**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 25 mg gastro-resistant hard capsules
PROCYSBI 75 mg gastro-resistant hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROCYSBI 25 mg gastro-resistant hard capsule

Each gastro-resistant hard capsule contains 25 mg of cysteamine (as mercaptamine bitartrate).

PROCYSBI 75 mg gastro-resistant hard capsule

Each gastro-resistant hard capsule contains 75 mg of cysteamine (as mercaptamine bitartrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule.

PROCYSBI 25 mg gastro-resistant hard capsule

Light blue size 3 (15.9 x 5.8 mm) hard capsules imprinted “25 mg” in white ink and a light blue cap imprinted with “PRO” in white ink.

PROCYSBI 75 mg gastro-resistant hard capsule

Light blue size 0 (21.7 x 7.6 mm) hard capsules imprinted “75 mg” in white ink and a dark blue cap imprinted with “PRO” in white ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PROCYSBI is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

### 4.2 Posology and method of administration

PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.
Cysteamine therapy must be initiated promptly once the diagnosis is confirmed (i.e., increased WBC cystine) to achieve maximum benefit.

Posology

White blood cell (WBC) cystine concentration may for instance be measured by a number of different techniques such as specific WBC subsets (e.g., granulocyte assay) or the mixed leukocyte assay with each assay having different target values. Healthcare professionals should refer to the assay-specific therapeutic targets provided by individual testing laboratories when making decisions regarding diagnosis and PROCYSBI dosing for cystinosis patients. For example the therapeutic goal is to maintain a WBC cystine level < 1 nmol hemicystine/mg protein (when measured using the mixed

leukocyte assay), 30 min after dosing For patients adherent to a stable dose of PROCYSBI, and who do not have easy access to an adequate facility for measuring their WBC cystine, the goal of therapy should be to maintain plasma cysteamine concentration > 0.1 mg/L, 30 min after dosing.
Measurement timing: PROCYSBI should be administered every 12 hours. The determination of WBC cystine and/or plasma cysteamine must be obtained 12.5 hours after the evening dose the day before, and therefore 30 minutes after the following morning dose is given.

*Transferring patients from immediate-release cysteamine bitartrate hard capsules*
Patients with cystinosis taking immediate-release cysteamine bitartrate may be transferred to a total daily dose of PROCYSBI equal to their previous total daily dose of immediate-release cysteamine bitartrate. Total daily dose should be divided by two and administered every 12 hours. The maximum recommended dose of cysteamine is 1.95 g/m$^2$/day. The use of doses higher than 1.95 g/m$^2$/day is not recommended (see section 4.4).
Patients being transferred from immediate-release cysteamine bitartrate to PROCYSBI should have their WBC cystine levels measured in 2 weeks, and thereafter every 3 months to assess optimal dose as described above.

*Newly diagnosed adult patients*
Newly diagnosed adult patients should be started on 1/6 to 1/4 of the targeted maintenance dose of PROCYSBI. The targeted maintenance dose is 1.3 g/m$^2$/day, in two divided doses, given every 12 hours (see below table 1). The dose should be raised if there is adequate tolerance and the WBC cystine level remains > 1 nmol hemicystine/mg protein (when measured using the mixed leukocyte assay). The maximum recommended dose of cysteamine is 1.95 g/m$^2$/day. The use of doses higher than 1.95 g/m$^2$/day is not recommended (see section 4.4).
The target values provided in the SmPC are obtained from using the mixed leucocyte assay. It should be noted that therapeutic targets for cystine depletion are assay-specific and different assays have specific treatment targets. Therefore, healthcare professionals should refer to the assay-specific therapeutic targets provided by individual testing laboratories.

*Newly diagnosed paediatric population*
The targeted maintenance dose of 1.3 g/m$^2$/day can be approximated according to the following table, which takes surface area as well as weight into consideration.

*Table 1: Recommended dose*

| **Weight in kilograms** | **Recommended dose in mg Every 12 hours*** |
|---|---|
| 0–5 | 200 |
| 5–10 | 300 |
| 11–15 | 400 |
| 16–20 | 500 |
| 21–25 | 600 |
| 26–30 | 700 |
| 31–40 | 800 |
| 41–50 | 900 |
| >50 | 1 000 |

*Higher dose may be required to achieve target WBC cystine concentration. The use of doses higher than 1.95 g/m$^2$/day is not recommended.

*Missed doses*
If a dose is missed, it should be taken as soon as possible. If it is within four hours of the next dose, the missed dose should be skipped going back to the regular dosing schedule. The dose should not be doubled.

*Special populations*

*Patients with poor tolerability*
Patients with poorer tolerability still receive significant benefit if white blood cell cystine levels are below 2 nmol hemicystine/mg protein (when measured using the mixed leukocyte assay). The cysteamine dose can be increased to a maximum of 1.95 g/m$^2$/day to achieve this level. The dose of 1.95 g/m$^2$/day of immediate-release cysteamine bitartrate has been associated with an increased rate of withdrawal from treatment due to intolerance and an increased incidence of adverse events. If cysteamine is initially poorly tolerated due to gastrointestinal (GI) tract symptoms or transient skin rashes, therapy should be temporarily stopped, then re-instituted at a lower dose and gradually increased to the appropriate dose (see section 4.4).

*Patients on dialysis or post-transplantation*
Experience has occasionally shown that some forms of cysteamine are less well tolerated (i.e. leading to more adverse events) when patients are on dialysis. A closer monitoring of the WBC cystine levels is recommended in these patients.

*Patients with renal impairment*
Dose adjustment is not normally required; however, WBC cystine levels should be monitored.

*Patients with hepatic impairment*
Dose adjustment is not normally required; however, WBC cystine levels should be monitored.

Method of administration

Oral use.

This medicinal product can be administered by swallowing the intact capsules as well as sprinkling the capsule contents (enteric coated beads) on food or delivery through a gastric feeding tube.
Do not crush or chew capsules or capsule contents.

*Administration with food*
Cysteamine bitartrate can be administered with an acidic fruit juice or water.
Cysteamine bitartrate should not be administered with food rich in fat or proteins, or with frozen food like ice-cream. Patients should try to consistently avoid meals and dairy products for at least 1 hour before and 1 hour after PROCYSBI dosing. If fasting during this period is not possible, it is acceptable to eat only a small amount (~ 100 grams) of food (preferentially carbohydrates) during the hour before and after PROCYSBI administration. It is important to dose PROCYSBI in relation to food intake in a consistent and reproducible way over time (see section 5.2).
In paediatric patients who are at risk of aspiration, aged approximately 6 years and under, the hard capsules should be opened and the content sprinkled on food or liquid listed in section 6.6.

For instructions about the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

- Hypersensitivity to the active substance, any form of cysteamine (mercaptamine), or to any of the excipients listed in section 6.1.
- Hypersensitivity to penicillamine.
- Breast-feeding.

## 4.4 Special warnings and precautions for use

The use of doses higher than 1.95 g/m$^2$/day is not recommended (see section 4.2).

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

If a pregnancy is diagnosed or planned, the treatment should be carefully reconsidered and the patient must be advised of the possible teratogenic risk of cysteamine (see section 4.6).

Intact capsules of PROCYSBI should not be administered to children under the age of approximately 6 years due to risk of aspiration (see section 4.2).

Dermatological

There have been reports of serious skin lesions in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts that have responded to cysteamine dose reduction. Physicians should routinely monitor the skin and bones of patients receiving cysteamine.

If skin or bone abnormalities appear, the dose of cysteamine should be reduced or stopped. Treatment may be restarted at a lower dose under close supervision, and then slowly titrated to the appropriate therapeutic dose (see sections 4.2). If a severe skin rash develops such as erythema multiforme bullosa or toxic epidermal necrolysis, cysteamine should not be re-administered (see sections 4.8).

Gastrointestinal

GI ulceration and bleeding have been reported in patients receiving immediate-release cysteamine bitartrate. 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.

GI tract symptoms including nausea, vomiting, anorexia and abdominal pain have been associated with cysteamine.

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 (1:1), 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.

Central Nervous System (CNS)

CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with cysteamine. If CNS symptoms develop, the patient should be carefully evaluated and the dose adjusted as necessary. Patients should not engage in potentially hazardous activities until the effects of cysteamine on mental performance are known (see section 4.7).

Leukopenia and abnormal liver function

Cysteamine has occasionally been associated with reversible leukopenia and abnormal liver function. Therefore, blood counts and liver function should be monitored.

Benign intracranial hypertension

There have been reports of benign intracranial hypertension (or pseudotumor cerebri (PTC)) and/or papilledema associated with cysteamine bitartrate treatment that has resolved with the addition of diuretic therapy (post-marketing experience with the immediate-release cysteamine bitartrate). Physicians should instruct patients to report any of the following symptoms: headache, tinnitus, dizziness, nausea, diplopia, blurred vision, loss of vision, pain behind the eye or pain with eye movement. A periodic eye examination is needed to identify this condition early and timely treatment should be provided when it occurs to prevent vision loss.

PROCYSBI contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

It cannot be excluded that cysteamine is a clinically relevant inducer of CYP enzymes, inhibitor of P-gp and BCRP at the intestinal level and inhibitor of liver uptake transporters (OATP1B1, OATP1B3 and OCT1).

Co-administration with electrolyte and mineral replacement

Cysteamine can be administered with electrolyte (except bicarbonate) and mineral replacements necessary for management of Fanconi syndrome as well as vitamin D and thyroid hormone. Bicarbonate should be administered at least one hour before or one hour after PROCYSBI to avoid potential earlier release of cysteamine.

Indomethacin and cysteamine have been used simultaneously in some patients. In cases of patients with kidney transplants, anti-rejection treatments have been used with cysteamine.

