

Risk Management Plan for PROCYSBI gastro-resistant hard capsules (25 and 75 mg), cysteamine bitartrate (as mercaptamine bitartrate)

RMP version to be assessed as part of this application:

RMP Version number: 8.0

Data lock point for this RMP: 28 February 2021

Date of final sign off: 31 August 2022

Rationale for submitting an updated RMP:

- Changes related to the new EU RMP format and guidelines
- Addition of a new formulation and strength: 75 mg and 300 mg gastro-resistant granules
- Changes related to requests from PRAC following Day 94 AR:
 - Reinstatement of Leukopenia as important identified risk
 - Removal of educational materials for Procysbi related to all potential risks
 - Update of Part III “Pharmacovigilance activities” and Part VI “Summary of activities in the risk management plan by medicinal product” in line with the above changes.
- Changes related to request from Rapporteurs second day 180 joint CHMP and PRAC AR:
 - Removal of Encephalopathy and Ehlers- Danlos-like syndrome from the summary of safety concerns. Other parts of the RMP are updated accordingly.

Summary of significant changes in this RMP:

- Removal of the following from the safety concerns:
 - Important identified risk: GI Symptoms (nausea, vomiting, diarrhoea, abdominal pain)
 - Missing information: Patients with heart disease, Patients with inflammatory bowel disease or resection of the small intestine, and In vivo studies lacking to confirm whether cysteamine bitartrate is an inducer of CYP1A2, CYP3A4, CYP2B6, and to characterize this effect if confirmed
- All PROCYSBI clinical studies are completed (RP103-04, RP103-16001, RP103-07, RP103-MITO-001, RP103-MITO-002)



- Other changes are related to the new EU RMP format and the addition of a new formulation and strength: 75 mg and 300 mg gastro-resistant granules
- Changes related to requests from PRAC following Day 94 AR:
 - Reinstatement of Leukopenia as important identified risk
 - Removal of educational materials for Procysbi related to all potential risks
 - Update of Part III “Pharmacovigilance activities” and Part VI “Summary of activities in the risk management plan by medicinal product” in line with the above changes.
- Changes related to request from joint CHMP and PRAC following second day 180 AR:
 - Removal of Encephalopathy and Ehlers- Danlos-like syndrome from the summary of safety concerns of this RMP.

Removal of follow-up forms for Encephalopathy and Ehlers- Danlos-like syndrome

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Cysteamine (INN: mercaptamine bitartrate)

Version number: 7.1

Approved with procedure: Centralized procedure

Date of approval (opinion date): 13 April 2018

QPPV name: Gian Nicola Castiglione

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List of Abbreviations

Abbreviation	Full form
ADR	Adverse drug reactions
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CHMP	The Committee for Medicinal Products for Human Use
CMS	Concerned Member State
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDS	Ehlers-Danlos-like Syndrome
EEA	European Economic Area
ERA-EDTA	European Renal Association - European Dialysis and Transplant Association
GFR	Glomerular filtration rate
GI	Gastrointestinal
HIV	Human immunodeficiency virus
ICSR	Individual Case Safety Reports
MedDRA	Medical Dictionary for Regulatory Activities
MAA	Mathematical Association of America
MAH	Marketing Authorisation Holder
NC	Nephropathic cystinosis
NOAEL	No observable adverse effect level
NOEL	No observed effect level
PAS	Prior Approval Supplement
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
Q12H	Every 12 hours (quaque 12 hora)
QC	Quality check
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SMQ	Standard MedDRA Query
WBC	White blood cell

Part I: Product(s) Overview

Table Part I.1 - Product Overview

Active substance (INN or common name)	Cysteamine bitartrate (also called mercaptamine bitartrate)
Pharmacotherapeutic group (ATC Code)	A16AA04
Marketing Authorisation Holder	Chiesi Farmaceutici S.p.A (Europe)
Medicinal products to which this RMP refers	PROCYSBI 25 mg gastro-resistant hard capsules PROCYSBI 75 mg gastro-resistant hard capsules PROCYSBI 75 mg gastro-resistant granules PROCYSBI 300 mg gastro-resistant granules
Invented name(s) in the European Economic Area (EEA)	PROCYSBI
Marketing authorisation procedure	Centralised procedure (Hybrid)
Brief description of the product	Chemical class: PROCYSBI (cysteamine bitartrate (also called mercaptamine bitartrate) is a cystine-depleting agent, which lowers the cystine content of cells in patients with cystinosis, an inherited defect of lysosomal transport. Summary of mode of action: Cysteamine reacts with cystine to form the mixed disulfide of cysteamine and cysteine. The mixed disulfide is then exported from the lysosomes by other intact, disulfide transporters. The decrease in the white blood cell (WBC) cystine levels is correlated to the cysteamine plasma concentration over the twelve hours following the administration of cysteamine (as mercaptamine bitartrate) gastro-resistant capsules. Cysteamine reduces cystine accumulation in cells of cystinosis patients and, when treatment is started early, it delays the development of renal failure. Important information about composition: Not applicable
Hyperlink to the Product Information	Not applicable
Indication(s) in the EEA	Current: PROCYSBI is indicated for the treatment of nephropathic cystinosis. Proposed (if applicable): Not applicable
Dosage in the EEA	Current: The assay-dependent therapeutic goal is to maintain a white blood cell (WBC) cystine level < 1 nmol hemicystine/mg protein, 30 min after

	dosing, by adjusting the dose. For patients who are 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. The maximum dosage is 1.95 grams/m² of body surface area per day. 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. The PROCYSBI dosing regimen is different for cysteamine-naïve patients and patients switching from immediate-release cysteamine. Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: Gastro resistant hard capsules, 25 mg and 75 mg cysteamine (as cysteamine bitartrate).
	Proposed (if applicable): Gastro resistant granules, 75 mg and 300 mg cysteamine (as cysteamine bitartrate).
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specificationPart II: Module SI - Epidemiology of the indication(s) and target population

Indication: Nephropathic cystinosis.

Incidence and prevalence:

Worldwide incidence has been estimated between 1 in 100,000 and 1 in 200,000 live births (Gahl and Renlund, 1989, Nesterova and Gahl, 2013, Gahl et al., 2002, McGowan-Jordan et al., 1999) with a higher rate in the Brittany region of France (Bois et al., 1976) and in northeastern Quebec (Braekeleer, 1991). The disease has been found worldwide in all ethnic groups with approximate prevalence of 2,000 cases.

The literature sources suggest that the prevalence of cystinosis in the EEA is well below 5 in 10,000 persons. Based on a merging of data from available studies and registry sources, the Marketing Authorisation Holder (MAH) conservatively estimates the prevalence to be 0.11 per 10,000 or 5,448 persons within the EEA.

In Canada, all available literature sources suggest that the prevalence of cystinosis in Canada is well below 1 in 10,000 persons, the incidence is higher in Newfoundland affecting 6 in 100,000 (www.cystinosis.ca), in some parts of French Canada the incidence of nephropathic cystinosis is estimated to be as high as 1 in 6,000 births (McGowan-Jordan et al., 1999). Based on a merging of data from available studies and registry sources, the MAH conservatively estimates the prevalence to be 0.2 per 100,000 within Canada.

In the USA, an estimated prevalence of nephropathic cystinosis is 500 cases with 15 new cases each year (www.cystinosisresearch.org).

Demographics of the population in the authorised indication:

Cystinosis is an autosomal recessive disorder characterised by an accumulation of intra-lysosomal cystine due to a defect in cystine transport (Gahl et al., 1982). Two clinical forms of cystinosis have been delineated based on severity of symptoms and age of onset (Antignac, 2005): infantile and juvenile forms. These forms are summarised below:

Infantile cystinosis

The manifestations of infantile cystinosis begin at 6 to 8 months of age as cystine deposits accumulate in many organs including the kidneys, resulting in renal Fanconi syndrome. If untreated, kidney failure can occur before the age of 10 years. Other clinical signs, including corneal crystal accumulation, retinal blindness, hypothyroidism, diabetes mellitus, swallowing difficulties and neurological deterioration appear because of cystine accumulation in various organs (Kalatzis et al., 2001).

