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New Drug Evaluation: Delayed Release Cysteamine

Month/Year of Review: January 2014
Generic Name: delayed-release cysteamine bitartrate
PDL Class: None

End date of literature search: December 1, 2013
Brand Name (Manufacturer): Procysbi ™ (Raptor Pharmaceuticals)
Dossier Received: Pending

FDA Approved Indication:[1]

Delayed-release (DR) cysteamine bitartrate is indicated for managing nephropathic cystinosis in adults and children ≥6 years of age and should be prescribed by a physician experienced with the disease's management.

Research Questions:

- Is cysteamine DR superior or noninferior to immediate release (IR) cysteamine bitartrate (Cystagon) for preventing treatment failure, relapse, or death from nephropathic cystinosis?
- Is there evidence cysteamine DR is safer than IR for treating nephropathic cystinosis?

Conclusions:

- At this time, the evidence supporting cysteamine DR is noninferior or superior to cysteamine IR is low, as only one phase 3, open-label crossover study in which patients received cysteamine DR for three weeks has been published.
- While the phase 3 study did demonstrate the DR formulation was noninferior to the IR formulation in depleting WBC cystine levels, the study did not address how effective cysteamine DR is in delaying complications associated with cystinosis and improving treatment adherence, quality of life, and life expectancy. The trial population also did not include patients with renal transplants, gastric tubes or proton pump inhibitor (PPIs) use.

  Although use of a surrogate endpoint and small patient numbers were shortcomings, cystinosis is a rare disease, which limits the subject pool. Also, the surrogate endpoint, depletion of cystine, has been associated with improved outcomes for patients with cystinosis.
- The greater incidence of adverse reactions, particularly gastrointestinal disorders, among patients taking cysteamine DR may offset the improvement in adherence one would expect from switching from every 6 hour dosing to every 12 hour dosing. In the phase 3 crossover study, 79% of patients taking cysteamine DR experienced treatment-related adverse reactions compared with 22% of cysteamine IR patients (NNH 2). This was primarily due to gastrointestinal adverse reactions (NNH 3). Despite the high number of patients experiencing an ADR, no patients discontinued the medication and only 1 patient experienced a serious ADR while taking the DR formulation compared with none while taking the IR formulation. As these observations were made over a 3 week period, long-term tolerance and adverse reaction profile for the DR formulation remain uncertain.

- Cysteamine is the only treatment for cystinosis, a disease that results in severe complications and mortality at an early age without constant and lifelong treatment. The DR formulation has twice daily dosing, as opposed to every 6 hour dosing; therefore, patients could sleep through the night.

Recommendations:

- Prior authorize cysteamine DR to limit its use to patients with documentation of nephropathic cystinosis and intolerance or nonadherence to cysteamine IR or inability to achieve a WBC cystine level <1 nmol ½ cystine per mg protein, preferably from a physician experienced in managing nephropathic cystinosis

Reason for Review:

Cysteamine DR**, is** a recently approved formulation of cysteamine bitartrate, the only treatment for nephropathic cystinosis. It costs approximately 1000 times more than the currently available immediate release formulation. This review will evaluate the evidence for the efficacy and safety of cysteamine DR.

Background:

Until the introduction of cysteamine DR, cysteamine IR (Cystagon) has been the only available FDA-approved cystine-depleting agent for treating cystinosis. Cysteamine IR's side effects and strict every six-hour dosing, which requires nightly awakening, negatively affect the quality of life for the estimated 500 U.S. patients who have cystinosis and their families.[2] [3] [4]

About 70 to 80% of cystinosis patients are non-adherent to the cysteamine IR regimen and nearly 8% of patients will not take the drug. About 69% of those who will not take cysteamine IR cite side effects and intolerance as the reason.[2] [5] In a Dutch study of cystinosis, only 23% of patients adhered to strict every 6 hour dosing. Failure to adhere to the cysteamine IR regimen results in more rapid disease progression.[5]

Cystinosis is a rare autosomal recessive disorder that results in early death even when treated. A defect in cystinosin, a lysosomal transmembrane protein that transports cystine to the cytoplasm where it is reduced to cysteine, leads to cystine accumulation in all organs and tissues.[3] Normal persons and cystinosis heterozygotes have WBC cystine levels <0.2 and usually <1 nmol ½ cystine per mg protein, respectively, while untreated nephropathic cystinosis patients have WBC cystine levels >2 nmol ½ cystine per mg protein.[1]

Cystinosis has been classified into three types:[5,6]

