PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrPROCYSBI®

Cysteamine delayed-release capsules

25 mg and 75 mg cysteamine (as cysteamine bitartrate, also called mercaptamine bitartrate)

ATC code: A16AA04
Amino Acids and Derivatives

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**PROCYSBI®**

Cysteamine delayed-release capsules
(as cysteamine bitartrate, also called mercaptamine bitartrate)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/ Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Delayed-release capsules, 25 mg and 75 mg cysteamine (as cysteamine bitartrate) | Methacrylic acid copolymer<br>*For a complete listing of ingredients see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

PROCYSBI (cysteamine delayed-release capsules) is indicated for the treatment of nephropathic cystinosis.

PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.

**Pediatrics (< 18 years):**
The safety and efficacy of PROCYSBI in patients under 1 year of age have not been established. See WARNINGS AND PRECAUTIONS, Special Populations and CLINICAL TRIALS.

**Geriatrics (≥ 65 years of age):**
The safety and efficacy of PROCYSBI in patients 65 years and older with cystinosis have not been established. See WARNINGS AND PRECAUTIONS, Special Populations and CLINICAL TRIALS.

### CONTRAINDICATIONS

PROCYSBI is contraindicated for use in patients:

- who are hypersensitive to cysteamine bitartrate, any form of cysteamine or to any ingredient in the formulation, including non-medicinal ingredients, or to any component of the container. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.
- who are hypersensitive to penicillamine.

## WARNINGS AND PRECAUTIONS

### General

*Ehlers-Danlos-like Syndrome:* Skin and bone lesions that resemble clinical features of Ehlers-Danlos syndrome have been reported in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts. These include purplish hemorrhagic lesions (which have been described as molluscoid pseudotumors), 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 increased to the appropriate therapeutic dose.

### Gastrointestinal

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 PROCYSBI.

Physicians should remain alert for signs of ulceration and bleeding and should inform patients and/or guardians about the signs and symptoms of serious GI toxicity and what steps to take if they occur. If severe GI tract symptoms develop, consider decreasing the dose of PROCYSBI.

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) was first described in cystic fibrosis patients who were given high doses of pancreatic enzymes in the form of tablets with an enteric coating of methacrylic acid- ethyl acrylate copolymer, one of the excipients in PROCYSBI. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy.

### Hepatic

PROCYSBI has not been studied in patients with hepatic impairment. Closer monitoring of the WBC cystine levels is recommended in these patients.

### Monitoring and Laboratory Tests:

*White blood cell (WBC) cystine levels*

WBC cystine levels should be routinely monitored to assess the effect of PROCYSBI treatment on intracellular cystine depletion.

Refer to the assay-specific therapeutic target for cystine depletion provided by individual testing laboratories. The target WBC cystine concentration measured using the traditional mixed

leukocyte assay is less than 1.0 nmol ½ cystine/mg protein. Assays using specific WBC subsets (e.g. granulocyte method) have different treatment targets.

Obtain blood samples for WBC cystine concentration measurement at drug trough (as close to 30 minutes post dosing as possible). See DOSAGE AND ADMINISTRATION. In addition, it is important to accurately record the time of the last dose, the actual dose consumed, and the time the blood sample was taken.

The recommended frequency of monitoring WBC cystine concentration is as follows:

- 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.
- Cysteamine-naive patients greater than 6 years: Obtain measurement every two to four weeks while titrating the dose of PROCYSBI until reaching the maintenance PROCYSBI dose (see Table 5, DOSAGE AND ADMINISTRATION for maintenance doses), then monthly for 3 months, quarterly for 1 year, and twice-yearly thereafter, at a minimum.
- Patients switching from immediate-release cysteamine to PROCYSBI: Obtain measurement every two weeks while titrating the dose of PROCYSBI, quarterly for 6 months, and twice yearly thereafter, at a minimum.

More frequent monitoring of WBC cystine concentration is recommended when drugs that increase the gastric pH are introduced and when dose adjustments occur. See DRUG INTERACTIONS

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 and laboratories 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.

*Leukopenia*

Cysteamine, as an immediate-release formulation, has been associated with reversible leukopenia. Monitor WBC counts. If WBC levels remain abnormally decreased, consider decreasing the dose or discontinuing PROCYSBI until values revert to normal.

*Alkaline Phosphatase*

Cysteamine, as an immediate-release formulation, has been associated with elevated alkaline phosphatase levels. Monitor alkaline phosphate levels. If values remain elevated, consider decreasing the dose or discontinuing PROCYSBI until values revert to normal.

**Neurologic**
Central nervous system (CNS) symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with immediate-release cysteamine bitartrate. 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.

*Benign intracranial hypertension* (pseudotumor cerebri; PTC) and/or papilledema have been reported in patients receiving immediate-release cysteamine bitartrate treatment. Physicians should 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.

**Ophthalmologic**
Oral cysteamine has not been shown to prevent eye deposition of cystine crystals. Therefore, where cysteamine ophthalmic solution is used for that purpose, its use should continue.

**Renal**
In patients with end-stage renal disease (ESRD), PROCYSBI exposure is affected by dosing relative to timing of hemodialysis (HD) with higher exposures observed when PROCYSBI is taken 3 hours prior to HD, compared to 1 hour after HD. See DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency.

**Skin**
Serious skin rashes such as erythema multiforme bullosa, Stevens-Johnson Syndrome (SJS), or toxic epidermal necrolysis have been reported in patients receiving immediate-release cysteamine bitartrate. If serious skin rashes develop, permanently discontinue use of PROCYSBI.

**Special Populations**

**Pregnant Women:**
There are no available data on PROCYSBI use in pregnant women. Cysteamine (administered as cysteamine bitartrate) was teratogenic and fetotoxic in rats at doses less than the recommended human maintenance dose. See TOXICOLOGY.

Before starting PROCYSBI in a woman of child-bearing potential, pregnancy status should be confirmed.

Patients should be advised of the potential risk to a fetus and the importance of ensuring adequate contraception while taking PROCYSBI. Women who become pregnant or are planning

to become pregnant should be instructed to immediately contact their physician. In the event of pregnancy, interruption of treatment with PROCYSBI should be considered or appropriate medical care instituted.

**Breastfeeding:**
There is no information on the presence of cysteamine in human milk, or its effects on the breast-fed infant. Cysteamine is present in the milk of lactating rats. Growth retardation and a decrease in survival occurred in neonatal rats nursed by mothers receiving cysteamine. See TOXICOLOGY, Reproductive Toxicology.

Because of the potential for serious adverse reactions in breastfed infants from cysteamine, breastfeeding is not recommended.

**Pediatrics (< 18 years of age):**
There are no data in children < 1 year of age from clinical trials of PROCYSBI. See CLINICAL TRIALS.

**Geriatrics (≥ 65 years of age)**:
The safety and efficacy of PROCYSBI in patients aged 65 years and older have not been established.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview
The adverse drug reactions (ADRs) reported most frequently (≥5%) for PROCYSBI in a short-term trial (Study 03) included nausea, vomiting (11.6% each), and abdominal pain (7.0%).

ADRs reported most frequently (>5%) with long-term treatment with PROCYSBI (Study 04) included vomiting (33.9%), nausea (16.9%), abdominal pain (13.6%), breath odour (11.9%), diarrhea (8.5%), skin odour abnormal (8.5%) and decreased appetite (5.1%)

In Study 03, one serious adverse event (SAE), abdominal discomfort in a patient receiving treatment with PROCYSBI, was considered drug-related. In Study 04, six SAEs were assessed as drug-related: vomiting (two SAEs), renal failure, constipation, diarrhea and acute gastroenteritis.

ADRs reported in patients 1 year to less than 6 years old naïve to cysteamine treatment (Study 08) were vomiting (20%), breath odor (20%), and diarrhea (6.7%).