Juvenile cystinosis

Juvenile cystinosis manifests as glomerular damage at around 10 to 12 years of age, and slowly progresses to glomerular insufficiency, photophobia, and late development of pigmentary retinopathy (Kalatzis et al., 2001). Late-onset (intermediate) cystinosis appears to be due to the inheritance of a mutation known to cause infantile disease in one allele and a relatively less clinically severe mutation in the other, or due to the inheritance of a relatively less severe mutation in both alleles.

Manz and colleagues reviewed a registry of 102 cystinosis patients and found that 94% had the infantile type and 5% had the juvenile type (Manz and Gretz, 1985). This approximate incidence was later confirmed in a separate series by Cochat (Cochat et al., 1999).

Hutchesson and colleagues compared the frequencies of various inborn errors of metabolism among different ethnic groups in the West Midlands, UK (Hutchesson et al., 1998). The authors performed a retrospective study of all children born in the West Midlands National Health Service district of the UK

during the decade immediately preceding the 1991 National Census. There were 21 patients with cystinosis diagnosed in this timeframe, and the authors state the disease frequency as 1 per 46,564 (0.21 per 10,000) for those of Northwestern European descent, and 1 per 3,613 (2.77 per 10,000) for those of Pakistani descent. The higher disease frequency for those of Pakistani descent was consistent with other inborn errors of metabolism, and the authors suggest that intermarriage may play a role in this phenomenon.

The main existing treatment options:

Cystinosis is normally treated with cysteamine. Patients with cystinosis are also often given sodium citrate to treat the blood acidosis, as well as potassium and phosphorus supplements. Patients with nephropathic cystinosis often end up on renal replacement therapy or receive a renal transplant.

Since the availability of cysteamine therapy in Europe in 1997 (Van't Hoff, 2005), it is believed that the progression to end-stage renal failure may be slowed, and some patients may maintain intact kidney function. Haffner and colleagues attempted to understand the long term outcome in paediatric patients with hereditary tubular disorders (Haffner et al., 1999). Among the 177 patients they assessed, 34 had cystinosis and 5 received oral cysteamine. Cystinosis patients had the highest absolute and relative numbers of patients with chronic renal failure and end-stage renal disease. The impact of cysteamine therapy was apparent, as 3 patients who received cysteamine therapy from early childhood did not require transplant and kept a GFR > 60 ml/mn/1.73 m² for longer than 5 and up to 9 years after diagnosis.

Natural history of the indicated condition in the population, including mortality and morbidity:

Cystinosis is a rare disease characterised by the accumulation of cystine and formation of crystals damaging various organs, especially the kidney, leading to Fanconi syndrome and progressive glomerular failure, with end-stage renal failure by the end of the first decade of life. In four studies of cystinosis patients before cysteamine was available, renal death (need for transplant or dialysis) occurred at median age of less than 10 years (Seegmiller et al., 1968, Mahoney et al., 1970, Schneider and Schulman, 1977, Gahl et al., 1986). The outcome of this disease is ultimately fatal without renal replacement therapy or renal transplant.

Important co-morbidities:

In addition to underlying impaired renal function, patients with nephropathic cystinosis experience growth failure, rickets, genu valgum, and photophobia due to cystine deposits in the cornea. With time, most organs are damaged, including the retina, muscles and central nervous system.

Encephalopathy was first described by Levine in 1982 and since then many studies reported symptoms of encephalopathy in patients with cystinosis and confirmed this first observation (Levine and Paparo, 1982, Müller et al., 2008). From their 26-patient study Broyer estimated that 50% of all untreated patients with cystinosis have signs of encephalopathy (Broyer et al., 1996).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- Single-dose toxicity

Single administration of cysteamine to rats indicated GI effects (see section Safety Pharmacology). No other effect was observed in this study.

Relevance to human usage: The gastro-resistant formulation of cysteamine may mitigate the GI effects (gastric and duodenal ulcers) seen with immediate-release cysteamine. GI symptoms are described in the reference safety information (RSI) (Summary of Product Characteristics (SmPC) in EU.

- Repeat-dose toxicity

Subacute toxicity with cysteamine was studied in a four-week oral study in 2 monkeys (150 mg/kg/day) and in a 13-week feeding study in rabbits (100 mg/kg/day). Chronic toxicity was only studied in 5 monkeys given 20-150 mg/kg/day orally for one year. No effect was observed in these studies.

Repeated cysteamine administration to rats indicated GI effects (see below). No other effect was observed in this study.

Relevance to human usage: The gastro-resistant formulation of cysteamine may mitigate the GI effects (gastric and duodenal ulcers) seen with immediate-release cysteamine. GI symptoms are described in RSI.

- Reproductive/developmental toxicity

Reproduction studies showed embryofoetotoxic 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/m²/day in the rat, which is less than the recommended clinical maintenance dose of cysteamine, i.e. 1.3 g/m²/day. A reduction in 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.

Relevance to human usage: The use of PROCYSBI is contraindicated in Europe and not recommended in Canada during breast feeding and if a pregnancy is diagnosed or planned, patients should be advised of the possible teratogenic risk of cysteamine as described in RSI. Teratogenicity was characterized as important potential risk and it is included in a list of safety concerns.

- Genotoxicity

Genotoxicity studies have been published using cysteamine, suggesting induction of chromosome aberrations in cultured eukaryotic cell lines. 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 RP103 (PROCYSBI IMP) and cysteamine bitartrate did not show any mutagenic effects in this test. Similarly, a bacterial reverse mutation test performed with RP103 drug product was also negative.

Relevance to human usage: Non-clinical data does not suggest any negative safety concern for humans regarding genotoxicity.

- Carcinogenicity

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

Relevance to human usage: Not applicable.

Safety pharmacology

- Effects on gastrointestinal (GI) tract

The GI tract is indicated as the target organ of toxicity for cysteamine in acute toxicity studies however this does not seem to have been observed in oral subacute and chronic studies in rabbits and monkeys.

Single and repeated administration to rats indicated that gastric and duodenal ulcers can be produced at high doses of 200 mg/kg and above by subcutaneous injection. Studies in rats with cysteamine confirmed a potential for duodenal and gastric ulcerogenic effects.

GI effects have been observed in rats with high doses of Eudragit (methacrylic acid ethyl acrylate copolymer, which is one of the excipients used in the enteric coating of PROCYSBI).

Relevance to human usage: The gastro-resistant formulation of cysteamine may mitigate the GI effects (gastric and duodenal ulcers) seen with immediate-release cysteamine. The dose for newly-diagnosed patients is gradually increased from 1/6 to 1/4 of the recommended maintenance dose over a period of 4-6 weeks. Patients transferring from immediate-release cysteamine bitartrate capsules should be transferred to a total daily dose of PROCYSBI equal to their previous total daily dose of cysteamine taken without food. GI symptoms are described in RSI.

- Effects on bone marrow

The cysteamine chronic toxicity study in monkeys and a 9-week study in rabbits showed effects on the bone marrow, occasionally associated with leukopenia. No further details are available.

Relevance to human usage: Leukopenia is described in RSI.

Other toxicity-related information or data

- Effects on somatostatin

Experimental administration of the drug causes depletion of somatostatin in several animal species. No further details are available.

Relevance to human usage: The relevance of these findings to humans is not known. Somatostatin level reduction and associated hormonal, behavioural or cognitive consequences is characterised as missing information.

- Mechanisms for drug interaction

It was demonstrated in rats that absorption of cysteamine is significantly greater at the level of the duodenum, where there is a greater density of organic cation transporter than in the rest of gastrointestinal tract.