1. Nephrotic or classic infantile cystinosis. When left untreated, this form is associated with proximal tubular Fanconi syndrome at 6 to 12 months of age, glomerular failure in the first decade of life, and various nonrenal complications, including photophobia, linear growth failure, and delayed puberty and hypogonadism in males. Over time, major complications develop, including blindness, progressive distal vacuolar myopathy, extraparenchymal restrictive lung disease, renal osteodystrophy, skeletal abnormalities, swallowing dysfunction, hepatomegaly, inflammatory bowel disease, insulin-dependent diabetes, cardiomyopathy, vascular calcifications, and neurobehavioral abnormalities.
2. Intermediate. This form of cystinosis has all of the manifestations of nephritic cystinosis but does not appear until adolescence.
3. Non-nephropathic or ocular cystinosis. This form is characterized by accumulation of cystine crystals in the cornea and photophobia.

Although the FDA approved cysteamine in 1994, physicians have used the drug since 1976 to treat cystinosis.[2,6] Cysteamine's ability to deplete cystine slows the deterioration of renal function and occurrence of extrarenal complications and improves growth. [6,7] However, cysteamine therapy has been burdensome. The cysteamine IR formulation is given in four divided doses, including during usual sleeping hours, with the goal of maintaining a WBC cystine level <1 nmol ½ cystine per mg protein 5 to 6 hours following the drug's administration. WBC cystine levels are used to evaluate treatment efficacy and appropriate dosage.[6,8]

Treatments for complications due to cystinosis add to the treatment burden. These include replacement of renal losses, nutritional support, full access to water, and supplementation with citrate, bicarbonate, acetate, potassium, phosphate, and vitamin D. Growth hormone for children, thyroid hormone replacement, and ACE inhibitors may be required. Furthermore, administration of some medications, such as cysteamine, by gastric tube is needed when feeding difficulties are present.[6]

Although cysteamine depletes cystinotic cells of >90% of their cystine content, the drug does not cure the disease but delays its progression and improves life expectancy. Even with early cysteamine therapy and good compliance, cysteamine accumulation continues and major complications often develop. [2] However, nearly every patient who does not receive early, diligent, long-term cysteamine therapy suffers a major complication by the age of 30. Therefore, cysteamine should be initiated as early as possible and maintained throughout life.[3,6]

Clinical Efficacy:

As of the writing of this review, the FDA has not published documentation regarding the approval of cysteamine DR. However, one trial has been published.

Langman et al (2012) performed an open-label, randomized, controlled, crossover, noninferiority trial comparing the DR formulation of cysteamine (Procysbi) with the IR formulation (Cystagon). The primary endpoint was the comparison between cysteamine DR vs cysteamine IR peak WBC cystine levels measured every morning over three consecutive days at the end of each three-week treatment crossover study period. The noninferiority margin was 0.3 nmol ½ cystine per mg protein.

The trial included 43 patients at three U.S. and five European Union study centers who were randomized to cysteamine DR or cysteamine IR for 6 weeks, crossing over at 3 weeks. Included were adults and children who were able to swallow cysteamine IR intact and take a stable dose of cysteamine IR sufficient to maintain a WBC cystine level ≤2 nmol ½ cystine per mg protein and have their own kidneys, with a GFR >30 mL/min per 1.73 m^2 BSA. Patients could continue all concomitant medications unchanged during both crossover periods, except for proton pump inhibitors (PPIs). Patients needed to discontinue PPIs while taking cysteamine DR but could restart them if needed.

Enrolled in the study were one adult (age >21), 15 adolescents (age 12 to 21), and 27 children (age 2-12) who together had an average daily cysteamine IR dose of 1849±536 mg/d (55.8±15.2 mg/kg/d) and average WBC cysteine level of 0.66±0.34 nmol ½ cystine per mg protein. Fifty-six percent of subjects were male, and 86% of subjects had a WBC cystine <1 nmol ½ cystine per mg protein.

After a two-week run-in period, during which cysteamine trough concentration and peak WBC cystine level were measured for three consecutive days, subjects were allocated to continue their usual every 6 hour daily cysteamine IR dose or to switch to an every 12 hour cysteamine DR dose equal to 70%

of their usual cysteamine IR dose. The researchers measured trough cysteamine concentrations and peak WBC cystine levels for three consecutive days at the beginning of each crossover period. The cysteamine DR dose could be increased once by 20 to 25% when the WBC cystine level was greater than the mean WBC cystine level during the run-in period or the previous crossover period under cysteamine IR.