### Clinical Trial Adverse Drug Reactions
*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information*

*from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Sixty-two patients with cystinosis (38 males and 24 females) received PROCYSBI in two clinical trials (Studies 03 and 04) at doses ranging from 0.29 grams/$m^2$ per day to 2.19 grams/$m^2$ per day. All patients were transitioned from immediate-release cysteamine bitartrate to PROCYSBI. Forty-three patients, aged 7 to 24 years, received PROCYSBI in an 9-week, open-label, randomized sequence, cross-over trial comparing 3 weeks of treatment with PROCYSBI to 3 weeks of treatment with immediate-release cysteamine bitartrate (Study 03). Forty of 43 patients continued PROCYSBI treatment in an open-label, uncontrolled extension trial (36 patients were treated with PROCYSBI for longer than 2 years of which 20 patients were treated for longer than 5 years) (Study 04). An additional 19 patients (6 patients with a renal transplant, and 13 patients aged 2 to 6 years) were enrolled directly into this trial (12 patients were treated with PROCYSBI for longer than 2 years of which 9 patients were treated longer than 5 years).

Overall, 14 patients (32.6%) in Study 03 experienced one or more treatment-emergent adverse events (TEAEs) that were assessed as treatment-related. ADRs reported with a frequency of ≥ 1% are shown in Table 1.

In the long-term extension trial, Study 04, 37 patients (63%) experienced one or more TEAEs which were assessed as treatment-related. ADRs reported with a frequency of ≥ 1% are shown in Table 2. ADRs are consistent with those reported in Study 03 and with those previously described for immediate-release cysteamine bitartrate. ADRs within the subpopulations of patients ≤ 6 years of age (n=13) and in the renal transplant recipients (n=6) suggest a similar safety profile to that observed in patients from Study 03 (n=40).

Seventeen cysteamine-naïve patients in Study 08 (fifteen patients between the ages of 1 and 5 years, one 9-year old and one 22-year old) received PROCYSBI in an open-label clinical trial. Adverse reactions occurring in at least 2 patients (>10%) were: breath odor (n=4) and vomiting (n=4). Adverse events which occurred in >10% of patients are shown in Table 3.

**Abnormal Hematologic and Clinical Chemistry Findings**

There were no changes observed in laboratory tests results for PROCYSBI during the clinical trials beyond that expected with nephropathic cystinosis.

**Table 1: Adverse Reactions[a] that Occurred in One or More Patients in the Randomized, Crossover Clinical Trial (Study 03)**

| **MedDRA System Organ Class** Preferred Term | **PROCYSBI N= 43 n (%)** | **Immediate-Release Cysteamine Bitartrate N= 41 n (%)** |
|---|---|---|
| **Cardiac disorders** | | |
| Atrioventricular block | 0 (0) | 1 (2.4) |
| **Gastrointestinal disorders[b]** | | |
| Vomiting | 5 (11.6) | 3 (7.3) |
| Nausea | 5 (11.6) | 2 (4.9) |
| Abdominal pain | 3 (7.0) | 0 (0) |
| Abdominal discomfort | 1 (2.3) | 0 (0) |
| Diarrhoea | 1 (2.3) | 1 (2.4) |
| **General disorders and administration site conditions** | | |
| Malaise | 1 (2.3) | 0 (0) |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 1 (2.3) | 1 (2.4) |
| **Nervous system disorders** | | |
| Dizziness | 1 (2.3) | 0 (0) |
| Headache | 1 (2.3) | 0 (0) |
| **Renal and urinary disorders** | | |
| Renal impairment | 2 (4.7) | 0 (0) |
| **Skin and subcutaneous tissue disorders** | | |
| Cold sweat | 1 (2.3) | 0 (0) |
| **Vascular disorders** | | |
| Flushing | 1 (2.3) | 0 (0) |

Note: A patient is counted once if he/she reported one or more events. Percentages are based on the number of patients in the safety population within each treatment group. Coded using MedDRA, Version 13.0.

[a] Defined as treatment emergent adverse events that have been assessed by the study Investigator to be possibly or probably related to study treatment.

[b] Use of gastric acid reducing medications, including proton pump inhibitors, was allowed during treatment with immediate-release cysteamine bitartrate but restricted to intolerable gastric upset during PROCYSBI treatment.

**Table 2: Adverse Reactions[a] that Occurred in One or More Patients while Receiving PROCYSBI in a Long-Term Clinical Trial (Study 04)**

| MedDRA System Organ Class<br>Preferred Term | Overall (N=59)<br>n (%) |
|---|---|
| **Blood and lymphatic system disorders** | |
| Neutropenia | 1 (1.7%) |
| Pancytopenia | 1 (1.7%) |
| **Gastrointestinal disorders** | |
| Vomiting | 20 (33.9%) |
| Nausea | 10 (16.9%) |
| Abdominal pain | 8 (13.6%) |
| Breath odour | 7 (11.9%) |
| Diarrhea | 5 (8.5%) |
| Abdominal pain upper | 2 (3.4%) |
| Constipation | 1 (1.7%) |
| Dyspepsia | 1 (1.7%) |
| Dysphagia | 1 (1.7%) |
| Flatulence | 1 (1.7%) |
| Gastroesophageal reflux disease | 1 (1.7%) |
| Peptic ulcer | 1 (1.7%) |
| **Hepatobiliary disorders** | |
| Liver disorder | 1 (1.7%) |
| **General disorders and administration site conditions** | |
| Device occlusion | 2 (3.4%) |
| Fatigue | 2 (3.4%) |
| Pain | 1 (1.7%) |
| **Infections and infestations** | |
| Gastroenteritis | 1 (1.7%) |
| **Metabolism and nutrition disorders** | |
| Decreased appetite | 3 (5.1%) |
| **Musculoskeletal and connective tissue disorders** | |
| Pain in extremity | 1 (1.7%) |
| **Nervous system disorders** | |
| Headache | 2 (3.4%) |
| **Renal and urinary disorders** | |
| Renal failure | 2 (3.4%) |
| **Skin and subcutaneous tissue disorders** | |
| Skin odour abnormal | 5 (8.5%) |
| Alopecia areata | 1 (1.7%) |
| Skin hypopigmentation | 1 (1.7%) |
| **Vascular disorders** | |
| Hot flush | 1 (1.7%) |

Note: A patient is counted once if he/she reported one or more events. Coded using MedDRA, Version 13.0.

[a] Defined as treatment emergent adverse events that have been assessed by the study Investigator to be possibly probably, or definitely related to the use of PROCYSBI.

**Table 3: Adverse Events in >10% of Patients with Nephropathic Cystinosis Naïve to Cysteamine Treatment in an Open-Label Trial (RP103-08)**

| Adverse Reaction | PROCYSBI N = 17 n (%) |
|---|---|
| Vomiting | 13 (77) |
| Gastroenteritis/viral gastroenteritis | 9 (53) |
| Diarrhea | 6 (35) |
| Breath odor | 4 (24) |
| Nausea | 3 (18) |
| Electrolyte imbalance | 2 (12) |
| Headache | 2 (12) |

## Post-Market Adverse Drug Reactions

*As post-market reports of adverse reactions are reported voluntarily from a population of uncertain size and demographics, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.*

*Post-marketing experience with PROCYSBI*

The most frequently reported serious adverse events include renal disorders (such as interstitial nephritis, renal transplant, kidney transplant rejection, renal failure, and dialysis) and dehydration.

*Post-marketing experience with immediate-release cysteamine*

The following adverse reactions have been identified during post-market experience with immediate release cysteamine: Musculoskeletal (joint hyperextension, leg pain, osteopenia, compression fracture, scoliosis, genu valgum); Skin (erythema multiforme bullosa, toxic epidermal necrolysis, Ehlers-Danlos-like syndrome, molluscoid pseudotumours, skin striae, skin fragility); Central Nervous System (seizures, lethargy, somnolence, depression, and encephalopathy, benign intracranial hypertension and/or papilledema); and Renal (nephrotic syndrome, due to membranous glomerulonephritis of renal allograft in one case, hypersensitivity interstitial nephritis in another). See WARNINGS AND PRECAUTIONS.