Eudragit L30D55 is used as enteric coating with dissolution above pH 5.5. Drugs that raise the gastrointestinal pH (anti-acid medications) may lead to an earlier release of cysteamine from RP103 capsules. The results of *in vitro* metabolism and transporter studies showed that cysteamine bitartrate is likely an inducer of CYP1A2 or CYP3A4, and possibly CYP2B6. Cysteamine bitartrate is not an inhibitor but it is a substrate of P-glycoprotein. It is neither a substrate nor inhibitor of a standard battery of *in vitro* transporter systems.

Relevance to human usage: During the clinical programme, 9 patients of study RP103-04 who stopped using PPIs during the previous trial (RP103-03) restarted PPI therapy on a daily basis for the later study. This had no impact on control of WBC cystine levels, the marker for disease control in NC, suggesting that 12-hour exposure to therapeutic levels of cysteamine, when taken with an acidic drink, was not compromised by PPI use. An increase in RP103 dose would have been necessary, had the PPIs impacted RP103 absorption. In

fact, doses decreased over time in over half of the patients who took PPIs regularly in the long-term extension study. Results from an interaction between RP103 and omeprazole in healthy volunteers confirms the lack of impact of PPIs on cysteamine pharmacokinetics when RP103 is administered with orange juice (RP103-HLTA-009, RP103-15001) or water (RP103-15001).

Part II: Module SIII - Clinical trial exposure

Table SIII.1 - Clinical Trial Exposure for all Clinical Trial Populations - Summary of Studies

Study Identifier	Number of Patients/ Healthy Volunteers	Duration of Treatment	Study Status
Healthy Volunteers			
RP103-02	18	2 Single doses	Completed
RP103-05	20	2 Single doses	Completed
RP103-06	20	2 Single doses	Completed
RP103-HLTA-009	20	2 Single doses	Completed
RP103-15001	32	Single dose	Completed
RP103-16001	64 ^a	Single dose	Completed
Cystinosis Patients			
RP103-01	9	Single dose	Completed
RP103-03	43	9 weeks	Completed
RP103-04	59 ^b	Greater than 24 months (48) Greater than 36 months (27) Greater than 48 months (9)	Completed
RP103-07	41	Up to 48 months	Completed
RP103-08	17	12 months minimum	Completed
Inherited Mitochondrial Disease Patients			
RP103-MITO-001	36	Up to 6 months	Completed
RP103-MITO-002	22 ^b	Up to 24 months (planned)	Completed
Total No. of Patients/ Healthy Volunteers	339 (174 Healthy Volunteers and 165 Patients)		

^a Included both healthy adults and those with impaired renal function

^b Forty (40) patients rolled over from RP103-03 to RP103-04, 22 patients rolled over from RP103-MITO-001 study to RP103-MITO-002 and were counted once under the total number of subjects.

Table SIII.2 – Cumulative subject exposure in completed clinical trials

Treatment	Number of Subjects
RP103 (PROCYSBI IMP)	339
Comparator	123
Placebo	0

Table SIII.3 – Cumulative subject exposure to RP103 from completed clinical trials by age and gender

Age Range	Number of Subjects		
	Male	Female	Total
Neonate (0-27 days)	0	0	0
Infant (1-23 months)	2	5	7
Pre-school children (2-5 years)	23	6	29
School children (6-11 years)	28	17	45
Adolescent (12-17 years)	20	30	50
Adult (18-29 years)	37	17	54
Adult (30-49 years)	59	25	84
Adult (50-64 years)	31	14	45
Elderly (>65 years)	19	6	25
Totals	219	120	339

Table SIII.4 – Cumulative subject exposure to RP103 from completed clinical trials by racial group

Racial/Ethnic Group	Number of Subjects
Asian	5
Black	36
Caucasian	286
Other	12
Total	339

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

- Females (of child-bearing potential), who are nursing, planning a pregnancy, known or suspected to be pregnant, or have a positive urine pregnancy screen.**

Reason for exclusion: It is a general concept of not including the pregnant or breast-feeding women into clinical developmental programme. Besides, *in vivo* studies showed embryofetotoxic effects, reduction in fertility and lactation in rats.

Is it considered to be included as missing information? No

Rationale: The use of PROCYSBI is contraindicated in Europe and not recommended in Canada during breast feeding and if a pregnancy is diagnosed or planned, patients should be advised of the possible teratogenic risk of cysteamine as described in RSI. Teratogenicity was characterized as important potential risk and it is included in a list of safety concerns.

- **History of allergic reactions to cysteamine, penicillamine or other related drugs.**

Reason for exclusion: It is a general concept of not including the patients with the history of allergic reactions to the active substance of the investigational product or related drugs.

Is it considered to be included as missing information? No

Rationale: The RSI contraindicates the use of PROCYSBI in patients who have developed hypersensitivity to the active substance, any form of cysteamine (mercaptamine), any of the excipients of the formulation, or to penicillamine.

- **Populations with active inflammatory bowel disease**

Reason for exclusion: The underlying gastrointestinal (GI) signs and symptoms could be confounded by PROCYSBI-induced GI adverse events. However, there has been no evidence to associate PROCYSBI with de novo inflammatory bowel disease (IBD) or worsening of pre-existing IBD.

Is it considered to be included as missing information? No

Rationale: Based on the available data, no evidence has been identified to associate PROCYSBI with worsening or development of IBD. Other than the product label, no additional risk mitigation measures are deemed necessary. Therefore, this population is not included as missing information.

- **Populations with heart disease**

Reason for exclusion: It is a common practice that subjects with certain significant concomitant medical conditions are excluded from clinical trials. There has been no evidence to associate PROCYSBI with heart disease.

Is it considered to be included as missing information? No

Rationale: Based on the available data, no safety concerns were identified in patients with heart disease. Therefore, this population is not included as missing information.

- **Patients on dialysis or post-renal transplant**

Reason for exclusion: It is a common practice that subjects with certain significant concomitant medical conditions are excluded from clinical trials. Dialysis may affect pharmacokinetics. Cystinosis patients with renal transplant indicate disease progression. Available data have suggested that no additional dosing instruction is necessary for patients under dialysis. No safety concern has been raised in PROCYSBI-treated patients with renal transplant.

Is it considered to be included as missing information? No

Rationale: Based on the available data (clinical and post marketing) regarding this population no safety concerns were observed specific to treatment with PROCYSBI in renal transplant patients or patients under dialysis.

- **Patients with positive urine drug or alcohol at screening**

Reason for exclusion: It is a common practice that subjects with positive urine drug or alcohol are excluded from clinical trials.

Is it considered to be included as missing information? No

Rationale: No effect on the treatment of these patients is expected.

- **Patients with any clinically significant laboratory abnormality, low haemoglobin level, or positive test for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)**

Reason for exclusion: It is a common practice that subjects with certain significant concomitant medical conditions are excluded from clinical trials. There has been no evidence to associate PROCYSBI with any one of these medical conditions.

Is it considered to be included as missing information? No

Rationale: There has been no evidence to associate PROCYSBI with any one of these medical conditions.

- **Patients with malignant disease**

Reason for exclusion: It is a common practice that subjects with certain significant concomitant medical conditions are excluded from clinical trials. There has been no evidence to suggest a carcinogenic potential by PROCYSBI.

Is it considered to be included as missing information? No

Rationale: There has been no evidence to suspect PROCYSBI-induced malignancy.

- **Populations with severe liver disease as defined as ALT or AST > 2 times the upper limit of normal**

Reason for exclusion: It is a common practice that subjects with certain significant concomitant medical conditions are excluded from clinical trials. There has been no evidence to suspect PROCYSBI-induced liver injury.

Is it considered to be included as missing information? No

Rationale: There has been no evidence to suspect PROCYSBI-induced liver injury. No dose adjustment is required for patients with impaired liver functions.

