Subject: Procysbi (cysteamine bitartrate delayed-release) 04/24	**Original Effective Date:** 10/20/2014
Policy Number: MCP-219	**Revision Date(s):**
Review Date(s): 12/16/2015, 9/15/2016, 6/22/2017, 3/8/2018	
MCPC Approval Date: 3/8/2018	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **cysteamine delayed-release (DR) capsule (Procysbi)** for the chronic management of nephropathic cystinosis when appropriate criteria are met.

- **PREFERRED:** Cystagon (cysteamine bitartrate immediate release) capsules

- There is no data in the FDA label or other reliable evidence that demonstrated any other advantages of cysteamine DR (Procysbi) over the immediate-release form cysteamine IR (Cystagon). There is no evidence of better safety tolerance, or morbidity/mortality associated with nephropathic cystinosis is improved with one product other than the other.
    - The most common adverse reactions of cysteamine DR (Procysbi) reported with an incidence of at least 5% include: vomiting, abdominal pain, anorexia, breath and skin odor, diarrhea, fatigue, dizziness, and rash.[a]
    - Additional rare, but serious adverse reactions include Ehlers-Danlos like syndrome (skin and bone lesions), gastrointestinal bleeding, leukopenia, and benign intracranial hypertension.[a]

- The pivotal study reported that GI adverse reactions occurred more frequently in the delayed-release (Procysbi) group than the immediate-release (Cystagon) group.

CLASSIFICATION: Endocrine and Metabolic Agents; Cysteine depleting agent

FDA INDICATIONS

- Procysbi (cysteamine bitartrate) is indicated for the treatment of **nephropathic cystinosis** in adults and children 6 years and older.

Available as: 25mg, 75mg delayed release capsules

Approved by the FDA: May 2013

Black Box Warnings: *None at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Procysbi (cysteamine bitartrate) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ☐ Board-certified nephrologist or other specialist experienced in the management of nephropathic cystinosis

2. Diagnosis/Indication [ONE]

- ☐ Documented diagnosis of nephropathic cystinosis
  - *The safety and effectiveness of cysteamine DR (Procysbi) in conditions other than nephropathic cystinosis have not been established.*

3. Age/Gender/Other restrictions [ALL]

- ☐ 6 years of age or older[a-f]
  - *The risks and benefits of treatment with cysteamine bitartrate delayed-release capsules in children younger than 6 years have not been established.*

- ☐ Prescriber agree to monitor: [BOTH]

  - ○ Target white blood cell (WBC) cysteine levels[a]
    - *The goal of therapy is to maintain a WBC cysteine level of less than 1 nmol 1/2 cystine/mg protein or a plasma cysteamine concentration of greater than 0.1 mg/L 30 minutes after dosing*.

  - ○ End organ damage

4. Step/Conservative Therapy/Other condition Requirements

- ❒ Documentation of inadequate response, intolerance to (*intolerability is defined as severe nausea, vomiting, anorexia, fever or lethargy that interferes with activity of daily living*), or FDA-labeled contraindication with immediate release cysteamine bitartrate (Cystagon). Prescriber submit a written documentation of stating the reason(s) the preferred product which is dosed four-times daily, Cystagon, is not appropriate for the member for review by a Molina Pharmacy/Medical Director.
  NOTE: This specific criterion is an additional Molina Healthcare requirement and will not be authorized if not met.

- ❒ For members previously on Cystagon: There were no compliance or adherence issues with prescribed dosing regimen as documented by Prescriber
  NOTE: Verify history of non-compliance or non-adherence in member's medication fill history or prescription drug profile [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

  - ➢ *Based on comparable efficacy between the medications, Procysbi will not be authorized for individual who fail to adhere to the standard Cystagon dosing regimen. The underlying cause of the nonadherence should be addressed and resolved.*

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to penicillamine or cysteamine

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.
NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Procysbi (cysteamine bitartrate) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

2. Compliance [ALL]

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Compliance in taking the medication as prescribed
  - ❍ No intolerable adverse effects or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

- ❑ History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Documentation that member is tolerating and responding to medication and there continues to be a medical need for the medication

- ❒ WBC cysteine levels must be kept <1nmol half cysteine/mg protein

  NOTE: If WBC cysteine level is >1nmol half cysteine/mg protein and the plasma cysteamine is >0.1mg/L, Prescriber confirm and submit documentation that patient is adherent and conforming to food administration restrictions.
  - ➢ *It may be necessary to increase the dose of cysteamine bitartrate to achieve these goals. If a dosage adjustment is necessary, it is recommended the adjustments occur in 10% increments. The maximum recommended dosage is 1.95 g/m^2/day to achieve the target white blood cell cystine or plasma cysteamine concentrations. If downward adjustments are necessary because of intolerance, they should be made in 10% increments also.*
  - ➢ *Patients should not eat for at least 2 hours before and at least 30 minutes after taking their dose of cysteamine bitartrate delayed-release capsules. If they are unable to take Procysbi without eating, they should eat only a small amount (1/2 cup) of food between 1 hour before and 1 hour after taking their dose.*

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity [Side-effects: fever 22%, lethargy 11%, rash 7%, vomiting 35%, anorexia 31%; severe skin rash such as erythema multiforme bullosa or toxic epidermal necrolysis]
- ❑ WBC cysteine level is > 1nmol half cysteine/mg protein and the plasma cysteamine is < 0.1mg/L [Prescriber confirm that patient is adherent and conforming to food administration restrictions. If patient is adherent must look at relationship of eating and dosing]
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy

  Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to penicillamine or cysteamine

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

- ❒ The recommended Procysbi™ maintenance dose is 1.3 gram/m^2/day, in two divided doses given every 12 hours.