# DRUG INTERACTIONS

## Overview

There is some potential for drug interaction based on the induction of CYP1A2 and CYP3A4 (and possibly CYP2B6) by cysteamine bitartrate based on *in vitro* data.

When drugs that increase the gastric pH are introduced, more frequent monitoring of WBC cystine concentration is recommended. Dose adjustment of PROCYSBI may be required when taken with these drugs.

Bicarbonate or carbonate should be administered at least one hour before or one hour after PROCYSBI.

Other than bicarbonate/carbonate (see above), PROCYSBI can be co-administered with electrolytes and mineral replacements necessary for management of Fanconi Syndrome, as well as vitamin D and thyroid hormone. See DOSAGE AND ADMINISTRATION, Administration.

Alcohol should be avoided while taking PROCYSBI.

**Drug-Drug Interactions**

**Drugs that Increase Gastric pH**

Drugs that increase the gastric pH (e.g. medications containing bicarbonate or carbonate) may cause premature release of cysteamine from PROCYSBI, and thus increase WBC cystine concentration. Therefore, more frequent monitoring of WBC cystine concentration is recommended when drugs that increase the gastric pH are introduced. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests. Dose adjustment of PROCYSBI may be required if taken with these drugs.

Bicarbonate or carbonate should be administered at least one hour before or one hour after PROCYSBI to avoid potential earlier release of cysteamine. See DOSAGE AND ADMINISTRATION.

Concomitant administration of 20 mg, multiple dose omeprazole did not affect the pharmacokinetics of cysteamine when PROCYSBI was administered with 240 mL of orange juice or with 240 mL of water.

See DETAILED PHARMACOLOGY, *In Vitro* Drug Interaction Studies, for additional information regarding other studies.

**Drug-Food Interactions**

Interactions with foods have not been established.

**Drug-Herb Interactions**

Interactions with herbal products have not been established.

**Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## Drug-Lifestyle Interactions

Avoid drinking alcohol while taking PROCYSBI. Consumption of alcohol with PROCYSBI may increase the rate of cysteamine release and/or adversely alter effectiveness and safety of PROCYSBI.

Patients should exercise caution when driving or engaging in other hazardous activities when taking cysteamine. Cysteamine may cause drowsiness. See WARNINGS AND PRECAUTIONS, Neurologic.

# DOSAGE AND ADMINISTRATION

## Dosing Considerations

Treatment with PROCYSBI should be started immediately after diagnosis of nephropathic cystinosis.

The PROCYSBI dosing regimen is different for cysteamine-naïve patients and patients switching from immediate-release cysteamine.
Titration of PROCYSBI dose is performed based on the assessment of WBC cystine concentrations, as well as drug tolerability. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Do not exceed 1.95 grams/$m^2$ per day due to an increased incidence of adverse reactions. See WARNINGS AND PRECAUTIONS.

If PROCYSBI is taken with drugs that increase gastric pH, such as medications containing bicarbonate or carbonate, more frequent monitoring of WBC cystine levels is recommended and dose adjustment of PROCYSBI may be required. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and DRUG INTERACTIONS.

## Recommended Dose and Dosage Adjustment

PROCYSBI is available as a capsule in 25 mg and 75 mg strengths. Directions for starting and maintenance dosages and methods of administration are presented below.

### Switching Patients from Immediate-Release Cysteamine

When switching patients from immediate-release cysteamine to PROCYSBI, the recommended starting total daily dose of PROCYSBI is equivalent to their previous total daily dose of immediate-release cysteamine.

For individuals for whom GI tolerability is a known concern, initiation of PROCYSBI at 75% of the immediate-release cysteamine dose may be considered. However, this may reduce the effectiveness of PROCYSBI; therefore, WBC cystine levels should be monitored more closely. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and CLINICAL TRIALS.

Measure WBC cystine concentration every two weeks while titrating the dose of PROCYSBI, then quarterly for one year, and twice yearly thereafter at a minimum. Titrate the PROCYSBI dose as needed to achieve target WBC cystine concentrations.

Do not exceed 1.95 g/$m^2$ per day. See Dose Titration.

**Starting Dose in Cysteamine-Naive Patients**
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.

Patients less than 6 years: Increase the dosage in 10% increments to the maintenance dosage, while monitoring WBC cystine concentrations. Allow a minimum of 2 weeks between dosage adjustments. If a patients achieves the therapeutic target WBC cystine concentration at a dosage below the recommended weight-based maintenance dosage, then stop dosage escalation and use the dosage as the patient's maintenance dosage.

Patients 6 years of age and older: Gradually increase the dosage over 4 to 6 weeks until the maintenance dose is achieved.

Table 4 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.

**Maintenance Dose in Cysteamine-Naive Patients**
The usual recommended maintenance dose of PROCYSBI for cysteamine-naive patients is 1.30 grams/$m^2$ per day, divided into two equal doses given every 12 hours.

Table 5 shows the recommended weight-based maintenance dosage of PROCYSBI and the number of capsules needed to achieve each dose. After the target maintenance dose has been achieved, measure the WBC cystine concentration monthly for 3 months, then quarterly for one year, and twice yearly thereafter at a minimum. Titrate the PROCYSBI dosage as needed to maintain target WBC cystine concentrations. See Dose Titration. Do not exceed 1.95 grams/$m^2$ per day.

**Dosing in Patients with Renal Impairment:**
In patients with ESRD, it is recommended that PROCYSBI is taken one hour after hemodialysis (HD) since exposure is higher when PROCYSBI is taken 3 hours prior to HD, compared to 1

hour after HD. See WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficency.

**Table 4: Recommended Weight-Based Starting Dosage (1/6 to ¼ of maintenance dosage)**

| | Target Maintenance Dosage | Starting Dosage as a Fraction of the Target 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 |
| | > 1000[a] | Calculate number of capsules required for the prescribed dose | | | |

[a] Do not exceed 1.95 grams/m² per day.

**Table 5: 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 and greater | 1000 | 13 | 1 |
| | > 1000[a] | Calculate number of capsules required for the prescribed dose | |

[a] Do not exceed 1.95 grams/m² per day.

### Dose Titration

- Adjust the dose of PROCYSBI to produce target WBC cystine levels. If the WBC cystine concentration is greater than the target level (See WARNINGS AND PRECAUTIONS, Monitoring And Laboratory Tests, WBC Cystine levels), 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.
- Measurement timing: WBC cystine levels should be obtained 12.5 hours after the

evening dose and therefore 30 minutes following morning dose (i.e. at drug trough). See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, WBC Cystine levels.

- If a dose adjustment is required, increase the dose by 10%. For patients less than 6 years of age, allow a minimum of 2 weeks between dose increments.
- **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. Patients with poor tolerability still receive benefit if white blood cell cystine levels are below 2 nmol ½ cystine/mg protein.

**Missed Dose**

Patients should be instructed that if a dose is missed, it should be taken 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, the patient should be instructed not to take the missed dose, and to take the next dose at the usual scheduled time. Patients should be instructed not to take 2 doses at the same time to make up for a missed dose.

**Administration**

Food should not be eaten for at least 2 hours before or for at least 30 minutes after taking PROCYSBI 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 30 minutes after taking PROCYSBI. Take PROCYSBI in a consistent manner in regard to food. Avoid food high in fat or proteins (e.g. dairy) close to dosing of PROCYSBI.

PROCYSBI capsules should be swallowed whole with fruit juice (except grapefruit juice) or water. Patients should not crush or chew capsules or capsule contents.
Avoid drinking alcohol while taking PROCYSBI (see Drug-Lifestyle Interactions).

