HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROCYSBI safely and effectively. See Full Prescribing Information for PROCYSBI.

PROCYSBI® (cysteamine bitartrate) delayed-release capsules, for oral use
Initial U.S. Approval: 1994

----------RECENT MAJOR CHANGES----------

Indication and Usage (1)	8/2015
Dosage and Administration, Laboratory Monitoring (2.3)	8/2015
Dosage and Administration, Administration (2.4)	8/2015

----------INDICATIONS AND USAGE ----------
PROCYSBI is a cystine-depleting agent indicated for the treatment of nephropathic cystinosis in adult and pediatric patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION ----------
Recommended Dosage in Cysteamine-Naïve Patients
- See Full Prescribing Information for weight-based dosing tables for the starting and maintenance dosage. (2.1)

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. (2.1)

Dose Titration
- Adjust dose to maintain a white blood cell (WBC) cystine concentration less than 1 nmol 1/2 cystine/mg protein. (2.2, 2.3)
- If a dose adjustment is required, increase the dose by 10%. Do not exceed 1.95 grams/m^2 per day due to an increased risk of adverse reactions (2.3)
- If adverse reactions occur, decrease the dose. For initial intolerance, temporarily discontinue and then re-start PROCYSBI at a lower dose and gradually increase to the target dose. Some patients may be unable to achieve their therapeutic target (2.3)

Administration (2.4)
- Swallow capsules whole. Do not crush or chew capsules or capsule contents
- Take with fruit juice (except grapefruit juice)
- For patients who have difficulty swallowing capsules or those with a gastrostomy tube, see full prescribing information for instructions for opening the capsule and administering with food or liquid.
- Do not eat for at least 2 hours before and for at least 30 minutes after taking PROCYSBI. If unable to take PROCYSBI without eating, take with food but limit the amount of food to approximately 4 ounces (1/2 cup) 1 hour before through 1 hour after administration. Avoid high fat food close to dosing (2.4)
- Avoid drinking alcohol while taking PROCYSBI.

----------DOSAGE FORMS AND STRENGTHS----------
Delayed-release capsules: 25 mg and 75 mg (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to penicillamine or cysteamine (4)

----------WARNINGS AND PRECAUTIONS----------
- Ehlers-Danlos-like Syndrome: Reduce dosage if skin and bone lesions occur. (5.1)
- Skin Rash: Discontinue if severe skin rash such as erythema multiforme bullosa or toxic epidermal necrolysis occurs. (5.2)
- Gastrointestinal (GI) Ulcers and Bleeding: Monitor for GI symptoms and consider decreasing the dose if severe symptoms occur. (5.3)
- Central Nervous System (CNS) Symptoms: Monitor for CNS symptoms; interrupt or reduce the dose for severe symptoms or those that persist or progress (5.4).
- Leukopenia and/or Elevated Alkaline Phosphatase Levels: Monitor white blood cell count and alkaline phosphatase levels; decrease or discontinue the dose until values revert to normal. (5.5)
- Benign Intracranial Hypertension: Monitor for signs and symptoms; interrupt or reduce the dose for signs/symptoms that persist, or discontinue if diagnosis is confirmed. (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5%) are: vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Raptor Pharmaceuticals Inc. at 1-855-888-4004 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
Drugs that Increase Gastric pH: Administer PROCYSBI at least 1 hour before or 1 hour after medications containing bicarbonate or carbonate. (2.4, 7.1)

----------USE IN SPECIFIC POPULATIONS (8)----------
Lactation: Breastfeeding is not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PROCYSBI is indicated for the treatment of nephropathic cystinosis in adult and pediatric patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Starting Dosage in Cysteamine-Naïve Patients

Treatment with cysteamine should be started immediately after diagnosis. The recommended starting dosage of PROCYSBI for cysteamine-naïve patients is 0.2 to 0.3 grams/m^2 per day divided into two doses given every 12 hours. Table 1 shows the recommended weight-based starting dosage and the number of capsules needed to achieve each dose. Increase the dosage gradually over 4 to 6 weeks until the maintenance dosage is achieved to help reduce the risk of adverse reactions *[see Dosage and Administration (2.2)]*.

Table 1: Recommended Weight-Based Starting Dosage (1/6 to ¼ of maintenance dosage)

	Target Maintenance Dosage	Starting Dosage as a Fraction of the Maintenance Dosage			
Weight in kilograms	PROCYSBI dosage in mg every 12 hours	Number of capsules every 12 hours			
		1/6 of target		¼ of target	
		75mg	25mg	75mg	25mg
0-5	200	0	1	0	2
6-10	300	0	2	1	0
11-15	400	1	0	1	1
16-20	500	1	1	1	2
21-25	600	1	1	2	0
26-30	700	1	2	2	1
31-40	800	1	2	2	2
41-50	900	2	0	3	0
51 and greater	1000	2	1	3	1

Maintenance Dosage in Cysteamine-Naïve Patients

The recommended maintenance dosage of PROCYSBI for cysteamine-naive patients is 1.3 gram/m^2 per day, divided into two equal doses given every 12 hours. Table 2 shows the recommended weight-based maintenance dosage of PROCYSBI and the number of capsules needed to achieve each dose. After maintenance dose has been achieved, measure the white blood cell (WBC) cystine concentration *[See Dosage and Administration (2.3)]*. Titrate the PROCYSBI dosage as needed to achieve target WBC cystine concentrations *[see Dosage and Administration (2.2)]*. Do not exceed 1.95 grams/m^2 per day.