Co-administration of the proton pump inhibitor omeprazole and PROCYSBI *in vivo* showed no effects on cysteamine bitartrate exposure.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be informed about the risk of teratogenicity and advised to use an adequate method of contraception during the course of treatment. A negative pregnancy test should be confirmed before starting treatment.

Pregnancy

There is no adequate data from the use of cysteamine in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenesis (see section 5.3). The potential risk for humans is unknown. The effect on pregnancy of untreated cystinosis is also unknown. Therefore, cysteamine bitartrate should not be used during pregnancy, particularly during the first trimester, unless clearly necessary (see section 4.4).

If a pregnancy is diagnosed or planned, the treatment should be carefully reconsidered.

Breast-feeding

Cysteamine excretion in human milk is unknown. However, due to the results of animal studies in breast-feeding females and neonates (see section 5.3), breast-feeding is contra-indicated in women taking PROCYSBI (see section 4.3).

Fertility

Effects on fertility have been seen in animal studies (see section 5.3). Azoospermia has been reported in male cystinosis patients.

## 4.7 Effects on ability to drive and use machines

Cysteamine has minor or moderate influence on the ability to drive and use machines.

Cysteamine may cause drowsiness. When starting therapy, patients should not engage in potentially hazardous activities until the effects of the medicinal product on each individual are known.

## 4.8 Undesirable effects

Summary of the safety profile

For the immediate-release formulation of cysteamine bitartrate, approximately 35% of patients can be expected to experience adverse reactions. These mainly involve the gastrointestinal and central nervous systems. When these reactions appear at the initiation of cysteamine therapy, temporary suspension and gradual reintroduction of treatment may be effective in improving tolerance.
In clinical studies with healthy volunteers, the most frequent adverse reactions were very common GI symptoms (16%) and occurred primarily as single episodes that were mild or moderate in severity. The adverse reactions profile for healthy subjects was similar to the adverse reactions profile in patients relative to GI disorders (diarrhoea and abdominal pain).

Tabulated list of adverse reactions

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

*Table 2: Adverse reactions*

| **MedDRA system organ class** | ***Frequency:* adverse reaction** |
|---|---|
| Blood and lymphatic system disorders | *Uncommon:* Leukopenia |
| Immune system disorders | *Uncommon:* Anaphylactic reaction |
| Metabolism and nutrition disorders | *Very common:* Anorexia |
| Psychiatric disorders | *Uncommon:* Nervousness, hallucination |
| Nervous system disorders | *Common:* Headache, encephalopathy |
| | *Uncommon:* Somnolence, convulsions |
| Gastrointestinal disorders | *Very common:* Vomiting, nausea, diarrhoea |
| | *Common:* Abdominal pain, breath odour, dyspepsia, gastroenteritis |
| | *Uncommon:* Gastrointestinal ulcer |
| Skin and subcutaneous tissue disorders | *Common:* Skin odour abnormal, rash |
| | *Uncommon:* Hair colour changes, skin striae, skin fragility (molluscoid pseudotumour on elbows) |
| Musculoskeletal and connective tissue disorders | *Uncommon:* Joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture, scoliosis. |
| Renal and urinary disorders | *Uncommon:* Nephrotic syndrome |
| General disorders and administration site conditions | *Very common:* Lethargy, pyrexia |
| | *Common:* Asthenia |
| Investigations | *Common:* Liver function tests abnormal |

Description of selected adverse reactions

*Clinical studies experience with PROCYSBI*
In clinical studies comparing PROCYSBI to the immediate-release cysteamine bitartrate, one third of the patients exhibited very common GI disorders (nausea, vomiting, abdominal pain). Common

nervous system disorders (headache, somnolence and lethargy) and common general disorders (asthenia) were also seen.

*Post-marketing experience with immediate-release cysteamine bitartrate*
Benign intracranial hypertension (or pseudotumor cerebri (PTC)) with papilledema; skin lesions, molluscoid pseudotumors, skin striae, skin fragility; joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture and scoliosis have been reported with immediate-release cysteamine bitartrate (see section 4.4).

Two cases of nephrotic syndrome have been reported within 6 months of starting therapy with progressive recovery after treatment discontinuation. Histology showed a membranous glomerulonephritis of the renal allograft in one case and hypersensitivity interstitial nephritis in the other.

A few cases of Ehlers-Danlos-like syndrome on elbows have been reported in children chronically treated with high doses of different cysteamine preparations (cysteamine chlorhydrate or cystamine or cysteamine bitartrate) mostly above the maximal dose 1.95 g/m$^2$/day. In some cases, these skin lesions were associated with skin striae and bone lesions first seen during an X-ray examination. Bone disorders reported were genu valgum, leg pain and hyperextensive joints, osteopenia, compression fractures, and scoliosis. In the few cases where histopathological examination of the skin was performed, the results suggested angioendotheliomatosis. One patient subsequently died of acute cerebral ischemia with marked vasculopathy. In some patients, the skin lesions on elbows regressed after immediate-release cysteamine dose reduction (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

An overdose of cysteamine may cause progressive lethargy.

Should overdosing occur, the respiratory and cardiovascular systems should be supported appropriately. No specific antidote is known. It is not known if cysteamine is removed by haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism product, amino acids and derivatives, ATC code: A16AA04.

Cysteamine is the simplest stable aminothiol and a degradation product of the amino acid cysteine. Cysteamine 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.

Normal individuals and persons heterozygous for cystinosis have white blood cell cystine levels of < 0.2 and usually below 1 nmol hemicystine/mg protein, respectively, when measured using the mixed leukocyte assay. Individuals with cystinosis have elevations of WBC cystine above 2 nmol hemicystine/mg protein.

WBC cystine is monitored in these patients to determine adequacy of dosing, levels being measured 30 minutes after dosing when treated with PROCYSBI.

A pivotal phase 3 randomised, crossover PK and PD study (which was also the first ever randomised study with immediate-release cysteamine bitartrate) demonstrated that at steady-state, patients receiving PROCYSBI every 12 hours (Q12H) maintained a comparable depletion of WBC cystine levels compared to immediate-release cysteamine bitartrate every 6 hours (Q6H). Forty-three (43) patients were randomised; twenty-seven (27) children (ages 6 to 12 years old), fifteen (15) adolescents (ages 12 to 21 years old) and one (1) adult with cystinosis and with native kidney function based on an estimated glomerular filtration rate (GFR) (corrected for body surface area) > 30 mL/minute/1.73 $m^2$ were randomised. Of those forty-three (43) patients, two (2) siblings withdrew at the end of the first crossover period, due to a prior planned surgery in one (1) of them; forty-one (41) patients completed the protocol. Two (2) patients were excluded from the per-protocol analysis because their WBC cystine level increased over 2 nmol hemicystine/mg protein during the immediate-release cysteamine treatment period. Thirty-nine (39) patients were included in the final primary per protocol efficacy analysis.

*Table 3: Comparison of WBC cystine levels following administration of immediate-release cysteamine bitartrate and PROCYSBI*

| **Per –Protocol (PP) Population (N=39)** | | |
|---|---|---|
| | Immediate-release cysteamine bitartrate | PROCYSBI |
| WBC cystine level (LS Mean ± SE) in nmol hemicystine/mg protein* | 0.44 ± 0.05 | 0.51 ± 0.05 |
| Treatment effect (LS mean ± SE; 95.8% CI; p-value) | 0.08 ± 0.03; 0.01 to 0.15; <0.0001 | |
| **All Evaluable Patients (ITT) Population (N=41)** | | |
| | Immediate-release cysteamine bitartrate | PROCYSBI |
| WBC cystine level (LS Mean ± SE) in nmol hemicystine/mg protein* | 0.74 ± 0.14 | 0.53 ± 0.14 |
| Treatment effect (LS mean ± SE; 95.8% CI; p-value) | -0.21 ± 0.14; -0.48 to 0.06; <0.001 | |

*Measured using the mixed leukocyte assay

Forty of forty-one (40/41) patients who completed the pivotal phase 3 study were entered in a prospective study with PROCYSBI that stayed open as long as PROCYSBI could not be prescribed by their treating physician. In this study, the WBC cystine measured using the mixed leukocyte assay was always on average under optimal control at < 1 nmol hemicystine/mg protein. The estimated glomerular filtration rate (eGFR) did not change for the study population over time.

## 5.2 Pharmacokinetic properties

Absorption

The relative bioavailability is about 125% as compared to immediate-release cysteamine.

Food intake reduces the absorption of PROCYSBI at 30 minutes pre-dose (approximately 35% decrease in exposure) and at 30 min post-dose (approximately 16 or 45% decrease in exposure for intact and open capsules respectively). Food intake two hours after administration did not affect the absorption of PROCYSBI.

Distribution

The *in vitro* plasma protein binding of cysteamine, primarily to albumin, is approximately 54% and independent of plasma drug concentration over the therapeutic range.

Biotransformation

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.

*In vitro* data suggests that cysteamine bitartrate is likely to be metabolised 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.

Elimination

The terminal half-life of cysteamine bitartrate is approximately 4 hours.

Cysteamine bitartrate is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 *in vitro*.

*In vitro*: Cysteamine bitartrate is a substrate of P-gp and OCT2, but not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT1. Cysteamine bitartrate is not an inhibitor of OAT1, OAT3 and OCT2.

Special populations

The pharmacokinetics of cysteamine bitartrate has not been studied in special populations.

