Patient: [Patient name]
Date of birth: [Date of birth]
Medical record number: [Medical record number]

Consider including the following patient documentation as appropriate upon submission:

Confirmation of cystinosis diagnosis

- ☐ History and current health status
- ☐ Treatment plan
- ☐ Genetic testing, if available
- ☐ White blood cell (WBC) test results
- ☐ Chart documentation
- ☐ Specialist notes/consultations

Past documentation of CYSTAGON® (cysteamine bitartrate) capsules use (if applicable)

- ☐ White blood cell (WBC) test results
- ☐ Patient experience on CYSTAGON (i.e. tolerance)
- ☐ Chart documentation

To personalize and strengthen your letter of medical necessity, you may want to include additional information that is applicable to your patient's situation, such as:

Nephropathic Cystinosis

Nephropathic cystinosis is a rare, inherited, progressive, metabolic disorder that affects about 500 to 600 people in the United States. **(Nesterova 2012; Elmonem 2016)**

Nephropathic cystinosis is a lysosomal storage disorder (LSD) that results in the amino acid cystine accumulating inside the lysosomes of nearly every cell. Cystine accumulation results in the formation of crystals that lead to cell damage and death in tissues and organs throughout the body. **(Elmonem 2016)**

Initial symptoms are commonly the result of cystine accumulation in the kidney tubules, which results in Fanconi syndrome. If untreated, this will lead to end-stage renal disease, requiring a kidney transplant by age 10 years. **(Gahl 2002; Gahl 2007)**

Also commonly affected in the first 6 to 18 months of life are the eyes, which can become photosensitive, and the bones, which can develop rickets. Damage to the thyroid further results in failure to thrive. **(Gahl 2002)**

Cystine-Depleting Therapy

Cystinosis can be managed by controlling cystine levels with cysteamine, a cystine-depleting therapy (CDT). **(Elmonem 2016; Gahl 2007)**

CDT is the only way to remove cystine and its crystals from lysosomes throughout the body. **(Elmonem 2016)**

With ongoing and consistent use of CDT, cystine levels may be controlled and some damage to organs may be prevented or limited. **(Elmonem 2016; Nesterova 2013)**

CYSTAGON® (cysteamine bitartrate) capsules is an immediate-release CDT taken every 6 hours (4 times daily). **(CYSTAGON PI)**

Patients often do not adhere to the strict Q6H dosing required of immediate-release cysteamine, which requires at least one dose to be taken during the night. **(Levtchenko 2006; Ariceta 2015)**

Importance of Continuous Cystine Control

Adherent use of CDT is critical to managing cystinosis, as cystine levels rise quickly. In a study, patients who delayed their dose of CDT by 3 hours (9 hours vs 6 hours) had white blood cell (WBC) cystine levels that were 65% higher and in excess of the target level. **(Levtchenko 2006; Langman 2016)**

Without treatment, cystine accumulates to toxic levels and causes irreversible harm to nearly every cell in the body, including the brain, thyroid, pancreas, muscles, throat, lungs, and male reproductive organs. **(Elmonem 2016; Nesterova 2013; Gahl 2002; Gahl 2007; Nesterova 2008; Langman 2016)**

PROCYSBI® (cysteamine bitartrate) delayed-release capsules and delayed-release oral granules

PROCYSBI is a cystine-depleting agent indicated for the treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older. **(PROCYSBI PI)**

PROCYSBI is contraindicated in patients with serious hypersensitivity reaction, including anaphylaxis to penicillamine or cysteamine. **(PROCYSBI PI)**

PROCYSBI is the only FDA-approved treatment for nephropathic cystinosis with 12-hour dosing (2 times daily). Delayed release of cysteamine in the plasma allows cystine levels to remain within therapeutic range for a full 12 hours. **(PROCYSBI PI; Langman 2012)**

PROCYSBI has been well studied in clinical trials in adults and children as young as age 1 year. (**PROCYSBI PI)**

SELECT IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
• **Ehlers-Danlos-like Syndrome:** Skin and bone lesions that resemble clinical findings for Ehlers-Danlos-like syndrome have been reported in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts. Monitor patients for development of skin or bone lesions and reduce PROCYSBI dosing if patients develop these lesions.

Please see Important Safety Information on pages 5-6 and accompanying Full Prescribing Information or visit PROCYSBIhcp.com.

In a phase 3 clinical trial, PROCYSBI given every 12 hours was found to be noninferior to immediate-release cysteamine bitartrate given every 6 hours. PROCYSBI maintained cystine below target levels over the entire 12-hour dosing period. **(PROCYSBI PI; Langman 2012)**

The effect of PROCYSBI on the kidneys was studied in adults and children aged 2 years and older. PROCYSBI maintained kidney function at 1 and 2 years. **(PROCYSBI PI; Langman 2014)**

PROCYSBI improved growth measures. Children (aged 1 year to <6 years) taking PROCYSBI capsules for 18 months (study exit) reached the 30th mean weight percentile. In the same patients, similar trends were observed for height. **(PROCYSBI PI)**

SELECT IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
• **Skin Rash:** Severe skin rashes such as erythema multiforme bullosa or toxic epidermal necrolysis have been reported in patients receiving immediate-release cysteamine bitartrate. Discontinue use if severe skin rash occurs.