Cysteamine DR was superior to cysteamine IR in the modified intent to treat (mITT) population and non-inferior in the per-protocol (PP) population. The mean peak WBC cystine levels (least-squares mean 6 SEM) measured in the mITT population (n=41) were 0.97±0.19 nmol ½ cystine per mg protein for patients treated with cysteamine IR and 0.70±0.19 nmol ½ cystine per mg protein in the patients treated with cysteamine DR, for a mean difference of -0.27±0.36 (98.5% CI: -0.63 to 0.09, p<0.001). The upper end of the CI was lower than the 0.3 noninferiority limit. The mean peak WBC cystine levels measured in the PP population of patients (n=38) treated with cysteamine IR was 0.54±0.05 nmol ½ cystine per mg protein and 0.62±0.05 nmol ½ cystine per mg protein for patients treated with cysteamine DR, for a mean difference of 0.08 nmol ½ cystine per mg protein (95.8% CI: 0.00 to 0.16, p<0.0001). The PP population excluded three subjects who had a 3-day average WBC cystine level >2 nmol ½ cystine/mg protein during one of the periods under cysteamine IR and so were not considered well-controlled under cysteamine IR.

Unanswered questions include the following:
How effective is cysteamine DR

- in delaying complications associated with cystinosis and improving treatment adherence, quality of life, and life expectancy?
- in a population with renal transplant or gastric tubes?
- in patients taking PPIs?
- over the lifetime of cystinotic patients?

Clinical Safety:[1]

Data on ADRs are based on 246 children with cystinosis receiving cysteamine or phosphocysteamine in three clinical trials, 40 healthy volunteers receiving cysteamine DR in three clinical trials, and 72 patients with nephropathic cystinosis receiving cysteamine DR in three clinical trials. In children, the most common reactions (>5% of subjects) were vomiting (35%), anorexia (31%), fever (22%), diarrhea (16%), lethargy (11%), and rash (7%). The most common reactions in healthy volunteers were diarrhea and nausea, abdominal pain/discomfort, headache, vomiting, and abnormal urine odor and in patients with nephropathic cystinosis were vomiting, abdominal pain/discomfort, headache, nausea, diarrhea, anorexia/decreasd appetite, breath odor, fatigue, dizziness, skin odor, and rash. Anaphylaxis and allergic reaction also were reported during clinical trials.

No unexpected SAEs were reported in clinical trials attributable to cysteamine DR. However, in the pivotal clinical trial for cysteamine DR, a greater incidence of adverse reactions was reported in patients on cysteamine DR compared with those on cysteamine IR. The adverse reactions that occurred in >5% of patients and in a greater percentage of patients while they were taking cysteamine IR than cysteamine DR were vomiting/emesis (19% vs 12%, respectively), nausea (16% vs 7%), abdominal pain/discomfort (14% vs 0%), headache (5% vs 0%) and dizziness (5% vs 0%). A greater percentage of patients experienced anorexia/loss of appetite while taking cysteamine IR (5%) than while taking cysteamine DR (2%).

In the extension study to the pivotal clinical trial, the most common adverse reactions among 43 patients treated 12 to 19 months were vomiting, abdominal pain, nausea, breath odor, diarrhea, and decreased appetite. After one year of cysteamine DR treatment, the average number of gastrointestinal adverse events per subject per month slightly declined (from 0.11 to 0.09) as well as the average number of total AEs/subject/month (from 0.15 to 0.08).

Adverse reactions identified post-approval of cysteamine IR include benign intracranial hypertension (or PTC) with papilledema, skin lesions, molluscoid pseudotumors, skin striae, skin fragility, joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture, and scoliosis.

Unanswered safety questions include the following:
What is the ADR profile of cysteamine DR with long-term use? How will the high incidence of gastrointestinal disorders with cysteamine DR use affect adherence?

COMPARATIVE CLINICAL EFFICACY[5]

Relevant Endpoints:

1) Life expectancy
2) Time to major complications
3) Adherence
4) WBC cystine level
5) Quality of life
6) Serious adverse reactions

Primary Study Endpoint:

