Procysbi_Cystagon (cysteamine bitartrate)
Policy Number: C6355-B

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
5/2019	07/03/2019	07/03/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J8499 (NOC)- Prescription drug, oral, non chemotherapeutic, nos	RxPA	Q3 2019 20190828C6355-B

PRODUCTS AFFECTED:
Procysbi (cysteamine bitartrate)- delayed release, Cystagon (cysteamine bitartrate)- immediate release

DRUG CLASS:
Anticystine Agent, Urinary Tract Product

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS: Cystagon CAPS 50MG, 150MG (500per bottle) Procysbi CPDR 25MG (60/bottle), Procysbi CPDR 75MG (250/bottle)

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

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: cystinosis

REQUIRED MEDICAL INFORMATION:
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
AND
2. 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).
AND
3. Prescriber attests to monitoring of target white blood cell (WBC) cysteine levels at a minimum of twice annually

DURATION OF APPROVAL:
Initial authorization: 3 months, Continuation of therapy: 6 months

QUANTITY:
Quantity sufficient to provide dosing up to a maximum of 1.95 grams/m2/day
75mg capsules: 180 for 30 days
25mg capsules: 2 capsules per 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

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified endocrinologist, nephrologist, or urologist an experienced in management of nephropathic cystinosis

AGE RESTRICTIONS:
Procysbi (cysteamine bitartrate)- 1 year of age and older
Cystagon (cysteamine bitartrate)- immediate release- no requirement

GENDER:
Male and female

CONTINUATION OF THERAPY:
A. NEPHROPATHIC CYSTINOSIS:
1. Member compliance with therapy as verified by Prescriber and member's medication fill history (review Rx history for compliance)
AND
2. Positive response to cysteamine bitartrate treatment 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 1/2 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
3. Documentation of WBC cysteine levels monitored at a minimum of twice annually
AND
4. Patient has NOT experienced any Intolerable adverse effects or drug toxicity, including but not limited to: severe skin rash such as erythema multiforme bullosa or toxic epidermal necrolysis, Benign intracranial hypertension (pseudotumor cerebri) and/or papilledema

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of cysteamine bitartrate are considered experimental/investigational and therefore, will follow Molina's Off-Label policy; Hypersensitivity, including anaphylaxis, to penicillamine or cysteamine.

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.

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 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.

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. 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.

APPENDIX: None

REFERENCES:

1. Procysbi (cysteamine) [prescribing information]. Lake Forest, IL: Horizon Pharma USA; December 2017.
2. Cystagon (cysteamine) [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals; January 2019.
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. Erratum in: 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.