Please see Important Safety Information on pages 5-6 and accompanying Full Prescribing Information or visit PROCYSBIhcp.com.

References

Ariceta G, Lara E, Camacho JA, et al. Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults. *Nephrol Dial Transplant.* 2015;30(3):475-480.

CYSTAGON (cysteamine bitartrate) capsules [prescribing information] Mylan Pharmaceuticals Inc.

Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet J Rare Dis*. 2016;11(47):1-17.

Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med*. 2002;347(2):111-121.

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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.

Langman CB, Greenbaum LA, Grimm P, et al. Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate. *J Pediatr*. 2014;165(3):528-533.

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Nesterova G, Gahl W. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol*. 2008;23(6):863-878.

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Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr Nephrol*. 2013;28(1):51-59.

PROCYSBI (cysteamine bitartrate) delayed-release capsules and delayed-release oral granules [prescribing information] Horizon.

Please see Important Safety Information on pages 5-6 and accompanying Full Prescribing Information or visit PROCYSBIhcp.com.

INDICATION and IMPORTANT SAFETY INFORMATION

INDICATION

PROCYSBI (cysteamine bitartrate) delayed-release capsules and delayed-release oral granules is a cystine-depleting agent indicated for the treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Patients with serious hypersensitivity reaction, including anaphylaxis to penicillamine or cysteamine.

WARNINGS AND PRECAUTIONS

- **Ehlers-Danlos-like Syndrome:** Skin and bone lesions that resemble clinical findings for Ehlers-Danlos-like syndrome have been reported in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts. Monitor patients for development of skin or bone lesions and reduce PROCYSBI dosing if patients develop these lesions.
- **Skin Rash:** Severe skin rashes such as erythema multiforme bullosa or toxic epidermal necrolysis have been reported in patients receiving immediate-release cysteamine bitartrate. Discontinue use if severe skin rash occurs.
- **Gastrointestinal (GI) Ulcers and Bleeding:** GI ulceration and bleeding have been reported in patients receiving immediate-release cysteamine bitartrate. Monitor for GI symptoms and consider decreasing the dose if severe symptoms occur.
- **Fibrosing Colonopathy:** Fibrosing colonopathy has been reported with postmarketing use of PROCYSBI. Evaluate patients with severe, persistent, and/or worsening abdominal symptoms for fibrosing colonopathy. If the diagnosis is confirmed, permanently discontinue PROCYSBI and switch to immediate-release cysteamine bitartrate capsules.
- **Central Nervous System (CNS) Symptoms:** CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with immediate-release cysteamine. Monitor for CNS symptoms; interrupt or reduce the dose for severe symptoms or those that persist or progress.
- **Leukopenia and/or Elevated Alkaline Phosphatase Levels:** Cysteamine has been associated with reversible leukopenia and elevated alkaline phosphatase levels. Monitor white blood cell counts and alkaline phosphatase levels; decrease or discontinue the dose until values revert to normal.
- **Benign Intracranial Hypertension:** Benign intracranial hypertension (pseudotumor cerebri; PTC) and/or papilledema has been reported in patients receiving immediate-release cysteamine bitartrate treatment. Monitor for signs and symptoms of PTC; interrupt or reduce the dose for signs/symptoms that persist, or discontinue if diagnosis is confirmed.

ADVERSE REACTIONS

The most common adverse reactions reported in PROCYSBI clinical trials *(≥ 5%)* were:

- *Patients 2 years of age and older previously treated with cysteamine:* vomiting, nausea, abdominal pain, headache, conjunctivitis, influenza, gastroenteritis, nasopharyngitis, dehydration, ear infection, upper respiratory tract infection, fatigue, arthralgia, cough, and pain in extremity.

- *Patients 1 year of age and older naïve to cysteamine treatment:* vomiting, gastroenteritis/viral gastroenteritis, diarrhea, breath odor, nausea, electrolyte imbalance, headache.

DRUG INTERACTIONS

- Drugs that increase gastric pH may alter the pharmacokinetics of cysteamine due to the premature release of cysteamine from PROCYSBI and increase WBC cystine concentration. Monitor WBC cystine concentration with concomitant use.
- Consumption of alcohol with PROCYSBI may increase the rate of cysteamine release and/or adversely alter the pharmacokinetic properties, as well as the effectiveness and safety of PROCYSBI.
- PROCYSBI can be administered with electrolyte (except bicarbonate) and mineral replacements necessary for management of Fanconi Syndrome as well as vitamin D and thyroid hormone.

USE IN SPECIFIC POPULATIONS

- *Lactation:* Because of the potential risk for serious adverse reactions in breastfed children from cysteamine, breastfeeding is not recommended during treatment with PROCYSBI.

Please see accompanying Full Prescribing Information or visit PROCYSBIhcp.com.