SIV.2 Limitations to detect adverse reactions in clinical trial development programme

The clinical development programme is unlikely to detect certain types of adverse reactions such as, rare adverse reactions.

117 patients with cystinosis have received RP103 (cysteamine bitartrate) in clinical trials, for durations of greater than 12 months; the mean exposure to RP103 was approximately 3 years. There was no evidence of cumulative effect or long latency adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
Children	131 patients below 18 years of age were included in the clinical development programme	
Elderly	25 patients were included in the clinical development programme	
Pregnant women	Not included in the clinical development programme	
Breastfeeding women		
Patients with relevant comorbidities: ○ Patients with hepatic impairment ○ Patients with cardiovascular impairment ○ Immunocompromised patients ○ Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme	
Patients with renal impairment	165 patients with nephropathic cystinosis (indication) were included in the clinical development programme	
Patients with renal replacement and / or renal transplantation	6 renal transplant patients were enrolled in study RP103-04	
Population with relevant different ethnic origin	Racial/Ethnic Group	Number of Subjects
	Asian	5
	Black	36
	Caucasian	286
	Other	12
	Total	339
Subpopulation carrying relevant genetic polymorphisms	Not included in the clinical development programme	

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Because of the rarity of nephropathic cystinosis and the distribution of PROCYSBI by patient support programs, its marketed use can be traced to individual patients. Therefore, it is possible to provide a relatively precise estimate of the number of patients who have received PROCYSBI in marketed setting by region and globally.

SV.1.2 Exposure

The global PROCYSBI patient exposure until 28-Febr-2021 was 835 patients since IBD as shown by region in Table SV.1. The EEA area includes Germany, Austria, Switzerland, Norway, Denmark, France, Sweden, Iceland, Finland, UK, Ireland, Portugal, Spain, Belgium and Netherlands; the Middle East includes Turkey, Kuwait, Saudi Arabia, United Arab Emirates and Israel.

It is of note, that some subjects who were treated in the clinical studies still receive PROCYSBI in the commercial setting and it is difficult to get an exact count of those who are counted under both clinical and post-marketing settings.

Table SV.1 – Cumulative PROCYSBI patient exposure in the marketed setting as of 28 February-2021

Country or Region	Cumulative number of patients treated at the DLP 28 Feb 2021
EEA ^(a)	227
Middle East ^(b)	8
US*	
Canada**	
Columbia	
Brazil	
Total	835

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The MAH is not aware of any evidence to suggest a potential for misuse or abuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1: Outline of Safety concerns:

The following safety concerns are identified from the non-clinical data available in the literature; however, all these concerns are adequately addressed by the clinical data, the proposed labelling, the relevance to human usage is not known or is not thought to be clinically relevant.

Summary of Safety concern:

SAFETY CONCERN (from non-clinical studies)	RELEVANCE TO HUMAN USAGE
Effects on GI Tract Subacute toxicity with cysteamine was studied in a four-week oral study in 2 monkeys (150 mg/kg/day) and in a 13 week feeding study in rabbits (100 mg/kg/day). Chronic toxicity was only studied in 5 monkeys given 20-150 mg/kg/day orally for one year. No GI effect was observed in these studies. Single and repeated administration to rats indicated that gastric and duodenal ulcers can be produced at high doses of 200 mg/kg and above by subcutaneous injection. Studies in rats with cysteamine confirmed a potential for duodenal and gastric ulcerogenic effects. GI effects have been observed in rats with high doses of Eudragit.	The GI tract is indicated as the target organ of toxicity for cysteamine in acute toxicity studies however, this does not seem to have been observed in oral subacute and chronic studies in rabbits and monkeys. Gastric and duodenal ulcers were observed after administration of high doses in rats by the s.c. route indicating a potential species-specific effect in the rat. The relevance of these findings in rats to humans is not known. The gastroresistant formulation for cysteamine bitartrate will help to mitigate the GI effects seen with immediate release cysteamine. The dose for newly diagnosed patients is gradually increased from 1/4 to 1/6 of the maintenance dose of a period of 4-6 weeks. 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/m²/day. The use of doses higher than 1.95 g/m²/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. The capsules may be taken whole or opened and the content sprinkled on food or liquid. Guidance is provided in section 4.2 of the proposed SmPC on suitable foods and liquids.
Effects on Bone Marrow The cysteamine chronic toxicity study in monkeys and a 9-week study in rabbits showed effects on the bone marrow. No further details are available.	Section 4.2 of the proposed SmPC recommends that WBC cystine levels should be measured 30 min after dosing and should be checked frequently when initiating therapy (e.g. monthly) and every 3-4 months when on a stable dose. Monitoring of blood cell count in patients is recommended on a regular basis in section 4.4 of the proposed SmPC.
Reproductive and Development Toxicity Reproduction studies showed embryofetotoxic 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/m²/day in the rat, which is slightly less than the recommended clinical maintenance dose of cysteamine, i.e. 0.9 g/m²/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.	These non-clinical findings are included in Section 5.3 of the proposed SmPC. The use of the cysteamine bitartrate (gastro-resistant) capsules is contraindicated during pregnancy and breast feeding (see sections 4.3 and 4.6 of the proposed SmPC).

Active substance: Cysteamine

Version: 8.0

Released on: 31 August 2022

High doses of cysteamine impair the ability of lactating mothers to feed their pups. Single doses of the drug inhibit prolactin secretion in animals.	
Effects on Somatostatin Experimental administration of the drug causes depletion of somatostatin in several animal species. No further details are available.	The relevance of these findings to humans is not known.

SVII.1.2 Recent study reports with implications for safety concerns

An interim clinical study report has been written for **study RP103-04** which is an extension of study RP103-03. This interim report was released on 11-Nov-2015 and presents all clinical safety and pharmacokinetic / pharmacodynamic data available for protocol RP103-04 collected at study visits completed through 31-Mar-2015 for all 59 enrolled subjects, and includes those cystinosis subjects, who continued from the RP103-03 study, newly enrolled cystinosis subjects less than 6 years of age and kidney transplant cystinosis subjects.

For the overall safety population (n=59), the estimated mean exposure to RP103 in study RP103-04 was approximately 3.0 years. The estimated mean duration of exposure in the RP103-03 subjects (n=40), in subjects ≤ 6 years (n=13), and in the kidney transplant subpopulation (n=6) was approximately 3.3 years, 2.5 years and 2.2 years, respectively. For the majority of subjects (81% [48/59]), the duration of exposure to RP103 was greater than 24 months and for 46% (27/59) of the subjects, the duration of exposure was greater than 36 months; nine subjects (15%) had a duration of exposure to RP103 greater than 48 months. **The duration of exposure in this study allows to consider that long-term (2+ years) use is no longer a missing information.**

The safety findings observed with long-term treatment (exposure of up to 4.6 years) with RP103 every 12 hours are consistent with those previously reported in study RP103-03 and with those previously described for Cystagon. The most common treatment related adverse events were gastrointestinal (vomiting, nausea, abdominal pain, breath odour, and diarrhoea) as well as skin odour, decreased appetite, fatigue, headache, and device occlusion. Gastrointestinal adverse events of vomiting and diarrhoea are important safety findings to monitor for in cystinosis. Patients with cystinosis have underlying Fanconi syndrome which is characterized by polyuria, hypokalaemia, and hypophosphatemia; thus, recurring vomiting and diarrhoea has the potential to contribute to additional concomitant perturbation of fluid and electrolyte balance. No deaths were reported in the study. Overall, adverse events were mild to moderate in nature and predominantly of the gastrointestinal system. SAEs reported were generally consistent with the overall safety profile observed previously in Study RP103-03 and with expected comorbidities associated with the underlying disease. Six out of 80 SAEs were considered related to RP103. Two subjects experienced non-serious AEs which resulted in discontinuation from the study.