Table 2: Target Weight-Based Maintenance Dosage

Weight in kilograms	PROCYSBI Maintenance Dosage in mg every 12 hours	Number of capsules every 12 hours	
		75 mg	25 mg
0-5	200	2	2
6-10	300	4	0
11-15	400	5	1
16-20	500	6	2
21-25	600	8	0
26-30	700	9	1
31-40	800	10	2
41-50	900	12	0
51 kg and greater	1000	13	1

Switching Patients from Immediate-release Cysteamine Bitartrate Capsules

When switching patient from immediate-release cysteamine bitartrate to PROCYSBI, starting total daily dose of PROCYSBI is equal to his/her previous total daily dose of immediate-release cysteamine bitartrate. Measure WBC cystine concentration two weeks after initiation of PROCYSBI *[See Dosage and Administration (2.3)]*. Titrate the PROCYSBI dose as needed to achieve target WBC cystine concentrations *[see Dosage and Administration (2.2)]*. Do not exceed 1.95 grams/m^2 per day.

2.2 Dose Titration

- The target WBC cystine concentration is less than 1.0 nmol ½ cystine/mg protein *[see Dosage and Administration (2.3)]*.
- If the WBC cystine concentration is greater than the target level of less than 1.0 nmol ½ cystine/mg protein, consider the following before dose adjustment: adherence to medication and dosing interval, the timing between the last dose and the blood draw for the laboratory measurement, and the timing of PROCYSBI administration in relation to food or other administration instructions.
- If a dose adjustment is required, increase the dose by 10%. Do not exceed a maximum dose of 1.95 grams/m^2 per day due to an increased risk of adverse reactions.
- If adverse reactions occur, decrease the PROCYSBI dose. For patients who have initial intolerance, temporarily discontinue PROCYSBI and then re-start at a lower dose and gradually increase to the target dose. Some patients may be unable to achieve their therapeutic target due to poor tolerability of PROCYSBI *[see Warnings and Precautions (5), Adverse Reactions (6.1)]*.

2.3 Laboratory Monitoring

- Because the measured WBC cystine concentration depends on the assays used for cystine and total protein content, individual patient sample concentration values from different assays may not be interchangeable. Consideration of assay results must be made with knowledge of the specific assays used. Therefore, communication should be maintained with the laboratory performing the assay *[see Clinical Pharmacology (12.2)]*.
- The recommended frequency of monitoring WBC cystine concentration is as follows:
  - For cysteamine-naive patients: Obtain measurement after reaching the maintenance PROCYSBI dose, then monthly for 3 months, quarterly for 1 year, and then twice-yearly, at a minimum.
  - For patients switching from immediate-release cysteamine to PROCYSBI: Obtain measurement after two weeks of PROCYSBI treatment while titrating the dose, then quarterly for 6 months, then twice yearly, at a minimum.
- Obtain blood samples for WBC cystine concentration measurement 12 hours after dosing with PROCYSBI. 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.

2.4 Administration

- Swallow PROCYSBI capsules whole.
- Do not crush or chew capsules or capsule contents.
- Take PROCYSBI capsules with fruit juice (except grapefruit juice).
- Do not eat for at least 2 hours before taking PROCYSBI and for at least 30 minutes after to maximize absorption. If patients are unable to take PROCYSBI without eating, take with food and limit the amount of food to approximately 4 ounces (1⁄2 cup) within 1 hour before taking PROCYSBI through 1 hour after taking PROCYSBI. Take PROCYSBI in a consistent manner in regard to food. Avoid high fat food close to dosing of PROCYSBI.
- Avoid drinking alcohol while taking PROCYSBI *[see Drug Interactions (7.2)]*.
- Administer PROCYSBI at least 1 hour before or 1 hour after medications containing bicarbonate or carbonate *[see Drug Interactions (7.1)]*.

For patients who have difficulty swallowing capsules, follow the instructions below for administration with food or liquid. *Administration of PROCYSBI with foods and liquids not included below has not been studied clinically and is not recommended.*

Administration with Applesauce or Berry Jelly:

1. Place approximately 4 ounces (1/2 cup) of either applesauce or berry jelly into a clean container
2. Open the capsule(s)
3. Sprinkle the intact granules on applesauce or berry jelly
4. Mix the granules with the applesauce or berry jelly
5. Consume the entire contents within 30 minutes of mixing. Do not chew the granules. Do not save the applesauce or berry jelly and granules for later use.

Administration with Fruit Juice (except grapefruit juice):

1. Pour approximately 4 ounces (1/2 cup) of fruit juice into a clean cup
2. Open the capsule(s)
3. Sprinkle the intact granules into the juice
4. Gently stir until mixed
5. Drink the entire contents within 30 minutes of mixing. Do not chew the granules. Do not save the fruit juice and granules for later use.

