Greenbaum LA, Grimm P, et al. Quality of Life is Improved and Kidney Function Preserved in Patients with Nephropathic Cystinosis Treated for 2 Years with Delayed-Release Cysteamine Bitartrate. *J Pediatr*. 2014;165(3):528-533.e1. doi:10.1016/j.jpeds.2014.05.013.

9. Ahlenstiel-Grunow T, Kanzelmeyer NK, Froede K, et al. Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study. *Pediatr Nephrol*. June 2016. doi:10.1007/s00467-016-3438-x.

Cysteamine Delayed-release (PROCYSBI®)

Goal(s):

- To restrict use of costly agents to appropriate patient populations.

Length of Authorization:

Up to 6 months

Requires PA:

- Cysteamine delayed-release capsules (PROCYSBI)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis nephropathic cystinosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient receiving medications through a gastrostomy tube?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Has the patient had an adequate trial of cysteamine immediate-release capsules (CYSTAGON) AND Is the prescriber experienced in managing metabolic diseases such as nephropathic cystinosis AND has documentation of justified patient non-adherence to cysteamine IR that prevents the patient from achieving WBC cysteine levels (<1 nmol ½ cysteine per mg protein)?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *11/16 (DM); 3/14 (MH)*
Implementation: *5/1/14*

Author: Moretz

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