Examination of safety parameters within the subpopulations of subjects ≤ 6 years of age (n=13) and in the kidney transplant recipients (n=6) suggest a similar safety profile to that observed in subjects from Study RP103-03 (n=40).

The duration of exposure to RP103 in the kidney transplant subpopulation (n=6) was approximately 2.2 years, examination of safety parameters within this subpopulation suggest a similar safety profile to that observed in subjects from Study RP103-03 (n=40). These results support the post-marketing experience on this subpopulation. A total of 70 cases involving a history of renal transplantation were received as of 23-Oct-2015. The analysis of these cases does not suggest any issues specific to renal transplant patients other than those associated with the renal transplant itself or with nephropathic cystinosis.

These results allow to consider that use in patients on renal replacement therapy and/or renal transplantation long-term (2+ years) use is no longer a missing information.

Study RP103-08 was a phase 3b, long-term, open-label study of the safety, tolerability and effectiveness of RP103 in cystinosis patients who are naïve to any form of cysteamine treatment. The primary objective of this study was to assess the safety and effectiveness of long-term repeat dosing of RP103 on WBC cystine level in cystinosis patients who are naïve to cysteamine treatment. The secondary objectives were (1) to determine the variability of a new treatment initiation methodology and (2) to assess steady state cysteamine PK/pharmacodynamics (PK/PD) in children less than 6 years old. Among the 17 enrolled patients, 15 were < 6 years of age. All patients received RP103 for orally or via gastrostomy tube (G-tube) every 12 hours for at least 12 months. All 15 subjects age <6 years (100%) had at least 1 TEAE. The most frequently reported types of TEAEs (by system organ class) were Infections and Infestations (100% of subjects) and Gastrointestinal Disorders (87% of subjects). The most frequently reported ($\geq 10\%$ of subjects) individual TEAEs were vomiting (80% of subjects); upper respiratory tract infection, gastroenteritis, and diarrhoea (33%-53% of subjects each); pyrexia, cough, rhinitis, breath odour, and nausea (20%-27% of subjects each); and electrolyte imbalance, rhinorrhoea, gastrostomy, headache, and dermatitis diaper (13% of subjects each). Twelve subjects (80.0%) had at least 1 SAE for a total of 36 SAEs. The most frequently reported ($\geq 10\%$ of subjects) SAEs were gastroenteritis, dehydration, vomiting, electrolyte imbalance, and gastrostomy. One case of death was reported. The events cardiopulmonary failure, Fanconi syndrome, gastroenteritis, and hypovolaemic shock which were leading to death were considered likely related to cystinosis and not related to the study drug. In conclusion, RP103 treatment to treatment-naïve subjects with nephropathic cystinosis resulted in lowering WBC cystine concentrations and improving growth parameters in subjects <6 years of age throughout the treatment period of 12 months. The safety findings in this study were not unexpected based on the subject population, the underlying nephropathic cystinosis, and the known safety profile of RP103. No new safety signals were identified, which further supports the favorable benefit risk profile of RP103.

Study RP103-15001 was a phase 1 study (RP103-15001) to satisfy a post-marketing study commitment to the FDA to conduct a PK study in healthy volunteers to evaluate the effects of administration methods on PK of cysteamine. The objective of this open-label, single dose, 3-period, randomized study was to evaluate the PK of cysteamine following oral administration of RP103 with orange juice, water, or omeprazole with water in healthy adult subjects. This study compared the PK of cysteamine after administration of RP103 capsules with water and with orange juice. In addition, this study evaluated the effects of a concomitant proton pump inhibitor on the PK of cysteamine after administration of RP103 capsules with water. A total of 32 healthy volunteers were enrolled in a single US site and received a 600 mg dose. Mean plasma cysteamine peak and total exposures were similar when RP103 was administered as a single dose with water or with orange juice, and with water as a single dose with and without omeprazole once daily for 5 days. The median t_{max} was 0.5 hours later when RP103 was administered with orange juice and was earlier by 0.5 hours when administered with omeprazole, in comparison to administration with water. Single doses of RP103, when administered with orange juice, water, or omeprazole with water, appeared to be safe and generally well tolerated by the healthy male and female adult subjects in this study. No SAE report was received in this study. No new safety issues have been identified for RP103 based on this analysis. Following key findings from study RP103-15001 are reflected in a Prior Approval Supplement (PAS) submitted on 31 Mar 2017 containing proposed updates to the US PI, patient information, and instructions for use:

- Whole PROCYSBI capsules may be administered with water (current label recommends that PROCYSBI capsules should be swallowed whole with fruit juice, directly in USPI and indirectly in EU SmPC, while PIL recommends not to take PROCYSBI at the same time as water)
- Concomitant use of proton pump inhibitors (investigated with omeprazole) does not affect the pharmacokinetics of cysteamine when PROCYSBI is administered with water.

SVII.1.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

All identified and potential risks described in this RMP are related to the active substance, except fibrosing colonopathy, which is a potential risk related to the ingredient in the enteric coating of cysteamine, as discussed below.

Eudragit L30 D-55, the ingredient in the enteric coating of cysteamine in RP103, is a methacrylic acid polymer composed with two surfactants, sodium lauryl sulfate and polysorbate 80. Animal studies have shown that methacrylic acid induces submucosal fibrosis (van Velzen et al., 1996) and there has been, to date, a single report describing the incidence of fibrosing colonopathy in a child that was associated with the ingestion of Eudragit-coated mesalazine for the treatment of ulcerative pancolitis (Prieto et al., 2009). Since a causal link could not be conclusively ruled out for methacrylic acid in this case report, the authors advised caution for the monitoring of related events due the relatively small number of patients exposed to Eudragit-coated drugs. Although rare, a dose-dependent lipase-induced fibrosing colonopathy has been reported in young children with cystic fibrosis treated with very high doses of pancreatic enzyme replacement therapy containing Eudragit (Smyth, 1996). Because the majority (53 to 100 percent) of the children in whom fibrosing colonopathy has been observed were taking high-strength pancreatic-enzyme products, the safety of the high-strength preparations was questioned. This led to the European consensus recommendation to remain below a dose of 10 000 IU lipase/kg body weight. The United Kingdom Committee on the Safety of Medicines has also restricted the use of high-strength pancreatic-enzyme products (MCA, 1995). On the basis of a study of 14 cases of fibrosing colonopathy in the United Kingdom, the committee also concluded that the risk was associated with high-strength products. The possibility of occurrence of fibrosing colonopathy even with lower doses has not been ruled out and is described in Table 25 below.

All identified and potential risks are described in the Tables 21 to 26 below, based on the data received from clinical trials and post-marketing sources as of 23 OCT 2020 as well as information from literature search.

Rates reflected in the tables below are conservatively estimated and do not necessarily reflect a high degree of specificity or diagnostic certainty (see MedDRA terms row for search strategies applied). Methods may be revised as more data accumulate.

Table 1 Identified Risk of GI symptoms

Identified Risk	Gastrointestinal (GI) symptoms: vomiting, nausea, diarrhoea, abdominal pain.
Frequency in all clinical trial populations	Cumulatively, a total of 69 SAE reports have been received. These 69 reports included a total of 100 events of which 74 were identified via search strategy (see search strategy under MedDRA terms below). Thirty-nine of those 74 events pertained to the primary SOC “Infections and Infestations” with the most frequently reported PTs Gastroenteritis (n=21) and Appendicitis (n=7). These events were not considered relevant for this risk due to their infectious character and hence are not further specified. The remaining 35 events all primarily pertained to the SOC “Gastrointestinal disorders” and occurred in a total of 30 cases. More than three-quarters of these SAEs (29/35, 83%) were made up of the PTs vomiting (n=19), nausea (n=2), diarrhoea (n=7) and abdominal pain (n=1). The most frequently reported events were vomiting and diarrhoea.