Administer PROCYSBI at least 1 hour before, or 1 hour after, medications containing bicarbonate or carbonate (see DRUG INTERACTIONS).

**In pediatric patients who are at risk of aspiration, aged approximately 6 years and under, the hard capsules should be opened and the content sprinkled on applesauce.**
**For patients who have difficulty swallowing capsules, follow the instructions below for administration with applesauce.**

*Administration with Applesauce:*

1. Place approximately 4 ounces (1/2 cup) of either applesauce into a clean container

2. Open the capsule(s)
3. Sprinkle the intact granules on applesauce
4. Mix the granules with the applesauce. Do not crush the granules.
5. Consume the entire contents within 30 minutes of mixing. Do not chew the granules. Do not save the applesauce and granules for later use.

*Administration with Applesauce via a Gastrostomy Tube (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(s) 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. Do not crush the granules.
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 4 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 (except grapefruit juice) into another syringe, swirly gently, and flush the tube.

**Administration of PROCYSBI with foods and liquids not included above or by other methods has not been studied clinically.**

**OVERDOSAGE**

Nausea, vomiting, abdominal discomfort, and dehydration have been reported following overdosage; the symptoms resolved with supportive care.

An overdose of cysteamine may cause progressive lethargy.

Should overdosing occur, adequate respiratory and cardiovascular systems support should be provided. There is no known antidote for cysteamine. Hemodialysis may be considered since cysteamine is poorly bound to plasma proteins.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

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

### Pharmacodynamics

Using the mixed leukocyte assay, normal individuals and persons heterozygous for cystinosis have WBC cystine levels 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.

In the open-label, randomized, cross-over trial, PROCYSBI administered every twelve hours maintained WBC cystine levels < 1 nmol ½ cystine/mg protein in patients who were previously receiving immediate-release cysteamine bitartrate administered every six hours. In the long-term extension study, 40 out of 41 patients continued treatment with PROCYSBI for approximately 36 months and maintained WBC cystine control below 1 nmol ½ cystine/mg protein for the study duration. See CLINICAL TRIALS.

### Pharmacokinetics

The pharmacokinetics of cysteamine with administration of PROCYSBI were evaluated in 43 patients with cystinosis and with an estimated glomerular filtration rate of > 30 mL/minutes/1.73m$^2$ (Study 03).

Table 6 shows the mean (± SD) pharmacokinetic parameters for PROCYSBI and immediate-release cysteamine bitartrate at steady state. The mean (± SD) dose for PROCYSBI was 656 ± 144 mg/m$^2$ (given every 12 hours) and for immediate-release cysteamine bitartrate was 404 ± 88 mg/m$^2$ (given every 6 hours).

**Table 6: Pharmacokinetic parameters for cysteamine at steady state administration of PROCYSBI or immediate-release cysteamine bitartrate at steady state (Study 03)**

| | **Immediate-release cysteamine bitartrate given every 6 hours** Mean ± SD | **PROCYSBI given every 12 hours** Mean ± SD |
|---|---|---|
| $C_{max}$ (mg/L) | 2.7 ± 1.4 | 3.6 ± 1.8 |
| $AUC_{0-6h}$ (min*mg/L) | 351 ± 153 | NA |
| $AUC_{0-12h}$ (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 cysteamine with administration of PROCYSBI are consistent with those of a delayed-release formulation; the mean $T_{max}$ for cysteamine was 188 minutes with PROCYSBI compared with 73 minutes for immediate-release cysteamine bitartrate. The mean plasma cysteamine peak and AUC were similar when a single PROCYSBI dose of 600 mg was administered with 240 mL orange juice or with 240 mL water. 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 $AUC_{0-t}$ by 32% compared to administration of a meal 2 hours post dose (see DOSAGE AND ADMINISTRATION).

Food intake two hours after administration did not affect the absorption of PROCYSBI.

*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.

*Metabolism:*
*In vitro* data suggests that cysteamine bitartrate is likely to be metabolized by multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. CYP2A6 and CYP3A4 were not involved in the metabolism of cysteamine bitartrate under the experimental conditions.

*Excretion:*
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 terminal half-life ($t_{½}$) was 253 minutes for PROCYSBI and 90 minutes for immediate-release cysteamine bitartrate.

The elimination of unchanged cysteamine in the urine has been shown to range between 0.3 % and 1.7% of the total daily dose in four patients; the bulk of cysteamine is excreted as sulphate.

**Special Populations and Conditions**

**Pediatrics (< 18 years):**
The safety and efficacy of PROCYSBI in patients under 2 years of age have not been established. See INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS, Special Populations, and CLINICAL TRIALS.

The pharmacokinetics of PROCYSBI at steady state were evaluated in 11 cysteamine treatment naïve patients between the ages of 1 and 5 years of age with nephropathic cystinosis. A mean (± SD) $C_{max}$ of 1.26 ± 0.86 mg/L was reached at an average $T_{max}$ of 199 ± 138 minutes and the mean (± SD) dose was 242 ± 93 mg/m$^2$. The mean exposure was calculated to be 206 ± 113 minutes*mg/L ($AUC_{last}$) and 231 ± 123 minutes*mg/L ($AUC_{inf}$). The mean $CL_{ss}/F$ was estimated to be 0.69 ± 0.37 L/minutes with an average half-life ($t_{1/2}$) of 270 ± 56 minutes. Overall, the pharmacokinetics in patients between the ages of 1 and 5 years of age is comparable with those in older children and adults.

**Geriatrics (≥ 65 years of age):**
The safety and efficacy of PROCYSBI in patients 65 years and older with cystinosis have not been established. See INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS, Special Populations, and CLINICAL TRIALS.

**Gender:**
The influence of gender on the pharmacokinetics of PROCYSBI has not been studied.

**Race:**
The influence of race on the pharmacokinetics of PROCYSBI has not been studied.

**Hepatic Insufficiency:**
PROCYSBI has not been studied in patients with hepatic impairment.

**Renal Insufficiency:**
In patients with end-stage renal disease (ESRD), PROCYSBI exposure is affected by dosing relative to timing of hemodialysis (HD) with higher exposures observed when PROCYSBI is taken 3 hours prior to HD, compared to 1 hour after HD. See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION. The pharmacokinetics of cysteamine with administration of a single oral dose of 600 mg PROCYSBI were evaluated in non-cystinosis subjects (healthy subjects) with renal impairment and normal renal function (eGFR >90 mL/min/1.73m$^2$) matched for age, body mass index and sex (Study 16-001).

The mean $AUC_{inf}$ and mean $C_{max}$ for cysteamine were 8%, and 3% lower, respectively, in subjects with mild renal impairment (eGFR 60 to 89 mL/min/1.73m$^2$) compared to healthy subjects. In subjects with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m$^2$) and severe renal impairment ($\leq$29 mL/min/1.73m$^2$), the mean $AUC_{inf}$ was 40% and 37% higher and the mean $C_{max}$ was 28% and 11% higher, respectively compared to healthy subjects. The mean $t_{½}$ was 7 hours, 8.3 hours, and 8.8 hours in subjects with mild, moderate, and severe renal impairment, respectively and ranged from 6.6 to 7.5 hours in healthy subjects. The mean CL/F was 1.57, 1.08, and 1.09 L/min in mild, moderate, and severe renal impairment subjects compared to 1.40 to 1.60 L/min in healthy subjects.

In subjects with end-stage renal disease receiving hemodialysis, the geometric mean $AUC_{inf}$ of cysteamine was 61% higher when PROCYSBI was administered 3 hours before hemodialysis, and 23% higher when administered 1 hour after completion of hemodialysis compared to healthy subjects. Approximately 4.3% (25.6 mg) of the 600 mg PROCYSBI dose was removed from the body with hemodialysis. The apparent clearance of cysteamine in subjects who received PROCYBI before hemodialysis was approximately 65 mL/min.