## 5.3 Preclinical safety data

In genotoxicity studies published for cysteamine, induction of chromosome aberrations in cultured eukaryotic cell lines has been reported. Specific studies with cysteamine did not show any mutagenic effects in the Ames test or any clastogenic effect in the mouse micronucleus test. A bacterial reverse mutation assay study ("Ames test") was performed with the cysteamine bitartrate used for PROCYSBI and cysteamine bitartrate did not show any mutagenic effects in this test.

Reproduction studies showed embryo-foetotoxic effects (resorptions and post-implantation losses) in rats at the 100 mg/kg/day dose level and in rabbits receiving cysteamine 50 mg/kg/day. Teratogenic effects have been described in rats when cysteamine is administered over the period of organogenesis at a dose of 100 mg/kg/day.

This is equivalent to 0.6 g/m$^2$/day in the rat, which is slightly less than the recommended clinical maintenance dose of cysteamine, i.e. 1.3 g/m$^2$/day. A reduction of fertility was observed in rats at 375 mg/kg/day, a dose at which body weight gain was retarded. At this dose, weight gain and survival of the offspring during lactation was also reduced. High doses of cysteamine impair the ability of lactating mothers to feed their pups. Single doses of the drug inhibit prolactin secretion in animals.

Administration of cysteamine in neonate rats induced cataracts.

High doses of cysteamine, either by oral or parenteral routes, produce duodenal ulcers in rats and mice but not in monkeys. Experimental administration of the drug causes depletion of somatostatin in several animal species. The consequence of this for the clinical use of the drug is unknown.

No carcinogenic studies have been conducted with cysteamine bitartrate gastro-resistant hard capsules.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content

microcrystalline cellulose
methacrylic acid - ethyl acrylate copolymer (1:1)
hypromellose
talc
triethyl citrate
sodium lauryl sulphate

Capsule shell

gelatin
titanium dioxide (E171)
indigo carmine (E132)

Printing ink

shellac
povidone K-17
titanium dioxide (E171)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years
In-use shelf life: 30 days.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.
Keep the container tightly closed in order to protect from light and moisture.
After opening do not store above 25°C.

### 6.5 Nature and contents of container

PROCYSBI 25 mg gastro-resistant hard capsule

50 mL white HDPE bottle containing 60 gastro-resistant hard capsules with one 2-in-1 desiccant cylinder and one oxygen absorber cylinder, with a child resistant polypropylene closure.
Each bottle contains two plastic cylinders used for additional moisture and air protection.
Please keep the two cylinders in each bottle during the use of the bottle. The cylinders may be discarded with the bottle after use.

PROCYSBI 75 mg gastro-resistant hard capsule

400 mL white HDPE bottle containing 250 gastro-resistant hard capsules with one 2-in-1 desiccant cylinder and two oxygen absorber cylinders, with a child resistant polypropylene closure.
Each bottle contains three plastic cylinders used for additional moisture and air protection.

Please keep the three cylinders in each bottle during the use of the bottle. The cylinders may be discarded with the bottle after use.

## 6.6 Special precautions for disposal and other handling

Handling

*Sprinkling on food*
Capsules for either the morning or evening dose should be opened and the contents sprinkled onto approximately 100 grams of apple sauce or fruit jam. Gently stir the contents into the soft food, creating a mixture of cysteamine granules and food. The entire amount of the mixture should be eaten. This may be followed by 250 mL of an acceptable acidic liquid - fruit juice (e.g., orange juice or any acidic fruit juice) or water. The mixture must be eaten within 2 hours after preparation and may be refrigerated from the time of preparation to the time of administration.

*Administering through feeding tubes*
Capsules for either the morning or evening dose should be opened and the contents sprinkled onto approximately 100 grams of apple sauce or fruit jam. Gently stir the contents into the soft food, creating a mixture of cysteamine granules and the soft food. The mixture should then be administered via gastrostomy tube, nasogastric tube or gastrostomy-jejunostomy tube using a catheter tip syringe. Before PROCYSBI administration: Unclasp the G-tube button and attach the feeding tube. Flush with 5 mL of water to clear the button. Draw the mixture up into the syringe. A maximum 60 mL mixture volume in a catheter tip syringe is recommended for use with a straight or bolus feeding tube. Place the opening of the syringe containing the PROCYSBI/apple sauce/fruit jam mixture into the opening of the feeding tube and fill completely with the mixture: pressing gently on the syringe and keeping the feeding tube horizontal during administration can help to avoid clogging issues. Using a viscous food such as apple sauce or fruit jam at a rate of about 10 mL every 10 seconds until the syringe is completely empty, is also suggested to avoid clogging. Repeat the above step until all of the mixture is given. After PROCYSBI administration, draw 10 mL of fruit juice or water up into another syringe and flush the G-tube ensuring that none of the apple sauce/fruit jam and granules mixture gets stuck on the G-tube.
The mixture must be administered within 2 hours after preparation and may be refrigerated from the time of preparation to the time of administration. Nothing of the mixture should be saved.

*Sprinkling in orange juice or any acidic fruit juice or water*
Capsules for either the morning or evening dose should be opened and the contents sprinkled into 100 to 150 mL of acidic fruit juice or water. Dose administration options are provided below:

- Option 1/Syringe: Mix gently for 5 minutes, then aspirate the mixture of cysteamine granules and acidic fruit juice or water into a dosing syringe.
- Option 2/Cup: Mix gently for 5 minutes in a cup or shake gently for 5 minutes in a covered cup (e.g., “sippy” cup). Drink the mixture of cysteamine granules and acidic fruit juice or water.

The mixture must be administered (drunk) within 30 minutes after preparation and may be refrigerated from the time of preparation to the time of administration.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/001
EU/1/13/861/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 September 2013
Date of latest renewal: 26 July 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 75 mg gastro-resistant granules
PROCYSBI 300 mg gastro-resistant granules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROCYSBI 75 mg gastro-resistant granules

Each sachet contains 75 mg of cysteamine (as mercaptamine bitartrate).

PROCYSBI 300 mg gastro-resistant granules

Each sachet contains 300 mg of cysteamine (as mercaptamine bitartrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gastro-resistant granules.

White to off-white granules.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PROCYSBI is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

### 4.2 Posology and method of administration

PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.
Cysteamine therapy must be initiated promptly once the diagnosis is confirmed (i.e., increased WBC cystine) to achieve maximum benefit.

Posology

White blood cell (WBC) cystine concentration may for instance be measured by a number of different techniques such as specific WBC subsets (e.g., granulocyte assay) or the mixed leukocyte assay with each assay having different target values. Healthcare professionals should refer to the assay-specific therapeutic targets provided by individual testing laboratories when making decisions regarding diagnosis and PROCYSBI dosing for cystinosis patients. For example the therapeutic goal is to maintain a WBC cystine level < 1 nmol hemicystine/mg protein (when measured using the mixed leukocyte assay), 30 min after dosing For patients adherent to a stable dose of PROCYSBI, and who do not have easy access to an adequate facility for measuring their WBC cystine, the goal of therapy should be to maintain plasma cysteamine concentration > 0.1 mg/L, 30 min after dosing.
Measurement timing: PROCYSBI should be administered every 12 hours. The determination of WBC cystine and/or plasma cysteamine must be obtained 12.5 hours after the evening dose the day before, and therefore 30 minutes after the following morning dose is given.

*Transferring patients from immediate-release cysteamine bitartrate hard capsules*
Patients with cystinosis taking immediate-release cysteamine bitartrate may be transferred to a total daily dose of PROCYSBI equal to their previous total daily dose of immediate-release cysteamine bitartrate. Total daily dose should be divided by two and administered every 12 hours. The maximum recommended dose of cysteamine is 1.95 g/m$^2$/day. The use of doses higher than 1.95 g/m$^2$/day is not recommended (see section 4.4).
Patients being transferred from immediate-release cysteamine bitartrate to PROCYSBI should have their WBC cystine levels measured in 2 weeks, and thereafter every 3 months to assess optimal dose as described above.

*Newly diagnosed adult patients*
Newly diagnosed adult patients should be started on 1/6 to 1/4 of the targeted maintenance dose of PROCYSBI. The targeted maintenance dose is 1.3 g/m$^2$/day, in two divided doses, given every 12 hours (see below table 1). The dose should be raised if there is adequate tolerance and the WBC cystine level remains > 1 nmol hemicystine/mg protein (when measured using the mixed leukocyte assay). The maximum recommended dose of cysteamine is 1.95 g/m$^2$/day. The use of doses higher than 1.95 g/m$^2$/day is not recommended (see section 4.4).
The target values provided in the SmPC are obtained from using the mixed leucocyte assay. It should be noted that therapeutic targets for cystine depletion are assay-specific and different assays have specific treatment targets. Therefore, healthcare professionals should refer to the assay-specific therapeutic targets provided by individual testing laboratories.

*Newly diagnosed paediatric population*
The targeted maintenance dose of 1.3 g/m$^2$/day can be approximated according to the following table, which takes surface area as well as weight into consideration.

*Table 1: Recommended dose*

| **Weight in kilograms** | **Recommended dose in mg Every 12 hours*** |
|---|---|
| 0–5 | 200 |
| 5–10 | 300 |
| 11–15 | 400 |
| 16–20 | 500 |
| 21–25 | 600 |
| 26–30 | 700 |
| 31–40 | 800 |
| 41–50 | 900 |
| > 50 | 1 000 |

*****Higher dose may be required to achieve target WBC cystine concentration. The use of doses higher than 1.95 g/m$^2$/day is not recommended.

To reach the targeted maintenance dose, the use of PROCYSBI 25 mg gastro-resistant hard capsules could be considered.

*Missed doses*
If a dose is missed, it should be taken as soon as possible. If it is within four hours of the next dose, the missed dose should be skipped going back to the regular dosing schedule. The dose should not be doubled.