Identified Risk	Gastrointestinal (GI) symptoms: vomiting, nausea, diarrhoea, abdominal pain.
	The 30 SAE reports pertaining to this risk occurred with a frequency of 0.18 (n=165 patients).
Frequency in post-marketing populations	Cumulatively, a total of 541 case reports for PROCYSBI capsules were received, containing 860 AEs pertaining to this risk, among approximately the 809 patients exposed to PROCYSBI in the post-marketing setting. Some reports may have involved the same patient. The most frequently reported events reported at least 3 times were the PTs of Vomiting (n=272), Nausea (n=250), Diarrhoea (n=86), Abdominal pain upper (n=71), Abdominal discomfort (n=66), Abdominal pain (n=26), Constipation (n=14), Abdominal distension (n=8), and Flatulence (n=4). One fatal event of Vomiting was received, which occurred in a patient with Pneumonia, Aspiration, and Seizure. Medical history included grand mal seizures and events were considered unrelated to PROCYSBI.
Seriousness/outcomes	<u>Clinical trial:</u> The outcome of the 35 events (identified via search strategy) pertaining to the risk GI symptoms SOC "Gastrointestinal disorders" were reported as recovered/resolved with sequel (n=3) and recovered/resolved (n=32). <u>Post-Marketing:</u> For the 860 (795 non-serious and 65 serious) events following outcomes were reported: The outcome of the 65 serious events was reported as fatal (n=1), not recovered/not resolved (n=8), recovering/resolving (n=9), recovered/resolved (n=20), and unknown (n=27). Action taken was dose increased (n=1), dose not changed (n=16), dose reduced (n=4), drug withdrawn(n=20), not applicable (n=5), and unknown (n=19). The outcome of the 795 non-serious events was reported as not recovered/not resolved (n=158), recovering/resolving (n=67), recovered/resolved (n=203), unknown (n=367). Action taken was dose increased (n=15), dose not changed (n=239), dose reduced (n=102), drug withdrawn (n=197), not applicable (n=3), unknown (n=230) and not reported (n=9).
Severity and nature of risk	In patients receiving randomised (crossover) treatment with both RP103 and Cystagon, most of the GI symptoms were classified as Grade 1 severity (16, 37.2%) or Grade 2 severity (7, 6.3%). Two reports, abdominal pain and abdominal discomfort, in the same patient, were deemed to be of Grade 3 severity. Diarrhoea of Grade 1 severity was only reported once. Such symptoms and signs are a risk because they may interfere with effectiveness of the product. Persistent severe gastrointestinal symptoms which do not respond to medical management may be linked to the potentially serious risk of fibrosing colonopathy. Eudragit L30 D-55, the ingredient in the enteric coating of cysteamine in RP103 has been clinically associated with this condition when used in certain other formulations

Identified Risk	Gastrointestinal (GI) symptoms: vomiting, nausea, diarrhoea, abdominal pain.
	such as high-strength pancreatic-enzyme supplements. However, no non-clinical studies have been able to reproduce this pathology in animals. To date, none of the cysteamine (as mercaptamine bitartrate) gastro-resistant hard capsule patients experiencing gastrointestinal signs and symptoms have been reported to have progressed to any disease entity.
Background incidence/prevalence	Unknown
Risk groups or risk factors	Rapid introduction or high doses of cysteamine increase the likelihood of nausea, vomiting and other gastrointestinal symptoms.
Potential mechanisms	Recent data in rats (Dohil et al., 2012) seem to support the fact that there would be enzyme induction with progressively more cysteamine eliminated over time, justifying a progressive dose increase.
Preventability	Warning in SmPC and Patient Information Leaflet (PIL). Temporarily suspending PROCYSBI treatment, then gradual re-introduction may be effective in improving tolerance. For newly-diagnosed patients with cystinosis, the starting dose should be 1/6 to 1/4 of the recommended maintenance dose, increased gradually over 4-6 weeks to minimise intolerance. For patients switching from treatment with a stable dose of immediate-release cysteamine bitartrate to treatment with cysteamine gastro-resistant, (expected to be ~ 80% of patients) their starting total daily dose of cysteamine gastro-resistant capsules should be equal to their total daily dose of immediate-release cysteamine bitartrate.
Impact on individual patient	Patients with cystinosis have underlying Fanconi syndrome which is characterized by polyuria, hypokalaemia, and hypophosphatemia; thus, recurring vomiting and diarrhoea has the potential to contribute to additional concomitant perturbation of fluid and electrolyte balance. Quality of life deteriorates.
Potential public health impact of safety concern	Suspending treatment as described above should mitigate against the likelihood of worsening symptoms and medically relevant sequelae such as dehydration.
Evidence source	Clinical trials with RP103 and from Cystagon, post-marketing data
MedDRA terms	SOC Gastrointestinal disorders (primary and secondary PTs)

Table 2 Identified risk of leukopenia

Identified risk of leukopenia	
Frequency in clinical trial population	Not reported.
Frequency in post-marketing populations	Cumulatively, 9 relevant case reports (including 10 events, 6 serious and 4 non-serious) pertaining to this risk have been received among approximately the 809 patients exposed to PROCYSBI in the post-marketing setting. The following PTs were included: White blood cell count decreased (n=5), Leukopenia (n=3), Agranulocytosis (n=1), Pancytopenia (n=1). In 2 cases, WBC results were reported in context of PROCYSBI dosing and likely refer to WBC cystine levels, a parameter used for monitoring and dose titration in patients treated with PROCYSBI. These 2 cases are therefore not considered for this risk. Five cases were confounded by immunosuppressive therapy in the post-transplant setting. Two remaining cases including the relevant PTs Pancytopenia and Leukopenia provided only limited information on the events and lacked details on diagnostic work-up.
Seriousness/outcomes	The outcome of the events was unknown for all post-marketing cases. In the general population, seriousness of leucopenia depends on the severity of the reduction in WBC counts. With appropriate management using pre-established procedures, with intravenous broad-spectrum antibiotic therapy and hematopoietic growth factors, the mortality rate is currently around 5% (Andrès and Maloisel, 2008). In idiosyncratic situations the excess 1-year mortality is reported to be mostly explained by the underlying disease state (van Staa et al., 2003).
Severity and nature of risk	Theoretically from mild and asymptomatic to severe and complicated leukopenia. Serious adverse event due to the frequency of severe infections (such as deep infections, septicemia and septic shock) in around two thirds of patients (Andrès and Maloisel, 2008). The risk of serious infection is known to increase as the ANC falls to the severely neutropenic range ($< 500/\mu\text{L}$). Modern management with broad spectrum antibiotics and hematopoietic growth factors is expected to improve the prognosis.
Background incidence/prevalence	Leukopenia/neutropenia is more likely to be acquired than congenital. The most common cause of acutely acquired neutropenia is cytotoxic chemotherapy or radiation therapy for malignant diseases, affecting up to 40% of patients given treatment (Munshi and Montgomery, 2000). Neutropenia can also be caused by drugs, some metabolic disease, nutritional deficiency, infections and malignancy. Drug reactions are the most common cause of isolated neutropenia, they are responsible of idiopathic severe neutropenia cases in about 2/3 of the cases in a general population (Kaufman et al., 1996, Andersohn et al., 2007). Crude incidence of drug-induced

	neutropenia has remained stable for decades (about 3–16 cases per million people per year) despite many new drugs on the market and disappearance of other. Drugs involved are mainly antibacterial, immunosuppressive, anti-thyroid, antiplatelet and nonsteroidal anti-inflammatory (Tesfa 2009). About 20–63% of kidney recipients will experience at least one episode of leukopenia/neutropenia (Yang et al., 2015).
Risk groups or risk factors	Mostly transplanted patients. It should be taken into account that a high portion of nephropathic cystinosis patients develop end stage renal disease and undergo kidney transplantation, thus receive immunosuppressive agents which may be causative of bone marrow suppression and leukopenia. Of note, patients who have renal insufficiency or bacteraemia at the time of presentation have a significantly higher mortality (Julia et al., 1991).
Potential mechanisms	The mechanism of cysteamine-induced leukopenia is unknown. The exact mechanisms for drug-induced neutropenia or agranulocytosis are not well established. Non-immune and cell-mediated immune mechanisms are discussed depending on the culprit drugs, and host genetic traits may play a role (Tesfa et al., 2009).
Preventability	- Warning in SmPC and PIL (blood count monitoring) - Frequent monitoring of clinical state - Regular monitoring of blood count Of note: this event is unpredictable but occurs preferably in the beginning of the treatment (van Staa et al., 2003).
Impact on individual patient	Increase of infection, possible fatal outcome. Increase of hospitalization, risk of hospital acquired infection.
Potential public health impact of safety concern	Increase of hospitalization costs, costs of additional care, decrease of ability to work.
Evidence source	Clinical evidence in literature Post marketing data
MedDRA terms	SMQ Haematopoietic leukopenia (narrow) SMQ Agranulocytosis (narrow)