1) Peak WBC cystine levels measured every morning over three consecutive days at the end of each three-week treatment crossover study period. The noninferiority margin was 0.3 nmol ½ cystine per mg protein.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (98.5% CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Langman (2012) Phase 3, open label, MC, crossover, noninferiority RCT	Cysteamine 1. DR: 70% of usual pre-study IR dose with option to increase the dose 20-25% 2. IR: Usual pre-study Q6H dose Duration: 6 weeks with crossover at 3 weeks	**Demographics (ITT):** Age (mean): 11.7±4.2 · Male (%): 56 · Age 2-12 (no.): 27 · Age 12-21 (no.): 15 · Age >21 (no.): 1 · Daily IR dose: 1849±536 mg/d (55.8±15.2 mg/kg) · WBC cystine (nmol ½ cystine/mg protein): 0.66±0.34 · WBC cystine <1 nmol ½ cystine/mg protein (%): 86 **Inclusion Criteria:** · Adults or children able to swallow IR intact and take a stable dose of IR sufficient to maintain a WBC cystine level ≤2 nmol ½ cystine/mg protein · have own kidneys w/ a GFR >30 mL/min per 1.73 m^2 BSA **Exclusion Criteria:** None	**mITT** 41	**WBC cystine level (nmol ½ cystine/mg protein):** 1. DR: 0.70±0.19 2. IR: 0.97±0.19 Difference: -0.27±0.36 (98.5% CI: -0.63 to 0.09, p<0.001)	NA	**Treatment-related AEs:** DR: 79% IR: 22% **Treatment-related gastrointestinal disorders:** DR: 55.8% IR: 19.5% **Treatment-related SAEs:** DR: 0.02% IR: 0% **Treatment-related AEs leading to D/C of study drug:** DR: 0% IR: 0%	57/2 36/3 NA NA	**Quality rating:** Poor **Internal Validity:** Selection: Randomized; allocated centrally, small patient numbers Performance: Lack of Blinding; open-label, not placebo-controlled Detection: Lack of Blinding; open-label Attrition: Low overall attrition; ITT analysis done **External Validity:** Patient Characteristics: ·The study did not include renal transplant patients and those using gastric tubes. · Use of proton pump inhibitors were discouraged during DR treatment. Setting: Insufficient length of study Outcomes: Surrogate endpoint used, the study does not address the effectiveness of DR vs IR in improving morbidity and mortality or adherence. **Analysis:** · The results of this study indicate cysteamine DR is as effective as IR in lowering WBC cystine levels over a 3 week period; however, · Patients had considerably more side effects, particularly gastrointestinal side effects, while taking DR vs IR. This could potentially offset some of the potential adherence benefits of DR vs IR dosing.

AEs: adverse events, D/C: discontinuation, DR: cysteamine delayed release, IR: cysteamine immediate release, mITT: modified intent to treat, NA: not applicable, MC: multicenter, RCT: randomized controlled trial, SAE: serious adverse event

REFERENCES

1. Procysbi prescribing information. *Raptor Pharmaceuticals Inc*. Novato, CA; 2013.
2. Cherqui S. Cysteamine therapy: a treatment for cystinosis, not a cure. *Kidney Int.* 2012;81(2):127-129. doi:10.1038/ki.2011.301.
3. Brodin-Sartorius A, Tête M, Niaudet P, et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney Int.* 2012;81(2):179-189. doi:10.1038/ki.2011.277.
4. Levtchenko EN, van Dael CM, Graaf-Hess AC de, et al. Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis. *Pediatr. Nephrol.* 2006;21(1):110-113. doi:10.1007/s00467-005-2052-0.
5. 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.
6. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr. Nephrol.* 2013;28(1):51-59. doi:10.1007/s00467-012-2242-5.
7. Gahl WA. Cysteamine therapy for children with nephropathic cystinosis. *New England Journal of Medicien*. 1987;316(16):971-977.
8. Cystagon prescribing information. *Mylan Pharmaceuticals Inc*. Morgantown, WV; 2007.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY [1,4]

Cysteamine bitartrate is an aminothiol that penetrates cell lysosomes and participates in a thiol-disulfide interchange reaction that converts cystine into cysteine and cysteine-cysteamine mixed disulfide. Both molecules can exit the lysosome through those disulfide transporters that function in patients with cystinosis.

PHARMACOKINETICS[1, (Langeman)]

in patients with nephropathic cystinosis

Parameter	Result
Oral Bioavailability	not available
Protein Binding	52%
Elimination	not available
Half-Life	254 minutes
Metabolism	not available