*Special populations*

*Patients with poor tolerability*
Patients with poorer tolerability still receive significant benefit if white blood cell cystine levels are below 2 nmol hemicystine/mg protein (when measured using the mixed leukocyte assay). The cysteamine dose can be increased to a maximum of 1.95 g/m$^2$/day to achieve this level. The dose of

1.95 g/m$^2$/day of immediate-release cysteamine bitartrate has been associated with an increased rate of withdrawal from treatment due to intolerance and an increased incidence of adverse events. If cysteamine is initially poorly tolerated due to gastrointestinal (GI) tract symptoms or transient skin rashes, therapy should be temporarily stopped, then re-instituted at a lower dose and gradually increased to the appropriate dose (see section 4.4).

*Patients on dialysis or post-transplantation*
Experience has occasionally shown that some forms of cysteamine are less well tolerated (i.e. leading to more adverse events) when patients are on dialysis. A closer monitoring of the WBC cystine levels is recommended in these patients.

*Patients with renal impairment*
Dose adjustment is not normally required; however, WBC cystine levels should be monitored.

*Patients with hepatic impairment*
Dose adjustment is not normally required; however, WBC cystine levels should be monitored.

Method of administration

Oral use.

This medicinal product can be administered by opening the sachet and sprinkling the sachet contents (enteric coated beads) on food or drink or delivering through a gastric feeding tube.
Do not crush or chew granules, as this impairs the gastro-resistant coating.

*Administration with food*
Cysteamine bitartrate can be administered with an acidic fruit juice or water.
Cysteamine bitartrate should not be administered with food rich in fat or proteins, or with frozen food like ice-cream. Patients should try to consistently avoid meals and dairy products for at least 1 hour before and 1 hour after PROCYSBI dosing. If fasting during this period is not possible, it is acceptable to eat only a small amount (~ 100 grams) of food (preferentially carbohydrates) during the hour before and after PROCYSBI administration. It is important to dose PROCYSBI in relation to food intake in a consistent and reproducible way over time (see section 5.2).

For instructions about the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

- Hypersensitivity to the active substance, any form of cysteamine (mercaptamine), or to any of the excipients listed in section 6.1.
- Hypersensitivity to penicillamine.
- Breast-feeding.

## 4.4 Special warnings and precautions for use

The use of doses higher than 1.95 g/m$^2$/day is not recommended (see section 4.2).

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

If a pregnancy is diagnosed or planned, the treatment should be carefully reconsidered and the patient must be advised of the possible teratogenic risk of cysteamine (see section 4.6).

Dermatological

There have been reports of serious skin lesions in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts that have responded to cysteamine dose reduction. Physicians should routinely monitor the skin and bones of patients receiving cysteamine.

If skin or bone abnormalities appear, the dose of cysteamine should be reduced or stopped. Treatment may be restarted at a lower dose under close supervision, and then slowly titrated to the appropriate therapeutic dose (see sections 4.2). If a severe skin rash develops such as erythema multiforme bullosa or toxic epidermal necrolysis, cysteamine should not be re-administered (see sections 4.8).

Gastrointestinal

GI ulceration and bleeding have been reported in patients receiving immediate-release cysteamine bitartrate. 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.

GI tract symptoms including nausea, vomiting, anorexia and abdominal pain have been associated with cysteamine.

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 (1:1), 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.

Central Nervous System (CNS)

CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with cysteamine. If CNS symptoms develop, the patient should be carefully evaluated and the dose adjusted as necessary. Patients should not engage in potentially hazardous activities until the effects of cysteamine on mental performance are known (see section 4.7).

Leukopenia and abnormal liver function

Cysteamine has occasionally been associated with reversible leukopenia and abnormal liver function. Therefore, blood counts and liver function should be monitored.

Benign intracranial hypertension

There have been reports of benign intracranial hypertension (or pseudotumor cerebri (PTC)) and/or papilledema associated with cysteamine bitartrate treatment that has resolved with the addition of diuretic therapy (post-marketing experience with the immediate-release cysteamine bitartrate). Physicians should instruct patients to report any of the following symptoms: headache, tinnitus, dizziness, nausea, diplopia, blurred vision, loss of vision, pain behind the eye or pain with eye movement. A periodic eye examination is needed to identify this condition early and timely treatment should be provided when it occurs to prevent vision loss.

PROCYSBI contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

## 4.5 Interaction with other medicinal products and other forms of interaction

It cannot be excluded that cysteamine is a clinically relevant inducer of CYP enzymes, inhibitor of P-gp and BCRP at the intestinal level and inhibitor of liver uptake transporters (OATP1B1, OATP1B3 and OCT1).

Co-administration with electrolyte and mineral replacement

Cysteamine can be administered with electrolyte (except bicarbonate) and mineral replacements necessary for management of Fanconi syndrome as well as vitamin D and thyroid hormone. Bicarbonate should be administered at least one hour before or one hour after PROCYSBI to avoid potential earlier release of cysteamine.

Indomethacin and cysteamine have been used simultaneously in some patients. In cases of patients with kidney transplants, anti-rejection treatments have been used with cysteamine.

Co-administration of the proton pump inhibitor omeprazole and PROCYSBI *in vivo* showed no effects on cysteamine bitartrate exposure.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be informed about the risk of teratogenicity and advised to use an adequate method of contraception during the course of treatment. A negative pregnancy test should be confirmed before starting treatment.

Pregnancy

There is no adequate data from the use of cysteamine in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenesis (see section 5.3). The potential risk for humans is unknown. The effect on pregnancy of untreated cystinosis is also unknown. Therefore, cysteamine bitartrate should not be used during pregnancy, particularly during the first trimester, unless clearly necessary (see section 4.4).

If a pregnancy is diagnosed or planned, the treatment should be carefully reconsidered.

Breast-feeding

Cysteamine excretion in human milk is unknown. However, due to the results of animal studies in breast-feeding females and neonates (see section 5.3), breast-feeding is contra-indicated in women taking PROCYSBI (see section 4.3).

Fertility

Effects on fertility have been seen in animal studies (see section 5.3). Azoospermia has been reported in male cystinosis patients.

## 4.7 Effects on ability to drive and use machines

Cysteamine has minor or moderate influence on the ability to drive and use machines.

Cysteamine may cause drowsiness. When starting therapy, patients should not engage in potentially hazardous activities until the effects of the medicinal product on each individual are known.

## 4.8 Undesirable effects

Summary of the safety profile

For the immediate-release formulation of cysteamine bitartrate, approximately 35% of patients can be expected to experience adverse reactions. These mainly involve the gastrointestinal and central nervous systems. When these reactions appear at the initiation of cysteamine therapy, temporary suspension and gradual reintroduction of treatment may be effective in improving tolerance.
In clinical studies with healthy volunteers, the most frequent adverse reactions were very common GI symptoms (16%) and occurred primarily as single episodes that were mild or moderate in severity. The adverse reactions profile for healthy subjects was similar to the adverse reactions profile in patients relative to GI disorders (diarrhoea and abdominal pain).

Tabulated list of adverse reactions

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

*Table 2: Adverse reactions*

| **MedDRA system organ class** | ***Frequency:* adverse reaction** |
|---|---|
| Blood and lymphatic system disorders | *Uncommon:* Leukopenia |
| Immune system disorders | *Uncommon:* Anaphylactic reaction |
| Metabolism and nutrition disorders | *Very common:* Anorexia |
| Psychiatric disorders | *Uncommon:* Nervousness, hallucination |
| Nervous system disorders | *Common:* Headache, encephalopathy |
| | *Uncommon:* Somnolence, convulsions |
| Gastrointestinal disorders | *Very common:* Vomiting, nausea, diarrhoea |
| | *Common:* Abdominal pain, breath odour, dyspepsia, gastroenteritis |
| | *Uncommon:* Gastrointestinal ulcer |
| Skin and subcutaneous tissue disorders | *Common:* Skin odour abnormal, rash |
| | *Uncommon:* Hair colour changes, skin striae, skin fragility (molluscoid pseudotumour on elbows) |
| Musculoskeletal and connective tissue disorders | *Uncommon:* Joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture, scoliosis. |
| Renal and urinary disorders | *Uncommon:* Nephrotic syndrome |
| General disorders and administration site conditions | *Very common:* Lethargy, pyrexia |
| | *Common:* Asthenia |
| Investigations | *Common:* Liver function tests abnormal |

Description of selected adverse reactions

*Clinical studies experience with PROCYSBI*
In clinical studies comparing PROCYSBI to the immediate-release cysteamine bitartrate, one third of the patients exhibited very common GI disorders (nausea, vomiting, abdominal pain). Common nervous system disorders (headache, somnolence and lethargy) and common general disorders (asthenia) were also seen.

*Post-marketing experience with immediate-release cysteamine bitartrate*
Benign intracranial hypertension (or pseudotumor cerebri (PTC)) with papilledema; skin lesions, molluscoid pseudotumors, skin striae, skin fragility; joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture and scoliosis have been reported with immediate-release cysteamine bitartrate (see section 4.4).

Two cases of nephrotic syndrome have been reported within 6 months of starting therapy with progressive recovery after treatment discontinuation. Histology showed a membranous glomerulonephritis of the renal allograft in one case and hypersensitivity interstitial nephritis in the other.