Table 3 Potential risk of encephalopathy

Potential Risk	Encephalopathy
Frequency in all clinical trial populations	No case of a medically confirmed encephalopathy was received. Cumulatively, a total of 19 SAE reports were identified via a safety database search using the SMQ “Noninfectious encephalopathy/delirium (SMQ narrow and broad)”.

Potential Risk	Encephalopathy
	The 19 reports included a total of 33 events of which 20 were identified via search strategy (see details under MedDRA terms below) pertaining to the risk Encephalopathy. The 20 events pertained to SOC “Nervous system disorders” (n=15) and “Psychiatric disorders” (n=5). The most frequently reported event was seizure (n=12). Loss of consciousness and abnormal behaviour occurred twice. Lethargy, confusional state, mental status changes, and psychotic disorder were reported only once. All SAEs from clinical trials were assessed as not related to PROCYSBI by the investigator and the MAH. The 19 SAE reports pertaining to this risk occurred with a frequency of 0.12 in relation to patients (n=165) exposed to PROCYSBI.
Frequency in post-marketing populations	No ICSR on a medically confirmed encephalopathy was received. Cumulatively, a total of 35 case reports (18 serious and 17 non-serious) were identified via a safety database search using the SMQ “Noninfectious encephalopathy/delirium (SMQ narrow and broad)”. None of the 35 cases contained any of the narrow-focus terms. The 35 cases included 44 MedDRA PTs belonging to the broad search terms in the above-listed SMQ. Of these 44 events 32 were non-serious and 12 were serious. The most frequently reported events were somnolence (n=11; all non-serious), dysphagia (n=7; all non-serious), seizure (n=4; all serious), and mood altered (n=3; 1 serious, 2 non-serious). The 12 serious events were seizure (n=4), amnesia (n=2), abnormal behaviour (n=1), loss of consciousness (n=1), mood altered, (n=1), personality disorder (n=1), psychotic disorder (n=1), restlessness (n=1). Case reports contained plausible alternative causes or risk factors for the AEs. None of the reports provided facts or evidence confirming PROCYSBI induced encephalopathy in these patients. The 35 case reports pertaining to this risk occurred with a frequency of 0.07 in relation to subjects (n=533) exposed to PROCYSBI.
Seriousness/outcomes	Clinical trials: The outcome of the 20 events (identified via search strategy) pertaining to the risk Encephalopathy was reported as recovered/resolved (n=18) and recovered/resolving with sequel (n=2). Post-marketing: The outcome of the 44 events (identified via search strategy) pertaining to the risk Encephalopathy was reported as fatal (n=1), not recovered/not resolved (n=8), recovered/resolved (n=13), recovered/resolving with sequel (n=4), and unknown (n=18).
Severity and nature of risk	Clinical risk unknown

Potential Risk	Encephalopathy
Background incidence/prevalence	Cystinosis-associated encephalopathy was first described by Levine in 1982 and since then many studies reported symptoms of encephalopathy in patients with cystinosis and confirmed this first observation (Levine and Paparo, 1982, Müller et al., 2008). From his 26-patient study Broyer estimated that 50% of all untreated patients with cystinosis have signs of encephalopathy (Broyer et al., 1996). This heavily confounds causality assessment with cysteamine.
Risk groups or risk factors	No specific risk groups or risk factors for the development of encephalopathy in nephropathic cystinosis patients have been identified. Published literature states that encephalopathy becomes more frequent with advancing age (Elmonem et al. Orphanet Journal of Rare Diseases (2016) 11:47).
Potential mechanisms	The relationship of reported suspected ADRs of non-specific neurological symptoms to pathological neurological disease is unknown.
Preventability	Warning in SmPC and PIL. If CNS symptoms develop, the patient should be carefully evaluated, and the dose adjusted as necessary
Impact on individual patient	Quality of life deteriorates
Potential public health impact of safety concern	Significant
Evidence source	Product information of immediate release cysteamine Clinical evidence in literature Post marketing data
MedDRA terms	Non-infectious encephalopathy/delirium (SMQ narrow and broad)

Table 4 Potential risk of teratogenicity

Potential Risk	Teratogenicity
Frequency in all clinical trial populations	No case of teratogenicity and no case pertaining to the PT Exposure during pregnancy was received. Cumulatively, 6 serious cases were identified via a safety database search using the SMQ "Pregnancy and neonatal topics (SMQ narrow and broad)". The 6 reports included a total of 9 events of which 6 were identified via search strategy (see search strategy under MedDRA terms below) pertaining to the risk Teratogenicity. The 6 events pertained to SOC "Congenital, familial and genetic disorders" (n=3), "Metabolism and nutrition disorders" (n=2) and "Pregnancy, puerperium and perinatal conditions" (n=1).

Potential Risk	Teratogenicity
	The most frequently reported event was failure to thrive (n=2). Abortion spontaneous, Arnold-Chiari malformation, Cryptorchism and Fanconi syndrome were reported only once. All SAEs from clinical trial were assessed as not related to PROCYSBI by the investigator and the MAH. The 6 SAE reports pertaining to this risk occurred with a frequency of 0.04 in relation to patients (n=165) exposed to PROCYSBI.
Frequency in post-marketing populations	No ICSR on a medically confirmed teratogenicity was received. Cumulatively a total of 5 cases (2 serious and 4 non-serious) were identified via a safety database search using the SMQ "Pregnancy and neonatal topics (SMQ narrow and broad)". The 5 cases included 6 MedDRA PTs belonging to the search terms in the above-listed SMQ. Of these 6 events 2 were serious and 4 were non-serious. The reported events were exposure during pregnancy (n=3; all non-serious), cystinosis (n=2; serious) and delivery (n=1; non-serious). Of note the, 2 serious cases identified in the post-marketing dataset that are classified as congenital anomalies were not considered events of teratogenicity, because the events of cystinosis in these cases [REDACTED] and [REDACTED] were in fact a worsening of the patient's underlying nephropathic cystinosis. These 5 case reports pertaining to this risk occurred with a frequency of 0.01 in relation to subjects (n=533) exposed to PROCYSBI.
Seriousness/outcomes	Clinical trials: The outcome of the 6 events (identified via search strategy) pertaining to this risk was reported as recovered/resolved (n=5), and fatal (n=1). Post-marketing: The outcome of the 6 events (identified via search strategy) pertaining to this risk was reported as recovered/resolved (n=3), recovered/resolving (n=1) and unknown (n=2).
Severity and nature of risk	Clinical risk unknown
Background incidence/prevalence	Unknown
Risk groups or risk factors	First trimester of pregnancy
Potential mechanisms	Resorptions and post-implantation losses
Preventability	Warning in SmPC and PIL