Administration with Applesauce via a Gastrostomy (G) Tube (14 French or larger)

A bolus (straight) feeding tube is recommended.

1. Flush the gastrostomy tube button first with 5 mL of water to clear the button
2. Open the capsule and empty the granules into a clean container with approximately 4 ounces (1/2 cup) of applesauce. Use only strained applesauce with no chunks. A minimum of 1 ounce (1/8 cup) of applesauce may be used for children ≤ 25 kg starting PROCYSBI at a dose of 1 or 2 capsules.
3. Mix the intact granules into the applesauce
4. Draw up the mixture into a syringe. Keep the feeding tube horizontal during administration and apply rapid and steady pressure (10 mL/10 seconds) to dispense the syringe contents into the tube within 30 minutes of preparation.
5. Repeat step 3 until all of the mixture is administered. Do not save the applesauce and granule mixture for later use.
6. Draw up a minimum of 10 mL of fruit juice into another syringe, swirl gently, and flush the tube.

Missed Doses

- If a dose is missed, take the dose as soon as possible up to 8 hours after the scheduled time. However, if a dose is missed and the next scheduled dose is due in less than 4 hours, do not take the missed dose and take the next dose at the usual scheduled time. Do not take 2 doses at one time to make up for a missed dose.

3 DOSAGE FORMS AND STRENGTHS

PROCYSBI delayed-release capsules:

- 25 mg: contains 74 mg cysteamine bitartrate, equivalent to 25 mg cysteamine. The capsules are light blue opaque cap imprinted with “Raptor” logo in white ink and light blue opaque body imprinted with “25 mg” in white ink.
- 75 mg: contains 221 mg cysteamine bitartrate, equivalent to 75 mg cysteamine. The capsules are dark blue opaque cap imprinted with “Raptor” logo in white ink and light blue opaque body imprinted with “75 mg” in white ink.

4 CONTRAINDICATIONS

The use of PROCYSBI is contraindicated in patients with a serious hypersensitivity reaction, including anaphylaxis, to penicillamine or cysteamine.

5 WARNINGS AND PRECAUTIONS

5.1 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. These include molluscoid pseudotumors (purplish hemorrhagic lesions), skin striae, bone lesions (including osteopenia, compression fractures, scoliosis and genu valgum), leg pain, and joint hyperextension. One

patient on immediate-release cysteamine bitartrate with serious skin lesions subsequently died of acute cerebral ischemia with marked vasculopathy. Monitor patients for development of skin or bone lesions and interrupt PROCYSBI dosing if patients develop these lesions. PROCYSBI may be restarted at a lower dose under close supervision, then slowly increase to the appropriate therapeutic dose *[see Dosage and Administration (2.2)]*.

5.2 Skin Rash

Severe skin rashes such as erythema multiforme bullosa or toxic epidermal necrolysis have been reported in patients receiving immediate-release cysteamine bitartrate. If severe skin rashes develop, permanently discontinue use of PROCYSBI *[see Contraindications (4)]*.

5.3 Gastrointestinal Ulcers and Bleeding

Gastrointestinal (GI) ulceration and bleeding have been reported in patients receiving immediate-release cysteamine bitartrate. GI tract symptoms including nausea, vomiting, anorexia and abdominal pain, sometimes severe, have been associated with cysteamine. If severe GI tract symptoms develop, consider decreasing the dose of PROCYSBI *[see Dosage and Administration (2.2)]*.

5.4 Central Nervous System Symptoms

Central Nervous System (CNS) symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with immediate-release cysteamine. Neurological complications have also been described in some patients with cystinosis who have not been treated with cysteamine. Carefully evaluate and monitor patients who develop CNS symptoms. Interrupt medication or adjust the dose as necessary for patients with severe symptoms or with symptoms that persist or progress. Inform patients that PROCYSBI may impair their ability to perform tasks such as driving or operating machinery.

5.5 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. If tests values remain elevated, consider decreasing the dose or discontinuing the drug until values revert to normal.

5.6 Benign Intracranial Hypertension

Benign intracranial hypertension (pseudotumor cerebri; PTC) and/or papilledema have been reported in patients receiving immediate-release cysteamine bitartrate treatment. Monitor patients for signs and symptoms of PTC, including headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision, pain behind the eye or pain with eye movement. If signs/symptoms persist, interrupt dosing or decrease the dose and refer the patient to an ophthalmologist. If the diagnosis is confirmed, permanently discontinue use of PROCYSBI.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Ehlers-Danlos-like Syndrome *[see Warnings and Precautions (5.1)]*
- Skin Rash *[see Warnings and Precautions (5.2)]*
- Gastrointestinal (GI) Ulcers and Bleeding *[see Warnings and Precautions (5.3)]*
- Central Nervous System Symptoms *[see Warnings and Precautions (5.4)]*
- Leukopenia and/or Elevated Phosphatase Levels *[see Warnings and Precautions (5.5)]*
- Benign Intracranial Hypertension *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to cysteamine in 328 patients with nephropathic cystinosis (246 patients receiving immediate-release cysteamine as cysteamine hydrochloride or phosphocysteamine, and 63 patients receiving PROCYSBI) in open-label clinical trials.