A few cases of Ehlers-Danlos-like syndrome on elbows have been reported in children chronically treated with high doses of different cysteamine preparations (cysteamine chlorhydrate or cystamine or cysteamine bitartrate) mostly above the maximal dose 1.95 g/m$^2$/day. In some cases, these skin lesions were associated with skin striae and bone lesions first seen during an X-ray examination. Bone disorders reported were genu valgum, leg pain and hyperextensive joints, osteopenia, compression fractures, and scoliosis. In the few cases where histopathological examination of the skin was performed, the results suggested angioendotheliomatosis. One patient subsequently died of acute cerebral ischemia with marked vasculopathy. In some patients, the skin lesions on elbows regressed after immediate-release cysteamine dose reduction (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

An overdose of cysteamine may cause progressive lethargy.

Should overdosing occur, the respiratory and cardiovascular systems should be supported appropriately. No specific antidote is known. It is not known if cysteamine is removed by haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism product, amino acids and derivatives, ATC code: A16AA04.

Cysteamine is the simplest stable aminothiol and a degradation product of the amino acid cysteine. Cysteamine 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.

Normal individuals and persons heterozygous for cystinosis have white blood cell cystine levels of < 0.2 and usually below 1 nmol hemicystine/mg protein, respectively, when measured using the mixed leukocyte assay. Individuals with cystinosis have elevations of WBC cystine above 2 nmol hemicystine/mg protein.

WBC cystine is monitored in these patients to determine adequacy of dosing, levels being measured 30 minutes after dosing when treated with PROCYSBI.

A pivotal phase 3 randomised, crossover PK and PD study (which was also the first ever randomised study with immediate-release cysteamine bitartrate) demonstrated that at steady-state, patients receiving PROCYSBI every 12 hours (Q12H) maintained a comparable depletion of WBC cystine levels compared to immediate-release cysteamine bitartrate every 6 hours (Q6H). Forty-three (43) patients were randomised; twenty-seven (27) children (ages 6 to 12 years old), fifteen (15) adolescents (ages 12 to 21 years old) and one (1) adult with cystinosis and with native kidney function based on an estimated glomerular filtration rate (GFR) (corrected for body surface area) > 30 mL/minute/1.73 $m^2$ were randomised. Of those forty-three (43) patients, two (2) siblings withdrew at the end of the first crossover period, due to a prior planned surgery in one (1) of them; forty-one (41) patients completed the protocol. Two (2) patients were excluded from the per-protocol analysis because their WBC cystine level increased over 2 nmol hemicystine/mg protein during the immediate-release cysteamine treatment period. Thirty-nine (39) patients were included in the final primary per protocol efficacy analysis.

*Table 3: Comparison of WBC cystine levels following administration of immediate-release cysteamine bitartrate and PROCYSBI*

| **Per –Protocol (PP) Population (N=39)** | | |
|---|---|---|
| | Immediate-release cysteamine bitartrate | PROCYSBI |
| WBC cystine level (LS Mean ± SE) in nmol hemicystine/mg protein* | 0.44 ± 0.05 | 0.51 ± 0.05 |
| Treatment effect (LS mean ± SE; 95.8% CI; p-value) | 0.08 ± 0.03; 0.01 to 0.15; <0.0001 | |
| **All Evaluable Patients (ITT) Population (N=41)** | | |
| | Immediate-release cysteamine bitartrate | PROCYSBI |
| WBC cystine level (LS Mean ± SE) in nmol hemicystine/mg protein* | 0.74 ± 0.14 | 0.53 ± 0.14 |
| Treatment effect (LS mean ± SE; 95.8% CI; p-value) | -0.21 ± 0.14; -0.48 to 0.06; <0.001 | |

*Measured using the mixed leukocyte assay

Forty of forty-one (40/41) patients who completed the pivotal phase 3 study were entered in a prospective study with PROCYSBI that stayed open as long as PROCYSBI could not be prescribed by their treating physician. In this study, the WBC cystine measured using the mixed leukocyte assay was always on average under optimal control at < 1 nmol hemicystine/mg protein. The estimated glomerular filtration rate (eGFR) did not change for the study population over time.

## 5.2 Pharmacokinetic properties

Absorption

The relative bioavailability is about 125% as compared to immediate-release cysteamine.

Food intake reduces the absorption of PROCYSBI at 30 minutes pre-dose (approximately 35% decrease in exposure) and at 30 min post-dose (approximately 16 or 45% decrease in exposure for intact and open capsules respectively). Food intake two hours after administration did not affect the absorption of PROCYSBI.

Distribution

The *in vitro* plasma protein binding of cysteamine, primarily to albumin, is approximately 54% and independent of plasma drug concentration over the therapeutic range.

Biotransformation

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.

*In vitro* data suggests that cysteamine bitartrate is likely to be metabolised 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.

Elimination

The terminal half-life of cysteamine bitartrate is approximately 4 hours.

Cysteamine bitartrate is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 *in vitro*.

*In vitro*: Cysteamine bitartrate is a substrate of P-gp and OCT2, but not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT1. Cysteamine bitartrate is not an inhibitor of OAT1, OAT3 and OCT2.

Special populations

The pharmacokinetics of cysteamine bitartrate has not been studied in special populations.

## 5.3 Preclinical safety data

In genotoxicity studies published for cysteamine, induction of chromosome aberrations in cultured eukaryotic cell lines has been reported. Specific studies with cysteamine did not show any mutagenic effects in the Ames test or any clastogenic effect in the mouse micronucleus test. A bacterial reverse mutation assay study ("Ames test") was performed with the cysteamine bitartrate used for PROCYSBI and cysteamine bitartrate did not show any mutagenic effects in this test.

Reproduction studies showed embryo-foetotoxic effects (resorptions and post-implantation losses) in rats at the 100 mg/kg/day dose level and in rabbits receiving cysteamine 50 mg/kg/day. Teratogenic effects have been described in rats when cysteamine is administered over the period of organogenesis at a dose of 100 mg/kg/day.

This is equivalent to 0.6 g/m$^2$/day in the rat, which is slightly less than the recommended clinical maintenance dose of cysteamine, i.e. 1.3 g/m$^2$/day. A reduction of fertility was observed in rats at 375 mg/kg/day, a dose at which body weight gain was retarded. At this dose, weight gain and survival of the offspring during lactation was also reduced. High doses of cysteamine impair the ability of lactating mothers to feed their pups. Single doses of the drug inhibit prolactin secretion in animals.

Administration of cysteamine in neonate rats induced cataracts.

High doses of cysteamine, either by oral or parenteral routes, produce duodenal ulcers in rats and mice but not in monkeys. Experimental administration of the drug causes depletion of somatostatin in several animal species. The consequence of this for the clinical use of the drug is unknown.

No carcinogenic studies have been conducted with cysteamine bitartrate gastro-resistant hard capsules.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

microcrystalline cellulose
methacrylic acid - ethyl acrylate copolymer (1:1)
hypromellose
talc
triethyl citrate
sodium lauryl sulphate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years
Unopened sachets may be stored for a single period of up to 4 months at temperatures below 25°C protected from light and moisture, after which the medicinal product must be discarded.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Keep the sachets in the outer carton in order to protect from light and moisture.

During the shelf-life, the medicinal product may be stored at room temperature (below 25°C) for a single period of 4 months (see section 6.3).

### 6.5 Nature and contents of container

Sachets consisting of multi-layer foil: polyethylene terephthalate, aluminium and low-density polyethylene (LDPE).

Pack size of 120 sachets.

### 6.6 Special precautions for disposal and other handling

Handling

Each sachet is for single use only.

*Sprinkling on food*
Sachets for either the morning or evening dose should be opened and the contents sprinkled onto approximately 100 grams of apple sauce or fruit jam. Gently stir the contents into the soft food, creating a mixture of cysteamine granules and food. The entire amount of the mixture should be eaten. This may be followed by 250 mL of an acceptable acidic liquid - fruit juice (e.g., orange juice or any acidic fruit juice) or water. The mixture must be eaten within 2 hours after preparation and may be refrigerated from the time of preparation to the time of administration.

*Administering through feeding tubes*
Sachets for either the morning or evening dose should be opened and the contents sprinkled onto approximately 100 grams of apple sauce or fruit jam. Gently stir the contents into the soft food, creating a mixture of cysteamine granules and the soft food. The mixture should then be administered via gastrostomy tube, nasogastric tube or gastrostomy-jejunostomy tube using a catheter tip syringe. Before PROCYSBI administration: Unclasp the G-tube button and attach the feeding tube. Flush with

5 mL of water to clear the button. Draw the mixture up into the syringe. A maximum 60 mL mixture volume in a catheter tip syringe is recommended for use with a straight or bolus feeding tube. Place the opening of the syringe containing the PROCYSBI/apple sauce/fruit jam mixture into the opening of the feeding tube and fill completely with the mixture: pressing gently on the syringe and keeping the feeding tube horizontal during administration can help to avoid clogging issues. Using a viscous food such as apple sauce or fruit jam at a rate of about 10 mL every 10 seconds until the syringe is completely empty is also suggested to avoid clogging. Repeat the above step until all of the mixture is given. After PROCYSBI administration, draw 10 mL of fruit juice or water up into another syringe and flush the G-tube ensuring that none of the applesauce/fruit jam and granules mixture gets stuck on the G-tube. The mixture must be administered within 2 hours after preparation and may be refrigerated from the time of preparation to the time of administration. Nothing of the mixture should be saved.

*Sprinkling in orange juice or any acidic fruit juice or water*
Sachets for either the morning or evening dose should be opened and the contents sprinkled into 100 to 150 mL of acidic fruit juice or water. Dose administration options are provided below:

- Option 1/Syringe: Mix gently for 5 minutes, then aspirate the mixture of cysteamine granules and acidic fruit juice or water into a dosing syringe.
- Option 2/Cup: Mix gently for 5 minutes in a cup or shake gently for 5 minutes in a covered cup (e.g., “sippy” cup). Drink the mixture of cysteamine granules and acidic fruit juice or water.