**Genetic Polymorphism:**
The influence of genetic polymorphism on the pharmacokinetics of PROCYSBI has not been studied.

## STORAGE AND STABILITY

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).
Do not remove desiccant or oxygen absorber(s) from the container. Keep bottles tightly closed and store away from light and moisture.

## SPECIAL HANDLING INSTRUCTIONS FOR THE PHARMACIST

Dispense PROCYSBI with a 3 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.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

PROCYSBI (cysteamine delayed-release capsules) is available in 25 mg and 75 mg strengths.

**25 mg Delayed-Release Capsules**:
Each 25 mg delayed-release capsule contains 73.7 mg cysteamine bitartrate, equivalent to 25 mg cysteamine in a size 3 capsule. The capsules have a light blue opaque cap imprinted with "PRO" in white ink and a light blue opaque body imprinted with "25 mg" in white ink.

PROCYSBI 25 mg delayed-release capsules are supplied in white high density polyethylene (HDPE) bottles with child-resistant closures containing 60 capsules per bottle. Each bottle includes one oxygen absorber canister and one desiccant canister.

**75 mg Delayed-Release Capsules**:
Each 75 mg delayed-release capsule contains 221.1 mg cysteamine bitartrate, equivalent to 75 mg cysteamine in a size 0 capsule. The capsules have a dark blue opaque cap imprinted with "PRO" in white ink and light blue opaque body imprinted with "75 mg" in white ink.

PROCYSBI 75 mg delayed-release capsules are supplied in white high density polyethylene (HDPE) bottles with child-resistant closures containing 250 capsules per bottle. Each bottle includes two oxygen absorber canisters and one desiccant canister.

PROCYSBI 25 mg and 75 mg delayed-release capsules contain the following inactive ingredients:

*Capsule Contents*: Hypromellose, methacrylic acid copolymer, microcrystalline cellulose, purified water, sodium lauryl sulfate, talc and triethyl citrate.
*Capsule Shell Ingredients*: FD&C Blue#2, gelatin and titanium dioxide.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

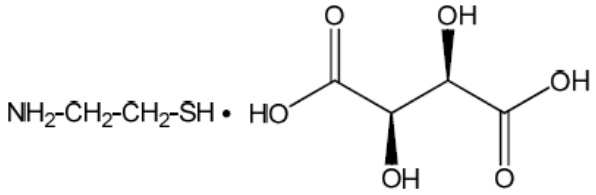
Common name: Cysteamine Bitartrate (also called mercaptamine bitartrate)

Chemical name: Ethanethiol, 2-amino,[R-(R*,R*)]-2,3-dihydroxybutanedioate(1:1) salt, or
Mercaptamine Bitartrate (INN), or
2-Aminoethanethiol Bitartrate

Molecular formula:
Cysteamine (free base): $C_2H_7NS$
Cysteamine bitartrate: $C_2H_7NS \bullet C_4H_6O_6$

Molecular mass:
Cysteamine (free base): 77.15 Da
Cysteamine bitartrate: 227.24 Da

Structural formula:




Physicochemical properties:

| | |
|---|---|
| Description: | White crystalline powder |
| Polymorphism: | Form A (monohydrate form); Form B (anhydrous form) |
| Solubility: | Cysteamine bitartrate is freely soluble in water (>100 mg/mL), and is freely soluble in aqueous media across pH 1.2 to 7.2 |
| Melting range: | 118 - 121°C |
| Acid pKa: | 8.19 |
| Basic pKa: | 10.61 |

**Table 7: Solubility of Cysteamine Bitartrate**

| pH condition | Cysteamine bitartrate concentration (mg/mL), Mean ±SD, n=3 |
|---|---|
| 1.2 (hydrochloric acid/potassium chloride buffer, 50 mM) | 158.9 ± 8.9 |
| 3.0 (potassium phosphate buffer, 50 mM) | 109.1 ± 0.6 |
| 4.5 (sodium acetate buffer, 50 mM) | 166.6 ± 13.2 |
| 6.8 (potassium phosphate buffer, 50 mM) | 216.6 ±3.3 |
| 7.2 (potassium phosphate buffer, 50 mM) | 222.4 ± 1.3 |

## CLINICAL TRIALS

The three clinical trials that support the efficacy and safety of PROCYSBI for the treatment of nephropathic cystinosis are listed in Table 8. Study 03 was an open-label, randomized, active-controlled, 9-week crossover study that compared the safety, efficacy, tolerability, pharmacokinetics, and pharmacodynamics of PROCYSBI administered every 12 hours (Q12H) to immediate-release cysteamine bitartrate administered every 6 hours (Q6H) in patients with cystinosis. Study 04 was a long-term, open-label extension study of RP103 in cystinosis subjects. The maximum treatment duration with PROCYSBI in Study 04 is approximately 6.7 years. Study 08 was an open-label to assess the safety and effectiveness of long-term, repeat dosing of PROCYSBI on white blood cell (SBC) cystine levels in cysteamine treatment naïve patients with cystinosis.

**Table 8: Summary of Patient Demographics for Study 03, 04, and 08 conducted with PROCYSBI in patients with Nephropathic Cystinosis**

| Study # | Trial design | Dosage, route of administration and duration | No of Study Patients Enrolled | Mean age (Range) | Sex (%) |
|---|---|---|---|---|---|
| Study 03 | Open-label, multicenter, randomized crossover | PROCYSBI 25 mg and 75 mg capsules Q12H vs. immediate-release cysteamine bitartrate 50 mg and 150 mg capsules Q6H; oral; 9 weeks | 43 | 12 (6 – 26) years | Male: 56<br>Female: 44 |
| Study 04 | Open-label,Multi-center, long-term, open label | PROCYSBI Q12H; oral;<br>Mean (SD) Days of Exposure: 1089 (394.4)<br>Min, Max: 35, 1677 | 60 | 10.9 (2 – 32) years | Male: 63<br>Female: 37 |
| Study 08 | Open-label, multicenter, long-term | PROCYSBI Q12H; oral or via G-tube;<br>Mean (SD) Days of exposure: 493.5 (156.6) | 17 | 3.8 (1 - 22) years | Male: 59<br>Female: 41 |

The safety and efficacy of PROCYSBI have been established in pediatric patients (6 years of age and older) that were enrolled in Study 03, patients aged 2 years and older that were enrolled in Study 04, and patients aged 1 year and older that were enrolled in Study 08. In total, there were 71/79 (90%) of patients who received PROCYSBI during these clinical studies in the pediatric age range of 1 to < 18 years. There were no patients enrolled in the clinical trials over the age of 65 years.

Study 03: Multi-Center, Open-Label, Randomized Clinical Trial

**Study demographics and trial design**
This clinical trial comparing immediate-release cysteamine bitartrate and PROCYSBI was conducted in 43 (40 pediatric and 3 adult) patients with nephropathic cystinosis. All but one patient were Caucasian (Per Protocol Population).

WBC cystine levels were measured using the mixed leukocyte assay. Patients with WBC cystine concentrations greater than 2 nmol ½ cystine/mg protein and estimated glomerular filtration rate 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 82% of the average total daily dose of immediate-release cysteamine bitartrate for patients at trial entry. There were 24/43 (56%) patients who had their dose of PROCYSBI up-titrated by the end of the 3 week treatment period.

The primary endpoint of the study was a non-inferiority comparison of PROCYSBI to immediate-release cysteamine bitartrate in terms of control of WBC cystine levels.

**Study results**
This trial demonstrated that at steady-state, PROCYSBI administered every 12 hours (over a 3 week period) was non-inferior to immediate-release cysteamine bitartrate administered every 6 hours (over a 3 week period) with respect to the depletion of WBC cystine concentrations (Table 9).