- ❒ The dose should be titrated to maintain a plasma cysteamine concentration > 0.1mg/L, or a white blood cell (WBC) cystine level <1 nmol half-cystine/mg protein. WBC cystine levels should be monitored monthly for three months, then quarterly for one year, then twice yearly.
  - ➢ *The dose of both Cystagon and Procysbi are based on the member' body surface area; the dose is titrated up to 1.3 gm/m^2. Cystagon is dosed every six hours; Procysbi is dosed every 12 hours.*
  - ➢ *Patients being switched from immediate-release cysteamine bitartrate to Procysbi should receive their previous total daily dose of cysteamine bitartrate in 2 divided doses given every 12 hours.*
  - ➢ *Patients should not eat for at least 2 hours before and at least 30 minutes after taking their dose of cysteamine bitartrate delayed-release capsules. If they are unable to take Procysbi without eating, they should eat only a small amount (1/2 cup) of food between 1 hour before and 1 hour after taking their dose.*

- ❒ Goal of therapy: Maintain a white blood cell cystine level of less than 1 nmol 1/2 cystine/mg protein or a plasma cysteamine concentration of greater than 0.1 mg/L 30 minutes after dosing. It may be necessary to increase the dose of cysteamine bitartrate to achieve these goals. If a dosage adjustment is necessary, it is recommended the adjustments occur in 10% increments. The maximum recommended dosage is 1.95 g/m^2/day to achieve the target white blood cell cystine or plasma cysteamine concentrations. If downward adjustments are necessary because of intolerance, they should be made in 10% increments also.

2. Authorization Limit [ALL]

- ❒ Quantity limit: quantity sufficient to provide dosing up to a maximum of 1.95 grams/m^2/day
  - ❍ 75mg capsules: 180 for 30 days
  - ❍ 25mg capsules: 60 for 30

- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time

- ❒ Duration of initial authorization: 3 months

- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every 3 months to determine continued need based on documented positive clinical response

3. Route of Administration [ALL]

- ❒ **C**ysteamine DR (Procysbi) is considered a **self-administered** medication

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

All other uses of that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY

Nephropathic Cystinosis is a rare autosomal recessive disease causing free cysteine accumulation and crystallization within lysosomes, damaging tissues and organs, specifically the kidneys. It results in the impaired transport of cystine from the lysosome into the cytoplasm and occurs at the rate of 1 case per 100,000 to 200,000 live births, generally manifesting within several months after delivery.

Cystine crystals can develop in almost all cells and tissues. Early detection and treatment are critical to minimize the negative impact on kidney function and the need for renal transplants, as well as to reduce the risks for thyroid fibrosis, hypothyroidism, and the formation of cystine crystals in thyroid tissue or the cornea. The initial symptoms are associated with the inability of renal tubules to reabsorb small molecules and the development of Fanconi syndrome. These patients can have excessive urinary loss of low-molecular weight protein, glucose, amino acids, phosphate, calcium, magnesium, sodium, potassium, bicarbonate, carnitine, and water. Some of the consequences of these changes include polyuria, causing dehydration and electrolyte deficiencies, and phosphaturia, which may cause hypophosphatemic rickets. Other changes can result in oral motor and swallowing dysfunction.
Treatment goals include decrease disease progression, kidney dysfunction, dialysis, need for transplant, organ failure, premature death. Therapy ranges from supportive care to specific treatments. Supportive care includes fluid and solute replenishment, nutritional supplementation, thyroid replacement therapy, and peritoneal dialysis or hemodialysis if renal failure occurs. Specific therapies include renal transplantation and the administration of cysteamine. Procysbi controls cystine levels by participating within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide which can exit the lysosome preventing accumulation within the cell.

Currently, the FDA approved drugs used to treat nephropathic cystinosis include Cystagon (cysteamine bitartrate), an immediate-release capsule, and Procysbi (cysteamine bitartrate), a delayed-release capsule.

- While Cystagon is taken every six hours, Procysbi is a long-acting formulation that is taken every 12 hours. Cystagon was FDA approved in 1994, and is available only as a brand formulation.
- Unlike Procysbi, Cystagon has been studied in children under 6 years of age and does not have a minimum age of use. Cysteamine is the standard treatment for cystinosis.
- The dose is titrated to reduce the leukocyte cystine concentration to below 1.0 nmol half-cystine/mg protein.
- Oral cysteamine therapy has proven effective in mitigating the effects of the disease by delaying renal failure, enhancing growth, preventing hypothyroidism, and preventing late complications. Cysteamine is not a cure for cystinosis, and long-term treatment is required.