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
25 mg or 75 mg DR capsule	oral	Two divided doses daily	Cysteamine bitartrate-naïve patients: 1⁄6 to 1⁄4 of the maintenance dose; then, raised gradually over 4 to 6 weeks. Recommended maintenance dose: 1.3 gram/m^2/day, in two divided doses given every 12 hours. The	No information specific to this population provided in prescribing information	No information specific to this population provided in prescribing information	Should be used upon diagnosis of nephropathic cystinosis in children >6 years. Risks and benefits of cysteamine in patients <6 years old not established	No information specific to this population provided in prescribing information	• Should be swallowed whole or opened and sprinkled on applesauce or berry jelly, or mixed in apple or orange juice • If possible, do not eat at least 2 hours before or 30 minutes after taking • Titrate dose based on WBC cystine or, if unavailable, plasma cysteamine level. Measure monthly for 3 months, then quarterly for 1 year, then twice yearly minimum for patients never before treated with cysteamine IR. Measure every two weeks, then quarterly for 6 months, then twice yearly minimum for patients switching from IR to DR. In well-controlled, adherent patients plasma cysteamine is >0.1 mg/L and WBC cysteine is <1.0 nmol ½ cystine/mg protein. • Adjust dose by 10% when adjustments are

			dose can be increased up to 1.95 grams/m^2/day if the WBC cystine level remains higher than the target WBC cystine level and/or the target cysteamine concentration has not been achieved. See chart below.					required. • Patients on cysteamine IR may be transferred to a total cysteamine DR dose equal to the IR dose

TABLE 1: Approximation of 1.3 gram/m^2/day dose of PROCYSBI

Weight in Pounds	mg of PROCYSBI Every 12 hours
0-10	200
11-20	300
21-30	400
31-40	500
41-50	600
51-70	700
71-90	800
91-110	900
>110	1000

DRUG SAFETY [1]

Serious (REMS, Black Box Warnings, Contraindications):

Cysteamine is contraindicated in patients hypersensitive to penicillamine

Warnings and Precautions:

- Skin and bone lesions resembling the clinical findings of Ehlers-Danlos syndrome have been reported in patients treated with high doses of cysteamine IR. Interrupt cysteamine DR in patients who develop lesions. The drug may be restarted at lower dose and slowly increased.
- Severe skin rashes, such as TEN, have been reported in patients taking cysteamine IR. Discontinue the cysteamine DR if the symptoms occur.
- GI ulcers and bleeding have been reported with cysteamine IR. Decrease the cysteamine DR dose if the symptoms occur.

- CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been reported with cysteamine IR. Interrupt the cysteamine DR or adjust the dose if symptoms occur.
- Leukemia and elevated alkaline phosphatase levels have been associated with cysteamine.
- Benign intracranial hypertension and papilledema have been reported in patients taking cysteamine IR, but causal relationships have not been established.

Monitoring: Monitor patients for skin or bone lesions and for signs and symptoms of pseudotumor cerebi. Monitor blood counts and alkaline phosphatase levels.

Drug-Drug interactions: Cysteamine DR should not be given with bicarbonate.

Food-Drug Interactions: Not reported

Allergy/Cross Reactive Substances: Penicillamine

Pregnancy/lactation rating: Category C. No adequate, well-controlled studies have been performed in pregnant women. However, cysteamine bitartrate is teratogenic and fetotoxic in rats at doses about 0.2 to 0.7 times the recommended human maintenance dose based on body surface area. Therefore, during pregnancy, the drug should be used only when the benefit justifies the risk. Whether cysteamine is present in the milk of nursing humans taking the drug is unknown. However, neonatal rats nursed by mothers receiving cysteamine have decreased survival; therefore, nursing while taking cysteamine is not recommended.

Carcinogenesis/Mutagenesis: Cysteamine has not been tested for its carcinogenicity in long-term animal studies. The drug produced a negative Ames test and *in-vitro* sister chromatid exchange assay in human lymphocytes but a positive response in hamster ovarian cells in a similar assay. In rats, cysteamine had no effect on fertility and reproductivity at 0.4 times the recommended human dose based on body surface area. At 1.7 times the RHMD, the drug reduced the fertility of the adult rats and the survival of their offspring.

Dose Index (efficacy/toxic): Rats died from a single oral dose of cysteamine 660 mg/kg. Acute toxicity symptoms were motor activity reduction and hemorrhage in the gastrointestinal tract and kidneys. Two human cases of cysteamine IR overdose with full recovery have been reported.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

NME Drug Name	Lexicomp	Clinical Judgment
LA/SA for cysteamine	none	cystadane cysteine
LA/SA for Procysbi	none	none

ADVERSE REACTIONS[1]

PROCYSBI™ (cysteamine bitartrate) delayed-release capsules

TABLE 2: Comparison of adverse reactions that occurred in 5% or more patients while receiving immediate-release cysteamine or PROCYSBI during Trial 3

Adverse Reaction	Immediate-release cysteamine (n = 41) %	PROCYSBI (n = 43) %
Vomiting/emesis	12	19
Nausea	7	16
Abdominal pain/discomfort	0	14
Headache	0	9
Dizziness	0	5
Anorexia/loss of appetite	5	2

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