Clinical Trials Experience with PROCYSBI

Sixty-two patients with cystinosis (38 males and 24 females) received PROCYSBI in two clinical trials at doses ranging from 0.29 grams/m^2 per day to 2.19 grams/m^2 per day *[see Clinical Studies (14.2)]*. All patients were switched from immediate-release cysteamine to PROCYSBI. Forty-three patients, ages 7 to 24 years old, received PROCYSBI in an 8-week, open-label, randomized, cross-over trial comparing PROCYSBI to immediate-release cysteamine bitartrate. Forty of 43 patients continued PROCYSBI treatment in an open-label extension trial, and were treated with PROCYSBI for longer than 2 years. An additional 19 patients (6 transplanted patients and 13 patients aged 2 to 6 years) were enrolled directly into this trial and were treated with PROCYSBI for up to 18 months.

In the open-label, randomized, cross-over trial, a higher incidence of adverse reactions was reported in patients during the PROCYSBI treatment period compared with the immediate-release cysteamine treatment period (see Table 3). Other significant adverse reactions reported during clinical trials included hypersensitivity reactions, including anaphylaxis.

Table 3: Adverse reactions that occurred in ≥5% of patients in the randomized, cross-over clinical trial

Adverse Reaction	Immediate-release cysteamine (n = 41) %	PROCYSBI (n = 43) %
Vomiting/emesis	12	19
Nausea	7	16
Abdominal pain/discomfort	0	14
Headache	0	9
Dizziness	0	5
Anorexia/loss of appetite	5	2

For all patients treated with PROCYSBI in both trials (N=62), the most commonly reported adverse reactions (>5%) were vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash, and headache.

Clinical Trials Experience with Immediate-Release Cysteamine

The most frequent adverse reactions involved the gastrointestinal and central nervous systems and were especially prominent at the initiation of cysteamine therapy. Most patients were able to resume therapy at lower doses. The most common reactions (>5%) were vomiting, anorexia, fever, diarrhea, lethargy, and rash. Other adverse reactions included nausea, bad breath, abdominal pain, headache, dizziness, and urticaria.

Withdrawals due to intolerance, vomiting, anorexia, lethargy, and fever occurred more frequently in those patients receiving 1.95 grams/m^2 per day as compared with 1.3 grams/m^2 per day of immediate-release cysteamine bitartrate.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of immediate-release cysteamine bitartrate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Musculoskeletal:* Joint hyperextension, leg pain, osteopenia, compression fracture, scoliosis, genu valgum *[see Warnings and Precautions (5.1)]*.
- *Skin*: Erythema multiforme bullosa, toxic epidermal necrolysis, Ehlers-Danlos-like syndrome, molluscoid pseudotumors, skin striae, skin fragility *[see Warnings and Precautions (5.1, 5.2)]*.

- *Central Nervous System*: seizures, lethargy, somnolence, depression.and encephalopathy *[see Warnings and Precautions (5.4)]*, benign intracranial hypertension (or PTC) and/or papilledema *[see Warnings and Precautions (5.6)]*.

7 DRUG INTERACTIONS

7.1 Drugs that Increase Gastric pH

Drugs that increase the gastric pH (e.g., proton pump inhibitors, medications containing bicarbonate or carbonate) may alter the pharmacokinetics of cysteamine due to the premature release of cysteamine from PROCYSBI and increase WBC cystine concentration. Concomitant administration of 20 mg omeprazole did not significantly affect the pharmacokinetics of cysteamine when PROCYSBI was administered with 240 mL of orange juice [*Clinical Pharmacology (12.3)*]. The effect of omeprazole on the pharmacokinetics of cysteamine was not studied after PROCYSBI administration with water. Monitor WBC cystine concentration when drugs that increase the gastric pH are concomitantly used *[see Dosage and Administration (2.4)]*.

7.2 Use with Alcohol

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. Therefore, do not consume alcoholic beverages during treatment with PROCYSBI *[see Dosage and Administration (2.4)]*.

7.3 Other Medications Used for the Management of Fanconi syndrome

PROCYSBI can be administered with other electrolyte and mineral replacements necessary for management of Fanconi syndrome, as well as vitamin D and thyroid hormone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on PROCYSBI use in pregnant women to inform any drug-associated risks for birth defects or miscarriage *[see Data]*. Cysteamine (administered as cysteamine bitartrate) was teratogenic and fetotoxic in rats at doses less than the recommended human maintenance dose.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

Embryo-fetal development studies were conducted in rats using oral administration of cysteamine bitartrate, with a dose range of 37.5 to 150 mg/kg per day of cysteamine equivalent (about 0.2 to 0.7 times the recommended human maintenance dose based on body surface area). Cysteamine bitartrate was fetotoxic and produced adverse developmental effects. Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly and exencephaly.