The mixture must be administered (drunk) within 30 minutes after preparation and may be refrigerated from the time of preparation to the time of administration.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/003
EU/1/13/861/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 September 2013
Date of latest renewal: 26 July 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Chiesi Farmaceutici S.p.A.
Via San Leonardo 96
43122 Parma
Italy

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 25 mg gastro-resistant hard capsules
cysteamine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 25 mg of cysteamine (as mercaptamine bitartrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant hard capsule

60 gastro-resistant hard capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

Discard 30 days after opening the foil seal.

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After opening do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PROCYSBI 25 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 25 mg gastro-resistant hard capsules
cysteamine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 25 mg of cysteamine (as mercaptamine bitartrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant hard capsule

60 gastro-resistant hard capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

Discard 30 days after opening the foil seal.
Open Date:
Discard Date:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After opening do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/13/861/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 75 mg gastro-resistant hard capsules
cysteamine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 75 mg of cysteamine (as mercaptamine bitartrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant hard capsule

250 gastro-resistant hard capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

Discard 30 days after opening the foil seal.

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After opening do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Via Palermo 26/A
43122 Parma
Italy

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PROCYSBI 75 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 75 mg gastro-resistant hard capsules
cysteamine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 75 mg of cysteamine (as mercaptamine bitartrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant hard capsule

250 gastro-resistant hard capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

Discard 30 days after opening the foil seal.
Open Date:
Discard Date:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After opening do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 75 mg gastro-resistant granules
cysteamine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 75 mg of cysteamine (as mercaptamine bitartrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant granules

120 sachets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Each sachet is for single use only.
Read the package leaflet before use.
Oral use.
Do not crush or chew.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the sachets in the outer carton in order to protect from light and moisture.
Unopened sachets may be stored for a single period of up to 4 months at temperatures below 25°C, after which the medicinal product must be discarded.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
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43122 Parma
Italy

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PROCYSBI 75 mg granules

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**SACHET**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

PROCYSBI 75 mg gastro-resistant granules
cysteamine

## 2. METHOD OF ADMINISTRATION

Oral use

Single use only.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENS BY WEIGHT, BY VOLUME OR BY UNIT

75 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 300 mg gastro-resistant granules
cysteamine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 300 mg of cysteamine (as mercaptamine bitartrate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gastro-resistant granules

120 sachets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Each sachet is for single use only.
Read the package leaflet before use.
Oral use.
Do not crush or chew.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the sachets in the outer carton in order to protect from light and moisture.
Unopened sachets may be stored for a single period of up to 4 months at temperatures below 25°C, after which the medicinal product must be discarded.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/861/004

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PROCYSBI 300 mg granules

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON THE SMALL PACKAGING**

**SACHET**

## 1. NAME OF THE MEDICINAL PRODUCT

PROCYSBI 300 mg gastro-resistant granules
cysteamine

## 2. METHOD OF ADMINISTRATION

Oral use

Single use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENS BY WEIGHT, BU VOLUME, OR BY UNIT

300 mg

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**PROCYSBI 25 mg gastro-resistant hard capsules**
**PROCYSBI 75 mg gastro-resistant hard capsules**

cysteamine (mercaptamine bitartrate)

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What PROCYSBI is and what it is used for

PROCYSBI contains the active substance cysteamine (also known as mercaptamine) and is taken for the treatment of nephropathic cystinosis in children and adults. Cystinosis is a disease affecting how the body functions, with an abnormal accumulation of the amino acid cystine in various organs of the body such as the kidney, eye, muscle, pancreas, and brain. Cystine build-up causes kidney damage and excretion of excess amounts of glucose, proteins, and electrolytes. Different organs are affected at different ages.

PROCYSBI is a medicine that reacts with cystine to decrease its level within the cells. Cysteamine therapy should be initiated promptly after confirmation of the diagnosis of cystinosis to achieve maximum benefit.

## 2. What you need to know before you take PROCYSBI

**Do not take PROCYSBI**
- If you are allergic to cysteamine (also known as mercaptamine) or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to penicillamine (this is not “penicillin”, but a medicine used for the treatment of Wilson’s disease).
- If you are breast-feeding.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking PROCYSBI.

- Since oral cysteamine doesn’t prevent deposits of cystine crystals in the eye, you should continue taking cysteamine eye drops as prescribed by your doctor.
- Whole cysteamine capsules should not be given to children under the age of 6 years due to the risk of choking (refer to section 3 “How to take PROCYSBI – Method of administration”).

- Serious skin lesions can occur in patients treated with high doses of cysteamine. Your doctor will routinely monitor your skin and bones and reduce or stop your treatment if needed (see section 4).
- Stomach and intestinal ulcers and bleeding can occur in patients receiving cysteamine (see section 4).
- Other intestinal symptoms including nausea, vomiting, anorexia and stomach ache can occur with cysteamine. Your doctor may interrupt and change your dose if these occur.
- Talk to your doctor if you have any unusual stomach symptoms or changes in stomach symptoms.
- Symptoms such as seizures, tiredness, sleepiness, depression, and brain disorders (encephalopathy) can occur with cysteamine. If such symptoms develop, tell your doctor who will adjust your dose.
- Abnormal liver function or reduced white blood cell count (leukopenia) can occur with use of cysteamine. Your doctor will routinely monitor your blood counts and liver function.
- Your doctor will monitor you for benign intracranial hypertension (or pseudotumor cerebri [PTC]) and/or swelling of the optic nerve (papilledema) associated with cysteamine treatment. You will receive regular eye examinations to identify this condition as early treatment can prevent vision loss.

**Other medicines and PROCYSBI**
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. If your doctor prescribes bicarbonate, do not take it at the same time as PROCYSBI; take bicarbonate at least one hour before or at least one hour after the medicine.

**PROCYSBI with food and drink**
For at least 1 hour before and 1 hour after taking PROCYSBI try to avoid meals, which are rich in fat or proteins as well as any food or liquid that could decrease the acidity in your stomach, like milk or yogurt. If this is not possible, you can eat a small amount (about 100 grams) of food (preferably carbohydrates e.g. bread, pasta, fruits) during the hour before and after taking PROCYSBI.
Take the capsule with an acidic drink (such as orange juice or any acidic juice) or water. For children and patients who have problems to swallow, please refer to section 3 “How to take PROCYSBI – Method of administration”.

**Pregnancy and breastfeeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use this medicine if you are pregnant, particularly during the first trimester. Before starting the treatment, you should have a pregnancy test with negative result, while during the course of treatment you should use an adequate method of contraception. If you are a woman planning a pregnancy or become pregnant, seek immediate advice from your doctor about stopping therapy with this medicine as continued treatment may be harmful to the unborn baby.

Do not use this medicine if you are breastfeeding (see section 2 under “Do not take PROCYSBI”).

**Driving and using machines**
This medicine may cause some drowsiness. When starting therapy, you should not drive, use machines, or engage in other dangerous activities until you know how the medicine affects you.

**PROCYSBI contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”

## 3. How to take PROCYSBI

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for you or your child will depend on your or your child's age and weight. The targeted maintenance dose is 1.3 g/m$^2$/day.

**Dosing schedule**
Take this medicine two times a day, every 12 hours. To get the most benefit from this medicine, try to avoid meals and dairy products for at least 1 hour before and 1 hour after PROCYSBI dosing. If this is not possible, you can eat a small amount (about 100 grams) of food (preferably carbohydrates e.g. bread, pasta, fruits) during the hour before and after PROCYSBI administration.

It is important to take PROCYSBI in a consistent way over time.

Do not increase or decrease the amount of medicine without your doctor's approval.

The total usual dose should not exceed 1.95 g/m$^2$/day.

**Duration of treatment**
Treatment with PROCYSBI should continue life-long, as instructed by your doctor.

**Method of administration**
You should take this medicine only by mouth.

In order for this medicine to work correctly, you must do the following:
- For patients who can swallow the whole capsule:
  Swallow the whole capsule with an acidic drink (such as orange juice or any acidic juice) or water. Do not crush or chew capsules or capsule contents. Children under 6 years of age may not be able to swallow gastro-resistant hard capsules and may choke them. You can give PROCYSBI to children under 6 years of age by opening the capsules and sprinkling the contents on food or liquid, as per the instructions given below.

  For patients who cannot swallow the whole capsule or who use a feeding tube:
  <u>Sprinkling on food</u>
  Open the gastro-resistant hard capsules and sprinkle the contents (granules) onto approximately 100 grams of food such as apple sauce or fruit jam.
  Gently stir the granules into the soft food, creating a mixture of granules and food. Eat the entire mixture. Then drink about 250 mL of an acidic drink (such as orange juice or any acidic juice) or water to ease the swallowing of the mixture.
  If you don't eat the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and eat it within 2 hours of preparation. Nothing of the mixture should be saved beyond 2 hours.

  <u>Administering through feeding tube</u>
  Open the gastro-resistant hard capsules and sprinkle the contents (granules) onto approximately 100 grams of apple sauce or fruit jam. Gently stir the granules into the soft food, creating a mixture of granules and the soft food. Administer the mixture by gastrostomy tube, nasogastric tube or gastrostomy jejunostomy tube using a catheter tip syringe. Before PROCYSBI administration: Unclasp the G-tube button and attach the feeding tube. Flush with 5 mL of water to clear the button. Draw the mixture up into the syringe. A maximum 60 mL mixture volume in a catheter tip syringe is recommended for use with a straight or bolus feeding tube. Place the opening of the syringe containing the PROCYSBI and food mixture into the opening of the feeding tube and fill completely with the mixture: pressing gently on the syringe and keeping the feeding tube horizontal during administration can help to avoid clogging issues. Using a viscous food such as apple sauce or fruit jam at a rate of about 10 mL every 10 seconds until the

syringe is completely empty is suggested to avoid clogging. Repeat the above step until all of the mixture is given. After PROCYSBI administration, draw 10 mL of fruit juice or water up into another syringe and flush the G-tube ensuring that none of the PROCYSBI and food mixture gets stuck in the G-tube.
If you don't consume the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and consume it within 2 hours of preparation. Nothing of the mixture should be saved beyond 2 hours.
Consult your child's doctor for complete instructions on how to properly administer the product through feeding tubes and if you experience clogging issues.

