cysteamine Delayed Release Capsules, Oral Granules (Procysbi®)

Policy # 00405
Original Effective Date: 02/19/2014
Current Effective Date: 08/09/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of cysteamine delayed release capsules and oral granules (Procysbi®)‡ for the treatment of nephropathic cystinosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for cysteamine delayed release capsules and oral granules (Procysbi) will be considered when all of the following criteria are met:

- Patient is 1 year of age or older; AND
- Patient has a diagnosis of nephropathic cystinosis; AND
- Patient has tried and failed, as indicated by their physician, cysteamine immediate release capsules (Cystagon®)‡, unless there is clinical evidence or patient history that suggests the use of this alternative will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use cysteamine delayed release capsules and oral granules (Procysbi) in the absence of a treatment failure with cysteamine immediate release capsules (Cystagon) to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of cysteamine delayed release capsules and oral granules (Procysbi) when patient selection criteria are not met to be **investigational*** (with the exception of those denoted above as **not medically necessary**).**

Based on review of available data, the Company considers the use of cysteamine delayed release capsules and oral granules (Procysbi) for indications other than those listed above to be **investigational.***

Background/Overview

Procysbi is a cystine depleting agent that lowers the cystine content of cells in patients with nephropathic cystinosis. Refer to the package insert for dosing information

Nephropathic Cystinosis

Cystinosis is a very rare autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal. It affects about 500 people in the United States. These patients can experience growth failure and rickets and these patients can also have cystine deposits in the cornea (which cause photophobia). The gene that is affected codes for cystinosin. Because of the defect in cystinosin, the cystine accumulates within lysosomes. This causes elevations in white blood cell cystine levels. Cystine can then form crystals in many tissues, including the kidneys, liver, bone marrow, pancreas, muscle, rectal mucosa, brain, and eye. Prior to the approval of Procysbi, the immediate release version of cysteamine was available to treat this condition, and is a much more economical (and equally efficacious) option.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Procysbi was approved in mid-2013 by the FDA for the treatment of adults and children aged 2 years and older with nephropathic cystinosis. In late 2017, the age for the indication was expanded to those that are 1 year of age or older.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Procysbi was established in a randomized, multicenter study in 43 patients with nephropathic cystinosis. Patients entered a 2-week run-in period in which trough cysteamine concentrations and peak white blood cell (WBC) cystine levels were measured in the morning. After the run-in period, patients were randomized to receive Procysbi or Cystagon for 3 weeks, after which patients crossed over to the other therapy for an additional 3 weeks. At the beginning and end of every cross over period, levels were measured every morning again for 3 consecutive days. The primary efficacy endpoint was based on a comparison between Procysbi and Cystagon WBC cystine levels measured every morning over 3 consecutive days after each of the crossover periods. This study found that Procysbi taken every 12 hours was non-inferior to Cystagon taken every 6 hours. The mean peak WBC cystine level was 0.62 +/- 0.05 nmol ½ cystine/mg protein while on Procysbi vs. 0.54 +/- 0.05 nmol ½ cystine/mg protein while on Cystagon, with a mean difference of 0.08 nmol ½ cystine/mg protein (95.8% confidence interval [CI]: 0.00, 0.16). This study found that Procysbi taken every 12 hours was non-inferior to Cystagon taken every 6 hours.

An open-label trial was also conducted in 17 patients between the ages of 1 and 5 (but also included a 9 year old and a 22 year old). In patients 1 year to less than 6 years, the mean (±SD) WBC cystine concentration on day 1, 30 minutes following the first dose, was 3.17±2.95 nmol ½ cystine/mg protein (n=15 patients). At 12 months (13 patients with samples), the mean WBC cystine concentration was 0.80 ± 0.60 nmol ½ cystine/mg protein at 30 minutes post dose. At 18 months (9 patients with samples) the mean WBC cystine concentration was 0.74 ± 0.64 nmol ½ cystine/mg protein at 30 minutes post dose.

References

1. Procysbi [package insert]. Raptor Pharmaceuticals, Inc. Novato, CA. February 2020.
2. Express Scripts Drug Evaluation. Procysbi. Updated July 8, 2013.

3. Dohil R, Fidler M, Gangoiti JA, Kaskel F, et al. Twice-daily cysteamine bitartrate therapy for children with cystinosis. J Pediatr. 2010;156:71-75.
4. Cystagon®‡ capsules 50 mg and 150 mg [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals, Inc.; June 2007.
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;7:1112-1120.
6. Langman CB, Greenbaum LA, Grimm PC, et al. Extended treatment with RP103 (Procysbi) in patients with nephropathic cystinosis. Presented at the American Society of Nephrology Kidney Week; Oct 30 – Nov 4, 2012; San Diego, CA. Poster #SA-PO1105.
7. Raptor Therapeutics Inc. Pilot study of safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) of RP103 compared to Cystagon in patients with cystinosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2013 Jun 3]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00872729?term=cysteamine+bitartrate+delayed-release&rank=5 NLM Identifier: NCT00872729.
8. Besouw M, Masereeuw R, van den Heuvel L, Levtchenko E. Cysteamine: an old drug with new potential. Drug Discov Today. 2013 in press.
9. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Cysteamine bitartrate delayed-release for the treatment of NAFLD in children (CyNCH). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2013 Jun 3]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01529268?term=cysteamine+bitartrate+delayed-release&rank=1 NLM Identifier: NCT01529268.
10. Raptor Pharmaceutical. Development status for RP103 for Huntington's disease. Available on: http://www.raptorpharma.com/RP103_huntingtons.html.
11. Raptor Pharmaceutical's Procysbi™ receives FDA approval for treatment of nephropathic cystinosis [press release]. Novato, CA: Raptor Pharmaceuticals Inc.; April 30, 2013. Available at: http://ir.raptorpharma.com/releasedetail.cfm?ReleaseID=760588. Tsilou E, Zhou M, Gahl W, et al. 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. Gahl WA, Thoene JG, Schneider JA, et al. NIH Conference. Cystinosis: progress in a prototypic disease. Ann Int Med. 1988;109:557-569.
13. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med. 2002;347(2):111-121.

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14. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. Pediatr Nephrol. 2011;26:205-215.
15. Levtchenko EN, van Dael CM, de Graaf-Hess AC, et al. Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis. Pediatr Nephrol. 2006;21:110-113.
16. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Minireview: Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. Mol Genet Metab. 2000;71:100-120.
17. Kleta R, Kaskel F, Dohil R, et al. First NIH/Office of Rare Diseases Conference on cystinosis: past, present, and future. Pediatr Nephrol. 2005;20(4):452-454.

Policy History

Original Effective Date: 02/19/2014
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02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. New policy.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. Changed age to match the latest FDA indication change. Updated background.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Changed the age for Procysbi to 1 year of age to match the package insert update.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/02/2020	Medical Policy Committee review

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07/08/2020	Medical Policy Implementation Committee approval. Added a new dosage form, oral granules, of Procysbi.
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2022

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.