8.2 Lactation

Risk Summary

There is no information on the presence of cysteamine in human milk, the effects on the breast-fed infant, or the effects on milk production. Cysteamine is present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in breastfed infants from cysteamine, breastfeeding is not recommended.

Data

A decrease in survival occurred in neonatal rats nursed by mothers receiving cysteamine *[see Nonclinical Toxicology (13)]*.

8.4 Pediatric Use

The safety and effectiveness of PROCYSBI have been established in pediatric patients aged 2 years and older for the treatment of nephropathic cystinosis. Use of PROCYSBI is supported by evidence from an open-label, randomized, cross-over trial in adult and pediatric patients aged 6 years and older, and an open-label extension trial which included patients aged 2 years and older *[see Clinical Trials (14.2)]*.

The safety and effectiveness of PROCYSBI in pediatric patients under 2 years of age have not been established.

8.5 Geriatric Use

No studies with PROCYSBI have been conducted in geriatric patients.

10 OVERDOSAGE

One case of overdosing with PROCYSBI has been reported. A 16-year old male patient suffered nausea and vomiting after he mistakenly took a second dose of PROCYSBI 30 minutes after his usual dose.

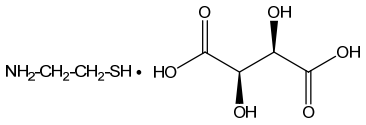
Two cases of overdosing with immediate-release cysteamine bitartrate have been reported in two patients. In the first case, the patient immediately vomited after ingesting an unknown dose and did not develop any symptoms. The second case involved an accidental ingestion of a 200 to 250 mg/kg dose by a healthy 13-month-old child. Vomiting and dehydration were experienced. The child was hospitalized and fluids were administered. The patient fully recovered from the overdosing.

Should overdosing occur, the respiratory and cardiovascular systems should be supported appropriately. No specific antidote is known. Hemodialysis may be considered since cysteamine is poorly bound to plasma proteins.

11 DESCRIPTION

PROCYSBI, for oral administration, is a cystine-depleting agent that lowers the cystine content of cells in patients with nephropathic cystinosis, an inherited defect of lysosomal transport.

PROCYSBI contains the bitartrate salt of cysteamine. The chemical name for cysteamine bitartrate is ethanethiol, 2-amino, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1) (salt). Cysteamine bitartrate is a highly water soluble white powder with a molecular weight of 227.24 and the molecular formula $C_2H_7NS \bullet C_4H_6O_6$. It has the following chemical structure:



Each 25 mg delayed-release capsule contains 74 mg cysteamine bitartrate, equivalent to 25 mg cysteamine. Each 75 mg delayed-release capsule contains 221 mg cysteamine bitartrate, equivalent to 75 mg cysteamine. PROCYSBI contains the following inactive ingredients: microcrystalline cellulose, Eudragit® L 30 D-55, hypromellose, talc, triethyl citrate, sodium lauryl sulfate, and purified water. Capsule shell ingredients are gelatin, titanium dioxide, blue ink and white ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cysteamine is an aminothiol that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in patients with cystinosis.

12.2 Pharmacodynamics

Normal individuals and persons heterozygous for cystinosis have WBC cystine concentrations of less than 0.2 and usually below 1 nmol ½ cystine/mg protein, respectively. Untreated patients with nephropathic cystinosis have elevations of WBC cystine concentration above 2 nmol ½ cystine/mg protein.

After the administration of a single dose of PROCYSBI, peak concentrations of WBC cystine were observed at 3 hours post-dose. The nadir of WBC cystine closely followed the peak concentrations at 3.5 hours post-dose, and returned to baseline WBC concentrations at 12 hours-post dose. The cystine concentration in WBC lysate was measured with LC/MS/MS and total protein content in human WBC lysate was measured using the bicinchoninic acid (BCA) assay. A correction factor was applied to the total protein content for the difference in results from the Lowry method. The cystine concentration in nmol ½ cystine/mg protein was calculated by multiplying nmol cystine/mg protein by 2 *[See Laboratory Monitoring (2.3)]*.

12.3 Pharmacokinetics

The pharmacokinetics of PROCYSBI were evaluated in 43 patients with cystinosis and with an estimated glomerular filtration rate of > 30 mL/minutes/1.73 m^2. Table 4 shows the mean PK parameters for PROCYSBI and immediate-release cysteamine bitartrate after one dose at steady state. The mean C_{max} and AUC_{inf} were 3.6 mg/L and 726 min*mg/L for PROCYSBI and 2.7 mg/L and 380 min*mg/L for immediate-release cysteamine bitartrate.

Table 4: PK parameters for cysteamine after a single dose of PROCYSBI or immediate-release cysteamine bitartrate at steady state

	Immediate-release cysteamine bitartrate	PROCYSBI
C_{max} (mg/L)	2.7± 1.4	3.6 ± 1.8
$AUC_{0\text{-}6h}$ (min*mg/L)	351 ± 153	NA
$AUC_{0\text{-}12h}$ (min*mg/L)	NA	726 ± 339
AUC_{inf} (min*mg/L)	380 ± 157	785 ± 358
T_{max} (min)	73 ± 31	188 ± 88
t½ (min)	90 ± 24	253 ± 403
Cl/F (L/min)	1.4 ± 0.8	1.2 ± 0.8
Vd/F (L)	198 ± 159	382 ± 404

Absorption

The pharmacokinetics of PROCYSBI are consistent with a delayed-release formulation; the mean T_{max} for PROCYSBI was 188 minutes compared with 73 minutes for immediate-release cysteamine bitartrate.