Sprinkling in orange juice or any acidic fruit juice or water
Open the gastro-resistant hard capsules and sprinkle the contents (granules) into about 100 to 150 mL of acidic fruit juice (such as orange juice or any acidic juice) or water. Mix the PROCYSBI drink mixture gently for 5 minutes, either mixing in a cup or shaking in a covered cup (e.g., "sippy" cup) and drink the mixture.
If you don't drink the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and drink it within 30 minutes after preparation. Nothing of the mixture should be saved beyond 30 minutes.

Administering a drink mixture by oral syringe
Aspirate the drink mixture into a dosing syringe and administer it into the mouth directly.
If you don't consume the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and consume it within 30 minutes after preparation. Nothing of the mixture should be saved beyond 30 minutes.

Your doctor may recommend or prescribe to include, in addition to cysteamine, one or more supplements to replace important electrolytes lost through the kidneys. It is important to take these supplements exactly as instructed. If several doses of the supplements are missed or weakness or drowsiness develops, call your doctor for instructions.

Regular blood tests to measure the amount of cystine inside white blood cells and/or the concentration of cysteamine in the blood are necessary to help determine the correct dose of PROCYSBI. You or your doctor will arrange for these blood tests to be performed. These tests must be obtained 12.5 hours after the evening dose the day before, and therefore 30 minutes after the following morning dose is given. Regular blood and urine tests to measure the levels of the body's important electrolytes are also necessary to help you or your doctor correctly adjust the doses of these supplements.

**If you take more PROCYSBI than you should**
You should contact your doctor or the hospital emergency department immediately if you have taken more PROCYSBI than you should. You may become drowsy.

**If you forget to take PROCYSBI**
If you missed a dose of medicine, you should take it as soon as possible. However, if it is within 4 hours of the next dose, skip the missed dose and go back to the regular dosing schedule.

Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor or nurse straight away if you notice any of the following side effects – you may need urgent medical treatment:**

- Severe allergic reaction (seen uncommonly): Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing; swelling of face, lips, tongue, or throat.

If any of the following side effects occur, please contact your doctor immediately. Since some of these side effects are serious, ask your doctor to explain their warning signs.

**Common side effects** (may affect up to 1 in 10 people):

- Skin rash: Tell the doctor right away if you get a skin rash. PROCYSBI may need to be temporarily stopped until the rash goes away. If the rash is severe, your doctor may discontinue cysteamine treatment.
- Abnormal liver function on blood tests. Your doctor will monitor you for this.

**Uncommon side effects** (may affect up to 1 in 100 people):

- Skin lesions, bone lesions, and joint problems: Treatment with high doses of cysteamine can cause skin lesions to develop. These include skin striae (which are like stretch marks), bone injuries (such as fractures), bone deformities, and joint problems. Examine your skin while taking this medicine. Report any changes to your doctor. Your doctor will monitor you for these problems.
- Low white blood cell count. Your doctor will monitor you for this.
- Central nervous system symptoms: Some patients taking cysteamine have developed seizures, depression, and become too sleepy (excessive sleepiness). Tell your doctor if you have these symptoms.
- Stomach and intestinal (gastrointestinal) problems: Patients taking cysteamine have developed ulcers and bleeding. Tell your doctor right away if you get stomach ache, or throw up blood.
- Benign intracranial hypertension, also called pseudotumor cerebri, has been reported with cysteamine use. This is a condition where there is high pressure in the fluid around the brain. Tell your doctor right away if you develop any of the following symptoms while taking PROCYSBI: buzzing or ”whooshing“ sound in the ear, dizziness, double vision, blurry vision, loss of vision, pain behind the eye or pain with eye movement. Your doctor will monitor you with eye examinations to find and treat this problem early. This will help lessen the chance of loss of eyesight.

The other side effects listed below are given with an estimation of the frequency with which they may occur with PROCYSBI.

**Very common side effects** (may affect more than 1 in 10 people):

- nausea
- vomiting
- loss of appetite
- diarrhoea
- fever
- sensation of sleep

**Common side effects**:

- headache
- encephalopathy
- abdominal pain
- dyspepsia
- unpleasant breath and body odour
- heartburn
- tiredness

**Uncommon side effects**:
- leg pain
- scoliosis (deviation of the vertebral column)
- bone fragility
- hair discolouration
- fits
- nervousness
- hallucination
- effect on the kidney manifested by swelling of the extremities and weight gain

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store PROCYSBI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.

Do not take this medicine if the foil seal has been open for more than 30 days. Discard the open bottle and use a new bottle.

Store in a refrigerator (2°C-8°C). Do not freeze.
After opening do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away the medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What PROCYSBI contains**
- The active substance is cysteamine (as mercaptamine bitartrate).
  PROCYSBI 25 mg gastro resistant hard capsules
  Each gastro-resistant hard capsule contains 25 mg of cysteamine.

  PROCYSBI 75 mg gastro resistant hard capsules
  Each gastro resistant hard capsule contains 75 mg of cysteamine.

- The other ingredients are:
  - In the capsules: microcrystalline cellulose, methacrylic acid - ethyl acrylate copolymer (1:1), hypromellose, talc, triethyl citrate, sodium lauryl sulfate (see section "PROCYSBI contains sodium").
  - In the capsule shell: gelatin, titanium dioxide (E171), indigo carmine (E132).
  - In the printing ink: shellac, povidone (K-17), titanium dioxide (E171).

**What PROCYSBI looks like and contents of the pack**
- PROCYSBI 25 mg is presented as blue gastro-resistant hard capsules (of size 15.9 x 5.8 mm). The light blue cap is imprinted with "PRO" in white ink and the light blue body is imprinted with "25 mg" in white ink. A white plastic bottle contains 60 capsules. The cap is child resistant

and has a foil seal. Each bottle contains two plastic cylinders used for additional moisture and air protection

– PROCYSBI 75 mg is presented as blue gastro-resistant hard capsules (of size 21.7 x 7.6 mm). The dark blue cap is imprinted with “PRO” in white ink and the light blue body is imprinted with “75 mg” in white ink. A white plastic bottle contains 250 capsules. The cap is child resistant and has a foil seal. Each bottle contains three plastic cylinders used for additional moisture and air protection.

– Please keep the cylinders in each bottle during the use of the bottle. The cylinders may be discarded with the bottle after use.

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**Manufacturer**
Chiesi Farmaceutici S.p.A.
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**This leaflet was last revised in**

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

**Package leaflet: Information for the user**

**PROCYSBI 75 mg gastro-resistant granules**
**PROCYSBI 300 mg gastro-resistant granules**

cysteamine (mercaptamine bitartrate)

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What PROCYSBI is and what it is used for

PROCYSBI contains the active substance cysteamine (also known as mercaptamine) and is taken for the treatment of nephropathic cystinosis in children and adults. Cystinosis is a disease affecting how the body functions, with an abnormal accumulation of the amino acid cystine in various organs of the body such as the kidney, eye, muscle, pancreas, and brain. Cystine build-up causes kidney damage and excretion of excess amounts of glucose, proteins, and electrolytes. Different organs are affected at different ages.

PROCYSBI is a medicine that reacts with cystine to decrease its level within the cells. Cysteamine therapy should be initiated promptly after confirmation of the diagnosis of cystinosis to achieve maximum benefit.

## 2. What you need to know before you take PROCYSBI

**Do not take PROCYSBI**
- If you are allergic to cysteamine (also known as mercaptamine) or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to penicillamine (this is not “penicillin”, but a medicine used for the treatment of Wilson’s disease).
- If you are breast-feeding.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking PROCYSBI.

- Since oral cysteamine doesn’t prevent deposits of cystine crystals in the eye, you should continue taking cysteamine eye drops as prescribed by your doctor.
- Serious skin lesions can occur in patients treated with high doses of cysteamine. Your doctor will routinely monitor your skin and bones and reduce or stop your treatment if needed (see section 4).

- Stomach and intestinal ulcers and bleeding can occur in patients receiving cysteamine (see section 4).
- Other intestinal symptoms including nausea, vomiting, anorexia and stomach ache can occur with cysteamine. Your doctor may interrupt and change your dose if these occur.
- Talk to your doctor if you have any unusual stomach symptoms or changes in stomach symptoms.
- Symptoms such as seizures, tiredness, sleepiness, depression, and brain disorders (encephalopathy) can occur with cysteamine. If such symptoms develop, tell your doctor who will adjust your dose.
- Abnormal liver function or reduced white blood cell count (leukopenia) can occur with use of cysteamine. Your doctor will routinely monitor your blood counts and liver function.
- Your doctor will monitor you for benign intracranial hypertension (or pseudotumor cerebri [PTC]) and/or swelling of the optic nerve (papilledema) associated with cysteamine treatment. You will receive regular eye examinations to identify this condition as early treatment can prevent vision loss.

**Other medicines and PROCYSBI**
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. If your doctor prescribes bicarbonate, do not take it at the same time as PROCYSBI; take bicarbonate at least one hour before or at least one hour after the medicine.

