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Policy Number: C6355-B

Procysbi, Cystagon (cysteamine bitartrate)

PRODUCTS AFFECTED

Procysbi (cysteamine bitartrate delayed release), Cystagon (cysteamine bitartrate)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Cystinosis

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. NEPHROPATHIC CYSTINOSIS:
1. Documented diagnosis of nephropathic cystinosis confirmed by the presence of increased cysteine concentration in leukocytes or presence of the CTNS gene mutation [DOCUMENTATION

REQUIRED]
AND

2. Prescriber attests to monitoring of target white blood cell (WBC) cysteine levels at a minimum of twice annually
   AND
3. Documentation of baseline WBC cysteine level [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Cystagon (cysteamine) include: patients who have developed hypersensitivity to it or to cysteamine or penicillamine; Contraindications to Procysbi (cysteamine) include: hypersensitivity to penicillamine or cysteamine]
   AND
5. FOR PROCYSBI ONLY:
   (a) 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)
   AND
   (b) Prescriber must provide relevant written documentation of laboratory and/or objective values [e.g., WBC cysteine levels, physician progress notes; or information representing the physician's interaction with the member] as well as clinical rationale explaining why Cystagon has not produced the same clinical results as would be expected with the use of Procysbi (They are the same chemical entity).

CONTINUATION OF THERAPY:

A. NEPHROPATHIC CYSTINOSIS:

1. Documented positive response to therapy as evidenced by a reduction in WBC cysteine levels compared to pre-treatment. [DOCUMENTATION REQUIRED includes WBC cysteine concentrations in the target range (less than 1 nmol half cystine/mg protein) using same assay method (since normal WBC cysteine ranges and therapeutic target concentrations for cysteine depletion may vary based on the assay method used)]
   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 member is compliant with regard to administration (including proper dosing interval and relationship between administration of medication and food) and the timing between last dose and blood draw.
   AND
2. Prescriber attests to monitoring of target white blood cell (WBC) cysteine levels at a minimum of twice annually
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., severe skin rash such as erythema multiforme bullosa or toxic epidermal necrolysis, benign intracranial hypertension (pseudotumor cerebri), papilledema, etc.)

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified endocrinologist, nephrologist, urologist, or physician experienced in management of nephropathic cystinosis. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Procysbi: 1 year of age and older
Cystagon: No restriction

QUANTITY:
Maximum 1.95 grams/m2/day
Switching from Immediate-release Cysteamine to Procysbi: Start with a total daily dose of Procysbi equal to the previous total daily dose of immediate-release cysteamine bitartrate

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Cystinosis Agents

FDA-APPROVED USES:
Indicated for the treatment of nephropathic cystinosis in adults and pediatric patients

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
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 members 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.
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 least5% include: vomiting, abdominal pain, anorexia, breath and skin odor, diarrhea, fatigue, dizziness, and rash.
Additional rare, but serious adverse reactions include Ehlers-Danlos like syndrome (skin and bone lesions), gastrointestinal bleeding, leukopenia, and benign intracranial hypertension.
The pivotal study reported that GI adverse reactions occurred more frequently in the delayed-release (Procysbi) group than the immediate-release (Cystagon) group.

Laboratory Monitoring

- WBC cystine concentration may be measured using the mixed leukocyte assay or by using assays for specific WBC subsets (e.g., granulocyte method). The methods used for measuring cystine and total protein content may also vary among individual laboratories.
- Normal WBC cystine ranges and therapeutic target levels for cystine depletion depend upon the assay method used by the individual laboratory. WBC cystine values obtained from using different assay methods may not be comparable. Refer to the assay-specific therapeutic target for cystine depletion. When using the mixed leukocyte assay, the recommended target WBC cystine concentration is less than 1 nmol ½ cystine/mg protein.
- The recommended frequency of monitoring WBC cystine concentration is as follows:
  - o Cysteamine-naïve patients 1 year to less than 6 years: Obtain measurement two weeks after initiation of PROCYSBI treatment and continue monitoring during dosage titration period until the therapeutic target WBC cystine concentration is achieved. Once the therapeutic target is achieved, continue monitoring monthly for 3 months, then quarterly for 1 year, and then twice yearly, at a minimum.
  - o Cysteamine-naïve patients greater than 6 years: Obtain measurement after reaching the maintenance PROCYSBI dosage, then monthly for 3 months, quarterly for 1 year, and then twice yearly, at a minimum.
  - o Patients switching from immediate-release cysteamine to PROCYSBI: Obtain measurement two weeks after initiation of PROCYSBI treatment and continue monitoring if further dosage titration is required to achieve therapeutic target WBC cystine concentration. Once the therapeutic target is achieved, continue monitoring quarterly for 6 months, then twice yearly, at a minimum.
- Obtain blood samples for WBC cystine concentration measurement 12 hours after the patient's last PROCYSBI dose, prior to administration of the next dose (i.e., trough concentration). In addition, it is important to accurately record the time of the last dose, the actual dose, and the time the blood sample was taken.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of cysteamine bitartrate are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to cysteamine bitartrate include: Hypersensitivity, including anaphylaxis, to penicillamine or cysteamine. Ehlers-Danlos-like clinical findings, including skin lesions (e.g., molluscoid pseudotumor, skin striae), bone lesions (osteopenia, compression fractures, scoliosis, and genu valgum), leg pain, and joint hyperextension, have occurred with high doses of the immediate-release formulation. Monitor for development of skin or bone lesions; interruption of therapy and subsequent dosage reduction with slow titration to therapeutic dose may be required if these symptoms develop.

OTHER SPECIAL CONSIDERATIONS:
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/m2/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.
Monitor blood counts and LFTs (including alkaline phosphatase) during therapy; monitor for signs and symptoms of GI ulceration and bleeding, skin and bone lesions, skin rashes, and pseudotumorcerebri. Perform periodic ophthalmic examinations.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Cystagon CAPS 150MG
Cystagon CAPS 50MG
Procysbi CPDR 25MG
Procysbi CPDR 75MG
Procysbi PACK 300MG
Procysbi PACK 75MG

REFERENCES

1. Procysbi (cysteamine) [prescribing information]. Lake Forest, IL: Horizon Pharma USA; February 2022.
2. Cystagon (cysteamine) [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals; August 2021.
3. 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. Erratumin: Clin J Am Soc Nephrol. 2013 Mar 7;8(3):468. PubMed PMID: 22554716
4. 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.
5. Gahl WA, Thoene JG, and Schneider JA, “Cystinosis,” N Engl J Med, 2002, 347(2):111-21.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Duration of Approval Age Restrictions Quantity Drug Class Available Dosage Forms	Q2 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Background Contraindication/Exclusions/Discontinuation References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file