The systemic exposure to cysteamine was similar when PROCYSBI was administered with orange juice as a whole capsule and sprinkled in applesauce in the fasted state. In a food effect study conducted in healthy subjects (n=20), administration of a meal 30 minutes following PROCYSBI administration (intact capsules) decreased C_{max} by 34% and $AUC_{0\text{-}t}$ by 32% compared to administration of a meal 2 hours post-dose *[see Dosage and Administration (2.4)]*.

Distribution

Cysteamine was moderately bound to human plasma proteins, predominantly to albumin, with mean protein binding of about 52%. Plasma protein binding was independent of concentration over the concentration range achieved clinically with the recommended doses. The volume of distribution (Vd/F) was 382 L for PROCYSBI compared with 198 L for immediate-release cysteamine bitartrate.

Elimination

After each dose of PROCYSBI the cysteamine concentration in the blood continues to decline for approximately 30 minutes and the WBC cystine concentration increases accordingly.

The apparent plasma clearance (Cl/F) was similar between PROCYSBI (1.2 L/min) and immediate-release cysteamine bitartrate (1.4 L/min).

The half-life was 253 minutes for PROCYSBI and 90 minutes for immediate-release cysteamine bitartrate.

Drug Interaction Studies

An *in vitro* study indicates cysteamine bitartrate is not an inhibitor of CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). The potential for cysteamine to affect the pharmacokinetics of other drugs via these enzymes is low.

Omeprazole

A single PROCYSBI dose of 600 mg was administered with 240 mL of orange juice in healthy subjects after administration of 20 mg of omeprazole once daily for 5 days. The pharmacokinetic parameters of cysteamine were not significantly different when PROCYSBI was administered with omeprazole compared to when PROCYSBI was administered alone *[see Drug Interactions (7.1)]*. The effect of omeprazole on the pharmacokinetics of cysteamine was not studied after administration of PROCYSBI with water *[see Dosage and Administration (2.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.

PROCYSBI was not mutagenic in the Ames test. It produced a negative response in an *in-vitro* sister chromatid exchange assay in human lymphocytes, but a positive response in a similar assay in hamster ovarian cells.

Repeat breeding reproduction studies were conducted in male and female rats. Cysteamine was found to have no effect on fertility and reproductive performance at an oral dose of 75 mg/kg per day (450 mg/m^2 per day, 0.4 times the recommended human dose based on body surface area). At an oral dose of 375 mg/kg per day (2250 mg/m^2 per day, 1.7 times the recommended human maintenance dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.

14 CLINICAL STUDIES

14.1 Clinical Trials with Immediate-Release Cysteamine

Efficacy of immediate-release cysteamine bitartrate was demonstrated in open-label clinical trials of cysteamine hydrochloride and phosphocysteamine.

An open-label clinical trial of cysteamine hydrochloride was conducted in 94 pediatric patients (mainly from the United States) with nephropathic cystinosis. Patients were treated with increasing doses of cysteamine hydrochloride (mean dose 54 mg/kg per day) to attain WBC cystine concentrations of less than 2 nmol ½ cystine/mg protein 5 to 6 hours post-dose. The clinical outcomes were compared with a historical control group of 17 pediatric patients who had been in the placebo group of a randomized placebo-controlled trial of ascorbic acid. Cysteamine-treated patients had been diagnosed at a mean age of 22 months and had a mean age of 46 months old at study entry; placebo patients had been diagnosed at about 29 months and had a mean age of about 52 months old at trial entry. The principal measures of effectiveness were serum creatinine and calculated creatinine clearance and growth (height).

The average median WBC cystine concentration during treatment was 1.7 ± 0.2 nmol ½ cystine/mg protein. There were 70 cysteamine-treated patients with a baseline serum creatinine of less than 2 mg/dL who were followed for at least 1 year, and 17 placebo patients. Twelve of the 94 cysteamine-treated patients required early dialysis or renal transplant. Median follow-up of cysteamine patients was over 32 months, and 20% were followed more than 5 years. Median follow-up of the placebo group was 20 months; only 1 patient was followed more than 24 months. Glomerular function among cysteamine-treated patients was maintained over time. Placebo-treated patients experienced a gradual rise in serum creatinine. Renal tubular function was not affected by treatment.

Calculated creatinine clearances were evaluated for two groups of pediatric patients, one with poor WBC cystine depletion (defined as median WBC cystine concentrations greater than 3 nmol ½ cystine/mg protein or WBC cystine concentrations not measured at least 2 times per year) and one with good WBC cystine depletion. The final mean creatinine clearance of the good depletion group was 20.8 mL/min/1.73 m^2 greater than the mean for the poor-depletion group.