**Table 9: Primary Analysis[a] of WBC Cystine in Study 03 (Per Protocol Population)**

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

[a] Statistical analysis performed using non-linear mixed models.
[b] Measured using the mixed leukocyte assay.
[c] Non-inferiority margin was 0.3 nmol ½ cystine/mg protein.
CI = confidence interval; LS = least squares; SE = standard error; WBC = white blood cell.

Study 04: Multi-Center, Single-Arm, Open-Label, Long-Term Extension Clinical Trial

**Study demographics and trial design**

Study 04 is a long-term, open-label study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of PROCYSBI in pediatric and adult cystinosis patients. Additional enrollment in Study 04 was opened to subjects ≤ 6 years of age and kidney transplant recipients. The estimated mean duration of exposure for subjects who continued in Study 04 after completing Study 03, for subjects newly enrolled in Study 04 who were ≤ 6 years of age, or who had previously received a kidney transplant was approximately 4.4 years (1591 days), 3.5 years (1275 days), and 3.3 years (1203 days), respectively.

**Table 10: Mean WBC Cystine (nmol ½ cystine/mg protein) over Time (Study 04 Pharmacokinetics/Pharmacodynamics Population)**

| Visit | Approx. Years in Study RP103-04 | Statistic | Subpopulation | | |
|---|---|---|---|---|---|
| | | | RP103-03 (N=40) | ≤ 6 Years of Age (N=13) | Transplant (N=6) |
| | | | WBC cystine (nmol ½ cystine/mg protein)[a] at 0.5 hour post-RP103 dose | | |
| First visit (M1 or D1)[b] | 0-0.1 year | Mean (SD) [n] | 0.43 (0.513) [n=39] | 1.41 (1.030) [n=13] | 2.40 (1.687) [n=5] |
| M6 | 0.5 year | Mean (SD) [n] | 0.46 (0.431) [n=38] | 2.00 (1.729) [n=13] | 1.75 (1.242) [n=5] |
| Q2 | 1.0 year | Mean (SD) [n] | 0.43 (0.358) [n=38] | 1.10 (0.578) [n=12] | 1.28 (0.830) [n=5] |
| Q4 | 1.5 years | Mean (SD) [n] | 0.49 (0.346) [n=37] | 1.22 (1.397) [n=13] | 1.57 (0.944) [n=4] |
| Q6 | 2.0 years | Mean (SD) [n] | 0.53 (0.300) [n=35] | 1.40 (2.188) [n=6] | 0.62 (0.368) [n=3] |
| | | | | | |
| Q10 | 3.0 years | Mean (SD) [n] | 0.39 (0.290) [n=20] | 1.13 (0.418) [n=5] | 1.69 (0.682) [n=3] |
| Q14 | 4.0 years | Mean (SD) [n] | 1.49 (1.899) [n=20] | 1.19 (1.232) [n=5] | 1.03 (0.172) [n=3] |
| Q18 | 5.0 years | Mean (SD) [n] | 1.20 (2.364) [n=19] | 0.40 (0.306) [n=2] | 1.48 (0.673) [n=3] |

[a] Measured using the mixed leukocyte assay.

[b] First available visit in Study RP103-04: Month 1 for subjects from Study 03 and Day 1 for the other two subpopulations. Visits shown are first visit and visits at approximately half-yearly increments through 2 years and yearly through 5 years.

D = day; M = month(ly) visit; N/A = not applicable; Q = quarter(ly) visit; SD = standard deviation; WBC = white blood cell.

In this study, all but one subject were Caucasian. Subjects from the transplant subpopulation tended to be older than subjects from the other two subpopulations (median age at baseline in the transplant subpopulation was 20.5 years compared to 5.0 years in the subpopulation of subjects ≤ 6 years of age and 11.0 years in the subpopulation of subjects who completed RP103-03).

**Study results**

WBC cystine levels were measured using the mixed leukocyte assay. The mean WBC cystine level for Study 03 patients at the first available visit in Study 04 was below 1.0 nmol ½ cystine/mg protein (mean of 0.43) reflecting the WBC cystine control achieved in Study 03 as

shown in Table 9. Mean WBC cystine levels remained below 1.0 through the duration of the study (mean of 0.54 at approximately 3.75 years; see Table 10).

Study 08: Multi-Center, Open-Label, Clinical Trial

**Study demographics and trial design**

Study 08 is an open-label, safety and effectiveness study of PROCYSBI in 17 patients with a documented diagnosis of nephropathic cystinosis who were naïve to cysteamine treatment (15 patients between the ages of 1 and 5 years, one 9-year old and one 22-year old). The PROCYSBI starting dose was 1/4 the maintenance dose of 1 gram/$m^2$/day (actual dosing was based on weight ranges using the available capsule strengths, as shown in Table 4 and Table 5) and the dosage was gradually increased by 10% every 2 weeks. Dosage adjustment was allowed throughout the trial and was based on subject-specific factors (e.g., weight, tolerability) and WBC cystine concentrations. WBC cystine concentrations were obtained 30 minutes after the morning dose collected bi-monthly until the patient's WBC cystine concentration (using the mixed leukocyte assay) was < 1 nmol ½ cystine/mg protein. Treatment duration was at least 12 months.

Fourteen of the 15 patients between 1 year and less than 6 years of age completed 12 months of treatment, and 10 patients completed 18 months of treatment. Thirteen of the 14 patients achieved their highest total daily dosage of PROCYSBI following the 9-month visit (9-month visit for 8 subjects, 12-month visit for 4 subjects, and 18-month visit for 1 subject).

In patients 1 year to less than 6 years, the mean (±SD) WBC cystine concentration on Day 1, 30 minutes following the first dose, was 3.17 ± 2.95 nmol ½ cystine/mg protein (n=15 patients). At 12 months (n=13) , the mean WBC cystine concentration was 0.80 ±0.60 nmol ½ cystine/mg protein at 30 minutes post dose. At 18 months (n=9) the mean WBC cystine concentration was 0.74 ±0.64 nmol ½ cystine/mg protein at 30 minutes post dose. Some patients did not have WBC cystine samples collected at each visit or the results were not reportable due to laboratory errors.

In patients 1 year to less than 6 years, the mean (±SD) weight percentiles at Day 1 (n=14), 12 months (n=13) and 18 months (n=10) were 3.5 ± 11.1, 11.9 ± 18.3, and 30.1 ± 28.2, respectively, and patient weight z-scores were -4.0 ±2.1, -2.2 ±1.7, and -1.3 ±2.0, respectively. In the same patients, the mean (±SD) height percentiles at Day 1, 12 months and 18 months were 2.6 ± 4.0, 32.7 ± 37.7, and 55.4 ± 43.9, respectively and patient height z-scores were -3.2 ± 1.6, -1.1 ± 1.9 and 0.05 ± 2.1.

**Study results**

This trial demonstrated that PROCYSBI administered to treatment-naïve subjects with nephropathic cystinosis resulted in lowering WBC cystine concentrations and improving growth parameters in subjects <6 years of age throughout the treatment period of 12 months.

## DETAILED PHARMACOLOGY

### *In Vitro* Drug Interaction Studies

*In vitro* data indicate cysteamine bitartrate is a substrate of P-gp and OCT2 but not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT1.

*In vitro* data indicate 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.

*In vitro* data indicate cysteamine bitartrate is not an inhibitor of uptake transporters OATP1B1, 1B3, OAT1, OAT3, OCT1 and OCT2 and efflux transporters P-gp and BCRP.

### Pharmacodynamics and Pharmacokinetics

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

The findings from *in vitro* and *in vivo* studies confirm the cystine depletion properties of cysteamine. Cysteamine also dose-dependently depletes brain somatostatin, noradrenaline, and pituitary/serum prolactin.