❖ The efficacy of Procysbi was evaluated in a pivotal randomized phase III multicenter (US and EU) randomized, crossover, immediate-release cysteamine bitartrate vs. Procysbi trial in 43 (40 pediatric and 3 adult) patients with nephropathic cystinosis.
  - ➢ Patients in the trial were on stable therapy with cysteamine IR (Cystagon) at the time of enrollment. Cysteamine DR (Procysbi) dosages were adjusted up to 100% of the cysteamine IR (Cystagon) dose.
  - ➢ Patient age ranged from 6 to 26 years. Prior to randomization, patients were to be on a stable dose of immediate-release cysteamine bitartrate administered every 6 hours. Procysbi dose adjustments of up to ~100% of the total daily dose of immediate-release cysteamine bitartrate were allowed by trial criteria. The average total daily dose of Procysbi for patients completing the clinical trial was ~91 % of the average total daily dose of immediate-release cysteamine bitartrate for patients at trial entry.
  - ➢ The primary endpoint, white blood cell (WBC) cystine level, is considered a clinically relevant for nephropathic cystinosis and the standard target of therapy. Control of WBC cystine level has been linked to slowing of renal deterioration.
  - ➢ Results:

- 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.
- Secondary end point(s) were GI adverse reactions, which occurred more frequently in the delayed-release group than the immediate-release group.

➢ Conclusion:
- No outcome data to prove adherence rates were improved with the twice-daily formulation. All published study end points were related to the drug's pharmacokinetics and impact on mean peak white blood cell cystine levels.
- The study demonstrated that at steady-state Procysbi (cysteamine bitartrate) delayed-release capsules administered every 12 hours was non-inferior to immediate release cysteamine bitartrate administered Q6H with respect to the depletion of WBC cystine levels.

➢ Open-label extension trial
- Forty out of forty-one patients completing this trial are continuing treatment with Procysbi in an Forty patients completing the trial are continuing treatment with Procysbi™ in an ongoing, open-label extension trial. An interim analysis was performed after all patients had been treated with Procysbi™ for at least 12 months. The analysis indicated that patients who switched from immediate-release cysteamine to Procysbi™ maintained a WBC level <1 nmol half-cystine/mg protein for up to 19 months at a total daily dose equal to their total daily dose of immediate-release cysteamine at entry.
- An interim analysis was performed after all enrolled patients from Trial 3 had been treated with Pocysbi for at least 12 months (n=33) and up to 19 months (n=3). The analysis indicated that patients switched from immediate-release cysteamine to a treatment regimen of Procysbi maintained a WBC level < 1 nmol/½ cystine/mg protein for up to 19 months at a total daily dose equal to their total daily dose of immediate release cysteamine at entry in the pivotal trial. During extended treatment there has been on average no worsening of the kidney function, as expressed by the estimated glomerular filtration rate (eGFR).

DEFINITIONS

N/A

APPENDIX

N/A

CODING INFORMATION CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
NA	5mg, 75mg delayed release capsules

ICD-9	Description [For dates of service *prior* to 10/01/2015]
270.0	Disturbances of amino-acid transport (Cystinosis)

ICD-10	Description [For dates of service *on or after* 10/01/2015]
E72.00	Disorders of amino-acid transport, unspecified
E72.04	Cystinosis

REFERENCES

Package Insert, FDA, Drug Compendia

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b. Procysbi™ Product Information. Raptor Pharmaceuticals Inc. Available online at: http://www.procysbi.com/docs/Procysbi-Full-Prescribing-Information.pdf. Last revised 04/2013.
c. AHFS Drug Information/Lexicomp. Wolters Kluwer Health. Copyright © 2014. American Society Of Health-System Pharmacists®, Bethesda, MD. Updated periodically. Accessed via subscription: www.statref.com
d. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
e. Drug Facts and Comparisons online. (www.drugfacts.com), Wolters Kluwer Health, St. Louis, MO. Updated periodically.
f. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard. Copyright©2014. URL: http://www.clinicalpharmacology.com.
g. FDA Press Release. FDA approves Procysbi for rare genetic condition. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm350091.htm. Updated May 5, 2013.

Clinical Trials, Definitions, Peer-Reviewed Publications

1. 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. Clinical journal of the American Society of Nephrology 2012 Jul;7(7):1112-20. doi: 10.2215/CJN.12321211. Epub 2012 May 3. Erratum in: Clin J Am Soc Nephrol. 2013 Mar 7;8(3):468. PubMed PMID: 22554716.

Government Agencies, Professional Societies, and Other Authoritative Publications

Brodin-Sartorius A, Tete MJ, Niaudet P et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. Kidney International. 2012; 81: 179-189.