Height-for-age measurements of treated patients were compared with height-for-age measurements of 143 patients initially screened for inclusion in the trial. Patients on treatment maintained growth (i.e., did not show increasing growth failure compared with normal scales) although growth velocity did not increase enough to allow patients to catch up to age norms for height.

In another open-label clinical trial, 46 patients who had completed the clinical trial of cysteamine hydrochloride (averaging 6.5 years of treatment) and 93 treatment naïve patients were treated with either cysteamine hydrochloride or phosphocysteamine (patient's choice). Patients had cystinosis diagnosed by elevated WBC cystine (mean 3.63 nmol ½ cystine/mg). Newly enrolled patients and the 46 continuing patients were required to have serum creatinine less than 3 mg/dL and 4 mg/dL, respectively. Patients were randomized to doses of 1.3 or 1.95 grams/m^2 per day and stratified according to whether the serum creatinine was above 1.2 mg/dL or not. Doses could be raised if WBC cystine concentrations were approximately 2 nmol ½ cystine/mg protein and lowered due to intolerance. The mean age of the newly enrolled patients was about 49 months for the cysteamine group and about 34 months for the phosphocysteamine group. The mean age of the patients in the long-term follow-up group was about 9 years.

Mean doses were 1.27 grams/m^2 per day and 1.87 grams/m^2 per day in the two groups and WBC cystine concentrations averaged 1.72 ± 1.65 nmol ½ cystine/mg protein and 1.86 ± 0.92 nmol ½ cystine/mg protein in the 1.3 g/m^2 per day and 1.95 grams/m^2 per day in the two groups, respectively. In new patients, serum creatinine was essentially unchanged over the period of follow-up (about half of the patients were followed for 24 months) and phosphocysteamine and cysteamine hydrochloride had similar effects. The long-term follow-up group also had essentially no change in renal function (almost 80% were followed at least 2 years). In four studies of patients with untreated cystinosis, renal death (need for transplant or dialysis) occurred at median age of less than 10 years. Both new patients and patients in the long-term follow-up group maintained height (although they did not catch up from baseline). There was no apparent difference in height maintenance between the two doses.

14.2 Clinical Trials with PROCYSBI

Multi-Center, Open-Label, Randomized Clinical Trial

This clinical trial comparing immediate-release cysteamine bitartrate and PROCYSBI was conducted in 43 (40 pediatric and 3 adult) patients with nephropathic cystinosis. Patient age ranged from 6 to 26 years (mean age 12 years) and 56% were male. Patients with WBC cystine concentrations greater than 2 nmol ½ cystine/mg protein and estimated glomerular filtration rate (eGFR corrected for body surface area) less than 30 mL/minute/1.73 m^2 at the time of screening were excluded from the trial. Prior to randomization, patients were to be on a stable dose of immediate-release cysteamine bitartrate administered every six hours. PROCYSBI dose adjustments of up to approximately 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 approximately 91% of the average total daily dose of immediate-release cysteamine bitartrate for patients at trial entry.

This trial demonstrated that at steady-state, PROCYSBI administered every 12 hours was non-inferior to immediate-release cysteamine bitartrate administered every 6 hours with respect to the depletion of WBC cystine concentrations (Table 5). Using a linear mixed effects statistical analysis model, the least-square-mean value of WBC cystine was 0.52 ± 0.06 nmol ½ cystine/mg protein after 12 hours under PROCYSBI and 0.44 ± 0.06 nmol ½ cystine/mg protein after 6 hours under immediate-release cysteamine; a difference of 0.08 ± 0.03 nmol ½ cystine/mg protein (95.8% Confidence Interval = 0.01 to 0.15).

Table 5: Comparison of WBC cystine concentrations in open-label, randomized, cross-over clinical trial participants, who were on a stable dose of immediate-release cysteamine prior to randomization, with WBC cystine less than 2 nmol ½ cystine/mg protein throughout the trial [1]

	Immediate-release cysteamine bitartrate	PROCYSBI
WBC cystine concentration in nmol ½ cystine/mg protein (LS Mean ± SE)	0.44 ± 0.06	0.52 ± 0.06
Difference in Treatment effect (LS mean ± SE) [95.8% CI; p-value]	0.08 ± 0.03 [0.01 to 0.15; <0.0001]	

[1] Per–Protocol (PP) Population (N=39)

Multi-Center, Single-Arm, Open-Label, Long-Term Extension Clinical Trial

Forty of the 41 patients completing the randomized trial continued treatment with PROCYSBI in an ongoing, open-label extension trial, for a total treatment duration ranging from 3 to 35 months. Thirty-four of the 36 patients continued treatment with PROCYSBI for at least 22 months in the extension trial and maintained their mean WBC cystine concentrations below 1 nmol ½ cystine/mg protein over this time period.