The pharmacokinetics of PROCYSBI were evaluated in 43 patients with cystinosis and with an estimated glomerular filtration rate of > 30 mL/minutes/1.73 $m^2$ (Study 03). The mean $C_{max}$, $AUC_{inf}$ and $T_{max}$ were 3.6 mg/L, 726 min*mg/L and 188 minutes, respectively.

## TOXICOLOGY

### Repeated-Dose Study

| Species | Route | Duration | Doses (mg/kg/day) | Results |
|---|---|---|---|---|
| Sprague-Dawley Rats | Oral (gavage) | 14 days (once daily) | 0, 75, 150, 300 [a] | Duodenal transmural ulceration (with perforation) was observed in one 300 mg/kg/day female, as well as gastric submucosal inflammation with edema and/or erosion/ulcerations at ≥150 mg/kg/day. The NOAEL is 75 mg/kg/day; however, one male had a depressed area in the stomach mucosa with submucosal inflammation but no ulceration. |
| Rhesus Monkeys | Stomach Tube | 4 weeks | 150 [b] | On the basis of the observed changes of sedation and tachycardia, central nervous and cardiovascular systems could be the target organs of toxicity and a dose of 150 mg/kg/day was toxic. Cysteamine use of up to 4 weeks did not improve tolerability. |
| Rhesus Monkeys | Stomach Tube | 58 weeks | Group 1: 0<br>Group 2: 20 [b]<br>Group 3: 20 to 150 [b] | One animal of five died in the dose titration group at a dose of 35 mg/kg in Week 6 of the study; this animal showed esophageal ulceration and hepatic toxicity. The gastrointestinal tract and liver are the target organs of toxicity. An oral dose of 20 mg/kg/day (0.2-fold the recommended human maintenance dose based on body surface area) produced minimum effects and could be considered as the NOAEL for this study. |
| Wistar rats | Oral (drinking water) | 6 months | Group 1: 0 mg/day<br>Group 2: 3 mg/day | Group 2 demonstrated skeletal and cardiovascular toxicity. Vertebral bodies were collapsed at the thoracolumbar junction and the midthoracic region, resulting in kyphosis. Longitudinal dissection of the aorta was seen histologically; degeneration of elastic fibers led to aortic aneurysm and rupture. |
| Long Evans neonatal rats | Subcutaneous | 8-11 days | Group 1: 0<br>Group 2: 100-250<br>Group 3: 200 | High mortality; delayed growth, eye opening, and sexual development; and permanent bilateral cataracts were observed in treated pups. |
| Sprague Dawley neonatal rats | Subcutaneous | 6 days | Group 1: 0<br>Group 2: 200 (day 1-6)<br>Group 3: 0 (day 10-16)<br>Group 4: 200 (day 10-16) | Cataract formation was seen in neonatal rats dosed with cysteamine hydrochloride for the first six days of life. However, delayed exposure of neonatal rats to cysteamine (treatment day 10 through 16) resulted in the absence of cataract formation. |

$AUC_{0\text{-last}}$ = area under the curve from time zero to last time point; $C_{max}$ = maximum concentration; NOAEL = No Observed Adverse Effect Level.

[a] Represents free base using a correction factor of 3.3445.

[b] Represents free base.

**Reproductive Toxicity**
Reproduction studies with cysteamine have been performed in pregnant rats at oral doses of 37.5, 75, 100, and 150 mg/kg/day. Doses of 100 and 150 mg/kg/day produce adverse effects on the fetus during organogenesis resulting in intrauterine growth retardation, fetal death, and malformations. Observed teratogenic findings were cleft palate vertebrae kyphosis, heart ventricular septal defects, and microcephaly. Cysteamine ≥ 100 mg/kg/day (about 0.5 times the recommended human maintenance dose based on body surface area) was fetotoxic and teratogenic. The NOAEL was considered to be 75 mg/kg/day (about 0.4 times the recommended human maintenance dose based on body surface area).

In a fertility and early embryonic development study in rats, orally administered cysteamine at 150 mg/kg/day (900 mg/m$^2$ per day, 0.7 times the recommended human maintenance dose based on body surface area) had no significant effects on the duration of estrous cycle, number of females who became pregnant, number of corpora lutea, number of implantation sites, or number of failed conceptions. In another study, 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), reduced the conception rate of the adult rats and the number of live births per litter.

In pre and postnatal development studies in rats, orally administered cysteamine at 375 mg/kg/day (2250 mg/m$^2$ per day, 1.7 times the recommended human maintenance dose based on body surface area) demonstrated post-natal toxicity. Pups nursed by females treated at this dose had growth retardation and reduced survival at weaning. No effects on pre and postnatal development were observed at 75 mg/kg per day (450 mg/m$^2$ per day, 0.4 times the recommended human dose based on body surface area).

**Genotoxicity**
Cysteamine was not mutagenic in bacterial reverse mutational assays (Ames tests). In *in vitro* assays for clastogenicity, cysteamine induced chromosome aberrations (in rat liver cells and human lymphocytes), and sister chromatid exchanges (in Chinese hamster cells but not human lymphocytes). Cysteamine was negative in an *in vivo* mouse micronucleus test.

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

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

**Pr PROCYSBI®**
**Cysteamine delayed-release capsules**

Read this carefully before you start taking **PROCYSBI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PROCYSBI**.

**What is PROCYSBI used for?**
PROCYSBI is used for treatment of nephropathic cystinosis.

**How does PROCYSBI work?**
Nephropathic cystinosis is a rare disease where the amino acid cystine builds up in organs and tissues, causing damage. PROCYSBI changes cystine so that it does not build up in the organs and tissues.

**What are the ingredients in PROCYSBI?**
Medicinal ingredient: Cysteamine bitartrate (also called mercaptamine bitartrate)
Non-medicinal ingredients:
*Capsule Contents*: Hypromellose, methacrylic acid copolymer, microcrystalline cellulose, purified water, sodium lauryl sulfate, talc and triethyl citrate.
*Capsule Shell Ingredients*: FD&C Blue#2, gelatin and titanium dioxide.

**PROCYSBI comes in the following dosage forms:**
Delayed-release capsules, 25 mg and 75 mg.

**Do not use PROCYSBI if you:**
- are allergic to cysteamine bitartrate or to any of the ingredients in PROCYSBI.
- are allergic to penicillamine.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PROCYSBI. Talk about any health conditions or problems you may have, including if you:**
- have skin or bone problems including rashes, stretch marks, fractures, painful joints.
- have a serious skin rash including severe skin peeling especially mouth and eyes, red or purple rash, flu-like symptoms.
- have or have had stomach or bowel (intestinal) problems including ulcers or bleeding or changes in stomach or bowel problems.
- have a history of seizures, lack of energy, unusual sleepiness, depression, ringing in the ear, double vision, loss of vision, pain behind the eye or pain with eye movement or changes in your ability to think clearly.

- have liver or kidney problems, including kidney failure, or if you are on hemodialysis treatment.
- have blood problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. PROCYSBI might harm your unborn baby. Tell your healthcare professional right away if you think that you are pregnant. Talk with your healthcare professional about the benefits and risks of taking PROCYSBI during pregnancy. You should also discuss the importance of using birth control during your treatment with PROCYSBI. Your healthcare professional can tell you which birth control options are best for you.
- are breastfeeding or plan to breastfeed. You should not breastfeed during treatment with PROCYSBI. Talk with your healthcare professional about the best way to feed your baby if you take PROCYSBI.

**Other warnings you should know about:**
**Driving and using machines**
Do not drive or operate heavy machinery until you know how PROCYSBI affects you. PROCYSBI can make you sleepy or less alert than normal.

If you are currently taking cysteamine eye drops, do not stop taking them without talking to your healthcare professional since PROCYSBI does not prevent deposits of cystine crystals in the eye.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with PROCYSBI:**
- Bicarbonates and carbonate used to reduce stomach acid.
- Do not take with alcohol.