**PROCYSBI with food and drink**
For at least 1 hour before and 1 hour after taking PROCYSBI try to avoid meals, which are rich in fat or proteins as well as any food or liquid that could decrease the acidity in your stomach, like milk or yogurt. If this is not possible, you can eat a small amount (about 100 grams) of food (preferably carbohydrates e.g. bread, pasta, fruits) during the hour before and after taking PROCYSBI.
See also section 3 “How to take PROCYSBI - Method of Administration”.

**Pregnancy and breastfeeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use this medicine if you are pregnant, particularly during the first trimester. Before starting the treatment, you should have a pregnancy test with negative result, while during the course of treatment you should use an adequate method of contraception. If you are a woman planning a pregnancy or become pregnant, seek immediate advice from your doctor about stopping therapy with this medicine as continued treatment may be harmful to the unborn baby.

Do not use this medicine if you are breastfeeding (see section 2 under “Do not take PROCYSBI”).

**Driving and using machines**
This medicine may cause some drowsiness. When starting therapy, you should not drive, use machines, or engage in other dangerous activities until you know how the medicine affects you.

**PROCYSBI contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free.”

## 3. How to take PROCYSBI

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for you or your child will depend on your or your child’s age and weight. The targeted maintenance dose is 1.3 g/m$^2$/day.

**Dosing schedule**
Take this medicine two times a day, every 12 hours. To get the most benefit from this medicine, try to avoid meals and dairy products for at least 1 hour before and 1 hour after PROCYSBI dosing. If this is not possible, you can eat a small amount (about 100 grams) of food (preferably carbohydrates e.g. bread, pasta, fruits) during the hour before and after PROCYSBI administration.

It is important to take PROCYSBI in a consistent way over time.

Do not increase or decrease the amount of medicine without your doctor's approval.

The total usual dose should not exceed 1.95 g/$m^2$/day.

**Duration of treatment**
Treatment with PROCYSBI should continue life-long, as instructed by your doctor.

**Method of administration**
You should take this medicine only by mouth.

Each sachet has to be used only once.

In order for this medicine to work correctly, you must do the following:

Open the sachet and sprinkle all granules on food (such as apple sauce or fruit jam) and eat or administer through feeding tubes, or mixed with an acidic drink (such as orange juice or any acidic juice) or water and drink. Do not crush or chew granules.

Sprinkling on food
Open the sachet and sprinkle all granules onto approximately 100 grams of food such as apple sauce or fruit jam. Gently stir the granules into the soft food, creating a mixture of granules and food. Eat the entire mixture. Then drink about 250 mL of an acidic drink (such as orange juice or any acidic fruit juice) or water to ease the swallowing of the mixture.
If you don't eat the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and eat it within 2 hours of preparation. Nothing of the mixture should be saved beyond 2 hours.

Administering through feeding tube
Open the sachet and sprinkle the granules onto approximately 100 grams of apple sauce or fruit jam. Gently stir the granules into the soft food, creating a mixture of granules and the soft food. Administer the mixture by gastrostomy tube, nasogastric tube or gastrostomy jejunostomy tube using a catheter tip syringe. Before PROCYSBI administration: Unclasp the G-tube button and attach the feeding tube. Flush with 5 mL of water to clear the button. Draw the mixture up into the syringe. A maximum 60 mL mixture volume in a catheter tip syringe is recommended for use with a straight or bolus feeding tube. Place the opening of the syringe containing the PROCYSBI and food mixture into the opening of the feeding tube and fill completely with the mixture: pressing gently on the syringe and keeping the feeding tube horizontal during administration can help to avoid clogging issues. Using a viscous food such as apple sauce or fruit jam at a rate of about 10 mL every 10 seconds until the syringe is completely empty is suggested to avoid clogging. Repeat the above step until all of the mixture is given. After PROCYSBI administration, draw 10 mL of fruit juice or water up into another syringe and flush the G-tube ensuring that none of the PROCYSBI and food mixture gets stuck in the G-tube.
If you don't consume the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and consume it within 2 hours of preparation. Nothing of the mixture should be saved beyond 2 hours.
Consult your child's doctor for complete instructions on how to properly administer the product through feeding tubes and if you experience clogging issues.

Sprinkling in orange juice or any acidic fruit juice or water
Open the sachet and sprinkle the granules into about 100 to 150 mL of acidic fruit juice (such as orange juice or any acidic juice) or water. Mix the PROCYSBI drink mixture gently for 5 minutes, either mixing in a cup or shaking in a covered cup (e.g., "sippy" cup) and drink the mixture.
If you don't drink the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and drink it within 30 minutes after preparation. Nothing of the mixture should be saved beyond 30 minutes.

Administering a drink mixture by oral syringe
Aspirate the drink mixture into a dosing syringe and administer it into the mouth directly.
If you don't consume the mixture immediately, you may refrigerate (2°C-8°C) it from the time of preparation to the time of administration and consume it within 30 minutes after preparation. Nothing of the mixture should be saved beyond 30 minutes.

Your doctor may recommend or prescribe to include, in addition to cysteamine, one or more supplements to replace important electrolytes lost through the kidneys. It is important to take these supplements exactly as instructed. If several doses of the supplements are missed or weakness or drowsiness develops, call your doctor for instructions.

Regular blood tests to measure the amount of cystine inside white blood cells and/or the concentration of cysteamine in the blood are necessary to help determine the correct dose of PROCYSBI. You or your doctor will arrange for these blood tests to be performed. These tests must be obtained 12.5 hours after the evening dose the day before, and therefore 30 minutes after the following morning dose is given. Regular blood and urine tests to measure the levels of the body's important electrolytes are also necessary to help you or your doctor correctly adjust the doses of these supplements.

**If you take more PROCYSBI than you should**
You should contact your doctor or the hospital emergency department immediately if you have taken more PROCYSBI than you should. You may become drowsy.

**If you forget to take PROCYSBI**
If you missed a dose of medicine, you should take it as soon as possible. However, if it is within 4 hours of the next dose, skip the missed dose and go back to the regular dosing schedule.

Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor or nurse straight away if you notice any of the following side effects – you may need urgent medical treatment:**
– Severe allergic reaction (seen uncommonly): Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing; swelling of face, lips, tongue, or throat.

If any of the following side effects occur, please contact your doctor immediately. Since some of these side effects are serious, ask your doctor to explain their warning signs.

**Common side effects** (may affect up to 1 in 10 people):
– Skin rash: Tell the doctor right away if you get a skin rash. PROCYSBI may need to be temporarily stopped until the rash goes away. If the rash is severe, your doctor may discontinue cysteamine treatment.

– Abnormal liver function on blood tests. Your doctor will monitor you for this.

**Uncommon side effects** (may affect up to 1 in 100 people):
– Skin lesions, bone lesions, and joint problems: Treatment with high doses of cysteamine can cause skin lesions to develop. These include skin striae (which are like stretch marks), bone injuries (such as fractures), bone deformities, and joint problems. Examine your skin while taking this medicine. Report any changes to your doctor. Your doctor will monitor you for these problems.
– Low white blood cell count. Your doctor will monitor you for this.
– Central nervous system symptoms: Some patients taking cysteamine have developed seizures, depression, and become too sleepy (excessive sleepiness). Tell your doctor if you have these symptoms.
– Stomach and intestinal (gastrointestinal) problems: Patients taking cysteamine have developed ulcers and bleeding. Tell your doctor right away if you get stomach ache, or throw up blood.
– Benign intracranial hypertension, also called pseudotumor cerebri, has been reported with cysteamine use. This is a condition where there is high pressure in the fluid around the brain. Tell your doctor right away if you develop any of the following symptoms while taking PROCYSBI: buzzing or ”whooshing“ sound in the ear, dizziness, double vision, blurry vision, loss of vision, pain behind the eye or pain with eye movement. Your doctor will monitor you with eye examinations to find and treat this problem early. This will help lessen the chance of loss of eyesight.

The other side effects listed below are given with an estimation of the frequency with which they may occur with PROCYSBI.

**Very common side effects** (may affect more than 1 in 10 people):
– nausea
– vomiting
– loss of appetite
– diarrhoea
– fever
– sensation of sleep

**Common side effects**:
– headache
– encephalopathy
– abdominal pain
– dyspepsia
– unpleasant breath and body odour
– heartburn
– tiredness

**Uncommon side effects**:
– leg pain
– scoliosis (deviation of the vertebral column)
– bone fragility
– hair discolouration
– fits
– nervousness
– hallucination
– effect on the kidney manifested by swelling of the extremities and weight gain

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store PROCYSBI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and the sachet after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.
Keep the sachets in the outer carton in order to protect from light and moisture.
Unopened sachets may be stored for a single period of up to 4 months outside the refrigerator at temperatures below 25°C. Thereafter, the medicine must be discarded.
Each sachet is for single use only.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away the medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What PROCYSBI contains**

– The active substance is cysteamine (as mercaptamine bitartrate).
  PROCYSBI 75 mg gastro resistant granules
  Each sachet of gastro-resistant granules contains 75 mg of cysteamine.

  PROCYSBI 300 mg gastro resistant granules
  Each sachet of gastro resistant granules contains 300 mg of cysteamine.

– The other ingredients are: microcrystalline cellulose, methacrylic acid - ethyl acrylate copolymer (1:1), hypromellose, talc, triethyl citrate, sodium lauryl sulfate (see section "PROCYSBI contains sodium").

**What PROCYSBI looks like and contents of the pack**

– PROCYSBI 75 mg is presented as white to off-white gastro-resistant granules in sachets. Each pack contains 120 sachets.

– PROCYSBI 300 mg is presented as white to off-white gastro-resistant granules in sachets. Each pack contains 120 sachets.

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Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.