Thirteen pediatric patients, aged 2 to 6 years, were also enrolled in the extension trial. All of them were on treatment with immediate-release cysteamine bitartrate at the time of enrollment. Twelve of the 13 patients received at least 12 months of treatment with PROCYSBI, and their mean ± SD WBC cystine concentration decreased from 1.40 ± 1.08 nmol ½ cystine/mg protein at screening to 1.13 ± 0.56 nmol ½ cystine/mg protein after 12 months of treatment. Seven of these pediatric patients were able to achieve a WBC cystine concentration of less than 1.0 nmol ½ cystine/mg protein after 12 months of treatment; their mean ± SD dose of PROCYSBI increased from 0.84 ± 0.22 grams/m^2 per day at screening to 1.06 ± 0.33 grams/m^2 per day after 12 months of treatment.

During extended treatment with PROCYSBI, mean estimates of renal function, as measured by the estimated glomerular filtration rate (eGFR), were maintained.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- **25 mg Delayed-release Capsule**: A hard gelatin capsule with light blue opaque cap imprinted with "Raptor" Logo in white ink and light blue opaque body imprinted with "25 mg" in white ink, supplied as bottle of 60 capsules (NDC 49663-001-06). Each bottle contains one desiccant canister and one oxygen absorber canister.
- **75 mg Delayed-release Capsule**: A hard gelatin capsule with dark blue opaque cap imprinted with "Raptor" Logo in white ink and light blue opaque body imprinted with "75 mg" in white ink, supplied as bottle of 250 capsules (NDC 49663-002 25). Each bottle contains one desiccant canister and two oxygen absorber canisters.

16.2 Instructions for the Pharmacist

- Dispense PROCYSBI with a 4 month expiration date
- Specify "Store at room temperature, 20°C to 25°C (68°F to 77°F)."
- Dispense only in original packaging. Do not subdivide or repackage.

16.3 Storage and Handling

- PHARMACIST: Prior to Dispensing: Store in a refrigerator, 2°C to 8°C (36°F to 46°F).
- PATIENT: Store at room temperature, 20°C to 25°C (68°F to 77°F).

- Protect from light and moisture.
- Do not remove desiccant or oxygen absorber(s) from the container. Keep bottles tightly closed in a dry place.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

Ehlers-Danlos-like Syndrome

Advise patients and caregivers that PROCYSBI may cause abnormalities of the skin, bones, and joints. Advise patients to report any skin changes or problems with their bones or joints to their physician *[see Warning and Precautions (5.1)]*.

Skin Rash

Advise patients and caregivers to contact their physician immediately if they experience a skin rash *[see Warning and Precautions (5.2)]*.

Gastrointestinal Ulcers and Bleeding

Advise patients and caregivers that PROCYSBI may cause ulcers and bleeding. Advise patients to contact their physician immediately if they experience stomach pain, nausea, vomiting, loss of appetite, or are vomiting blood *[see Warning and Precautions (5.3)]*.

Central Nervous System Symptoms

Advise patients and caregivers that PROCYSBI may impair their ability to perform tasks such as driving or operating machinery. Advise patients to contact their physician immediately if they experience seizures, lethargy, somnolence, depression, and encephalopathy *[see Warning and Precautions (5.4)]*.

Benign Intracranial Hypertension

Advise patients and caregivers that PROCYSBI may cause benign intracranial hypertension. Advise patients to contact their physician immediately if they experience headache, tinnitus, dizziness, nausea, double vision, blurry vision, loss of vision, or eye pain *[see Warning and Precautions (5.6)]*.

Use by Pregnant Women

Advise patients and to contact their physician immediately if they suspect they may be pregnant. Discuss with the patient the individual risks and benefits of continuing PROCYSBI during pregnancy *[see Use in Specific Populations (8.1)]*.

Breastfeeding

Advise patients that breastfeeding is not recommended while taking PROCYSBI *[see Use in Specific Populations (8.2)]*.

Administration

- Advise patients and caregivers to follow the instruction below for taking PROCYSBI capsules whole.
  - Swallow PROCYSBI capsules whole. Do not crush or chew capsules or capsule contents
  - Take PROCYSBI capsules with fruit juice (except grapefruit juice)
- For patients who have difficulty swallowing capsules or those with a Gastrostomy (G) tube, follow the instructions in the Instructions for Use for opening the capsule and administering with food or liquid.
- Do not eat for at least 2 hours before and for at least 30 minutes after taking PROCYSBI. If unable to take PROCYSBI without eating, take with food but limit the amount of food to approximately 4 ounces (1⁄2 cup) 1 hour before through 1 hour after administration. Avoid high fat food close to dosing of PROCYSBI
- Avoid drinking alcohol while taking PROCYSBI
- Administer PROCYSBI at least 1 hour before or 1 hour after medications containing bicarbonate or carbonate
- Take PROCYSBI consistently and to not miss doses. If a dose is missed, take the dose as soon as possible up to 8 hours after the scheduled time. However, if a dose is missed and the next scheduled dose is due in less than 4 hours, do not take the missed dose, and to take the next dose at the usual scheduled time. Do not take 2 doses at one time to make up for a missed dose *[see Dosage and Administration (2.4)]*.

Laboratory Monitoring

Discuss with the patient and caregivers the importance of required laboratory testing to determine the correct dose of PROCYSBI *[see Dosage and Administration (2.3)]*.

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