**How to take PROCYSBI:**
- PROCYSBI should be taken exactly as you are told by your healthcare professional.
    - Ask your healthcare professional on when to take PROCYSBI if you are on hemodialysis.
- Your healthcare professional will do blood tests before you start treatment with PROCYSBI to decide on the dose that is best for you. You will also have blood tests regularly while you are taking PROCYSBI.
- Your healthcare professional may start you on a low dose of PROCYSBI, and slowly increase your dose to help avoid side effects, especially if you have not taken a medicine that contains cysteamine bitartrate before.
- Do not change your dose of PROCYSBI unless you are told to by your healthcare professional.
- Take PROCYSBI without food.
    - Do not eat for at least 2 hours before taking PROCYSBI and at least 30 minutes after.

- If you cannot take PROCYSBI without food:
    - Take up to 4 ounces (1⁄2 cup) of food within 1 hour before taking PROCYSBI and 30 minutes after taking PROCYSBI.
- Avoid eating foods that are high in fat and protein (e.g. dairy) close to the time that you will take a dose of PROCYSBI.
- Swallow PROCYSBI capsules whole with fruit juice (except grapefruit juice) or water. Do not crush or chew PROCYSBI or the capsule contents.
- For children who are at risk of choking on the capsules (approximately 6 years of age and younger) and for adults who cannot swallow the capsules whole, the capsules can be opened and the capsule contents taken with applesauce (see instructions below). PROCYSBI can also be given through a gastrostomy tube, size 14 French or larger (see instructions below).

**Taking PROCYSBI with applesauce:**
**Do not take PROCYSBI with any food other than applesauce.**

Step 1**:** Place about ½ cup (4 ounces) of applesauce into a clean container. Do not use any other food.
Step 2: Open the PROCYSBI capsule. You may need to use more than 1 PROCYSBI capsule for the dose prescribed by your healthcare professional.
Step 3: Sprinkle the granules that are inside of the capsule or capsules onto the applesauce.
Step 4: Mix the granules with the applesauce. Do not crush the granules.
Step 5: Swallow the applesauce and granule mixture within 30 minutes of mixing. Do not chew the granules. Do not save the applesauce and granules for later use.

**Giving PROCYSBI through a gastrostomy tube (G-tube) size 14 French or larger:**

- It is best to use a straight (bolus) feeding tube.

**Use only strained applesauce with no chunks when giving PROCYSBI through a gastrostomy tube (G-tube).**

Step 1: Flush the gastrostomy tube button with 5 mL of water to clear the button.
Step 2: Place about ½ cup (4 ounces) of applesauce into a clean container. Use at least 1/8 cup (1 ounce) of applesauce for children 25 kg or less starting PROCYSBI at a dose of 1 or 2 capsules.
Step 3: Open the PROCYSBI capsule. You may need to use more than 1 PROCYSBI capsule for the dose prescribed by your healthcare professional.
Step 4: Sprinkle the granules that are inside the capsule(s) on the applesauce. Gently mix the granules with the applesauce. Do not crush granules.
Step 5: Place the tip of a catheter tip syringe at the bottom of the container of applesauce and granule mixture. For an adult dose, draw up about 40 mL of the mixture. When giving to a child, draw up at least 10 mL of the mixture for doses of 1 or 2 capsules.
Step 6: Place the tip of the catheter tip syringe into the feeding tube that will be connected to the gastrostomy tube. Fill the feeding tube with the applesauce and granule mixture.
Step 7: Hold the feeding tube in a horizontal (straight across) position. Give the applesauce and granule mixture through the gastrostomy tube at a quick and steady rate of 10 mL over 10 seconds.

Step 8: Repeat Steps 5 through Step 7 until all of the applesauce and granule mixture is given. **Give all of the applesauce and granule mixture through the gastrostomy tube within 30 minutes of mixing.** Do not save the applesauce and granule mixture for later use.

Step 9: Draw up at least 10 mL of fruit juice(except grapefruit juice) into another catheter tip syringe. Gently swirl the syringe. Flush the gastrostomy tube with the fruit juice (except grapefruit juice) or water. Use enough fruit juice (except grapefruit juice) to flush the gastrostomy tube so that there is no applesauce and granule mixture left in the gastrostomy tube.

**Usual dose:**
Your healthcare professional will tell you how many PROCYSBI capsules to take. PROCYSBI is taken 2 times each day, every 12 hours.

**Overdose:**

If you think you have taken too much PROCYSBI, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
If you miss a dose, take it as soon as possible. If it is within 4 hours of the time the next dose is due, skip the missed dose. Take the next dose at your regularly scheduled time. Do not take 2 doses at one time to make up for a missed dose.

**What are possible side effects from using PROCYSBI?**
These are not all the possible side effects you may feel when taking PROCYSBI. If you experience any side effects not listed here, contact your healthcare professional.

- vomiting
- nausea
- stomach (abdominal) pain and discomfort
- loss of appetite
- breath odour
- diarrhea
- dehydration
- skin odour
- tiredness
- skin rash
- headache
- dizziness
- flushing
- leg pain
- knee pain, misaligned knees

- excess joint movement (joint hyperextension)
- bone density loss (osteopenia)
- blurred or double vision

PROCYSBI can cause abnormal blood test results. You healthcare professional will decide when to perform blood tests and will interpret the results.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom/effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **COMMON**<br>**Stomach and bowel (intestinal) problems:** flu-like symptoms like fever, vomiting and diarrhea. | | ✔ | |
| **UNCOMMON**<br>**Central nervous system symptoms:** seizures, depression, becoming very sleepy, headache, nausea, vomiting, ringing in the ears, dizziness, double vision, loss of vision, confusion, memory loss, personality changes, pain behind the eye or pain with eye movement | | ✔ | |
| **Ehlers-Danlos-like Syndrome:** Purplish marks on the skin, streaking of the skin, bone problems (including thinning of the bones, spine fractures, curvature of the spine, and "knock knees"), leg pain, and hyperextension of the joints. | | ✔ | |
| **Hypersensitivity reactions:** hives, difficulty breathing, swelling of face, lips, tongue, and/or throat. | | | ✔ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom/effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **Kidney disorder/problems:** swollen hands or legs, or unusual weight gain (from retaining fluid), decreased or increased urination, nausea, vomiting, fever, fatigue, thirst, dry skin, irritability, dark urine, blood in the urine, rash, weight gain loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma) | | ✔ | |
| **Stomach and bowel (intestinal) problems:** vomiting blood or blood in the stool (ulcers). | | | ✔ |
| **VERY RARE**<br>**Serious skin reactions** (erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, hypersensitivity Syndrome, Ehlers-Danlos-like syndrome, molluscoid pseudotumours)**:** red or purple itchy or burning rash with blisters and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, soft skin, bruised skin, scars, stretch marks, lumps over pressure points like elbows and knees, fragile or stretchy skin, fever, chills, headache, cough, body aches or joint pain, dark urine, yellow skin or eyes. | | | ✔ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- Store PROCYSBI at room temperature between 20 °C to 25 °C and in a dry place away from light.
- Dispose of any unused capsule(s) by the "Use by" date entered by the pharmacist on bottle.
- Discard expired capsules per your local or provincial regulations.
- Keep PROCYSBI tightly closed in the original bottle.

The 25 mg PROCYSBI bottle contains one desiccant canister and one oxygen absorber canister. The 75 mg PROCYSBI bottle contains one desiccant canister and two oxygen absorber canisters. Do not eat or throw away the desiccant canister or oxygen absorber canister(s).

Keep out of reach and sight of children.

**If you want more information about PROCYSBI:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website http://www.horizontherapeutics.ca, or by calling 1-844-380-7850.

This leaflet was prepared by Horizon Therapeutics Ireland DAC.

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