Potential Risk	Teratogenicity
Impact on individual patient	Women of child-bearing age have to be careful, particularly during the first trimester as there is a risk of teratogenicity if foetus is exposed to the drug.
Potential public health impact of safety concern	Significant
Evidence source	Non-clinical data
MedDRA terms	Pregnancy and neonatal topics (SMQ narrow and broad)

Table 5 Potential risk of fibrosing colonopathy

Potential Risk	Fibrosing colonopathy
Frequency in all clinical trial populations	No case of a medically confirmed fibrosing colonopathy was identified in the clinical trial dataset: No case has been identified via a safety database search using the PT Fibrosing colonopathy. Two (2) serious case reports were detected via an additional analysis (see MedDRA terms at the bottom of this risk) in the clinical trial dataset, which were reviewed for potential fibrosing colonopathy. The 2 reports included a total of 3 events (all identified via search strategy (see details under MedDRA terms below)) pertaining to the risk fibrosing colonopathy. The 3 events pertained to SOC “Gastrointestinal disorders” (n=2) and “Metabolism and nutrition disorders” (n=1). The reported events (constipation, hypokalaemia and vomiting) were reported only once and do not provide strong evidence for fibrosing colonopathy. Two SAEs from clinical trial were assessed as possibly related and one SAE was assessed as not related to PROCYSBI by the investigator and the MAH. The 2 cases pertaining to this risk occurred with a frequency of 0.012 in relation to patients (n=165) exposed to PROCYSBI.
Frequency in post-marketing populations	There have been no reports of medically confirmed fibrosing colonopathy identified in the post-marketing dataset: Cumulatively, one serious case has been identified via a safety database search using the PT Fibrosing colonopathy and 12 case reports (reporting on 27 events pertaining to SOC gastrointestinal disorders) were detected via an additional analysis (see MedDRA terms at the bottom of this risk) in the post-marketing dataset, which were reviewed for potential fibrosing colonopathy. Of these 27 events 22 were non-serious and 5 were serious. The most frequently reported events were vomiting (n=7; 6 non-serious, 1 serious), abdominal pain upper (n=3; all non-serious), diarrhoea (n=3; 2 non-serious, 1 serious) and nausea (n=3; 2 non-serious, 1 serious). The 5 serious events were anal incontinence, diarrhoea, fibrosing colonopathy, nausea, and vomiting (n=1 each). In none of these cases there was strong evidence for fibrosing colonopathy. In only one of these cases extensive work-up including diagnostic colonoscopy with biopsy was reported. The results of the colonoscopy were normal, but the results of the biopsy were not provided. Cumulatively, 13 cases pertaining to this risk occurred with a frequency of 0.02 in relation to subjects (n=533) exposed to PROCYSBI.
Seriousness/outcomes	Clinical trials: The outcome of the 3 events (identified via search strategy) pertaining to the risk fibrosing colonopathy was reported as recovered/resolving with sequel (n=3). Post-marketing:

Potential Risk	Fibrosing colonopathy
	The outcome of the 28 events (identified via search strategy) pertaining to the risk fibrosing colonopathy was reported as not recovered/not resolved (n=4), recovered/resolved (n=2), recovering/resolving (n=7), and unknown (n=15).
Severity and nature of risk	The maximum daily dose of RP103 (8 capsules taken every 12 hours) contains 908.16 mg of Eudragit L 30 D-55, with each capsule containing 113.52 mg Eudragit L 30 D-55. This equates to 8-19 mg/kg/day of Eudragit L 30 D-55 exposure, in the patients studied in the CYST-HD clinical study, while cases have been reported at doses of Eudragit L 30 D-55 between 30 and 255 mg/kg/day.
Background incidence/prevalence	Unknown
Risk groups or risk factors	Overdose and abuse
Potential mechanisms	Reported cases of fibrosing colonopathy with Eudragit were almost exclusively limited to young aged cystic fibrosis patients, who received pancreatic enzyme supplements at extreme doses, which went far beyond all published recommendations for these preparations. Though a thoroughly performed case control study conducted in the US reported that “the strength, coating, and manufacturer of the products used were not associated with the risk of fibrosing colonopathy”, it cannot be excluded that high dosages of Eudragit L 30 D-55 /L 100-55 may contribute to the pathogenesis of fibrosing colonopathy. However, no non-clinical studies have been able to reproduce this pathology in animals and this could appear only after a long-term, chronic treatment of patients.
Preventability	Respect of the dose. Warning in SmPC and PIL
Impact on individual patient	Quality of life deteriorates
Potential public health impact of safety concern	Unknown
Evidence source	Clinical evidence in the literature for other products containing Eudragit
MedDRA terms	PT: Fibrosing colonopathy An additional analysis was performed of cases in which non-specific gastrointestinal symptoms (all PTs occurring in SOC Gastrointestinal disorders) appeared 1 year after starting PROCYSBI treatment (i.e. onset date at least one year after start of treatment with PROCYSBI) and which seem to be resistant to treatment (i.e. GI events with outcome reported as “recovered” do not support the diagnosis of fibrosing colonopathy and were therefore excluded). For the post-marketing setting, cases were considered for further analysis if both event start date and start date of PROCYSBI treatment were provided.

Table 6 Potential risk of Ehlers-Danlos-like syndrome

Potential Risk	Ehlers-Danlos-like syndrome (EDS)
Frequency in all clinical trial populations	There have been no reports of medically confirmed Ehlers-Danlos like syndrome identified in the clinical trial dataset. Noteworthy, 4 reports on knee deformity/genu valgum and 1 report on scoliosis were identified which could be indicative for Ehlers-Danlos like syndrome, since these symptoms may occur in the context of symptoms resembling clinical features of Ehlers-Danlos syndrome. However, none of these cases reported on a convincing evidence of a causal relationship between PROCYSBI treatment and new occurrence of these events. In addition, these clinical features of Ehlers-Danlos (like) syndrome overlap with clinical manifestations of cystinosis. 1 case reported on peripheral artery thrombosis, however the most likely aetiology of this event was not study drug related. Cumulatively, a total of 39 SAE reports were identified via a safety database search using the SOC "Skin and subcutaneous tissue disorders", SOC "Musculoskeletal and connective tissue disorders", SOC "Vascular disorders" and SMQ Embolic and thrombotic events (with all Sub-SMQs) The 39 reports included a total of 54 events of which 45 were identified via search strategy (see details under MedDRA terms below) pertaining to the risk Ehlers-Danlos-like syndrome. The 45 events pertained to SOC "Infections and infestations" (n=4), "Injury, poisoning and procedural complications" (n=18), "Musculoskeletal and connective tissue disorders" (n=12), "Nervous system disorders" (n=5), "Respiratory, thoracic and mediastinal disorders" (n=1) and "Vascular disorders" (n=5). The most frequently reported events were arteriovenous fistula site complication (n=9), knee deformity (n=9), arteriovenous fistula site haemorrhage (n=4) and hypertension (n=3). All other events were reported once. All SAE from clinical trial were assessed as not related to PROCYSBI by the investigator and the MAH. The 39 SAE reports pertaining to this risk occurred with a frequency of 0.24 in relation to patients exposed to PROCYSBI.
Frequency in post-marketing populations	There have been no reports of medically confirmed Ehlers-Danlos like syndrome identified in the post-marketing dataset. Cumulatively, a total of 169 case reports (45 serious and 124 non-serious) were identified via a safety database search using the SOC "Skin and subcutaneous tissue disorders", SOC "Musculoskeletal and connective tissue disorders", SOC "Vascular disorders" and SMQ Embolic and thrombotic events (with all Sub-SMQs). The 169 cases included 217 MedDRA PTs belonging to the search terms. Of these 217 events 188 were non-serious and 29 were serious. The most frequently reported events were skin odour abnormal (n=67; 66 non-serious, 1 serious), device occlusion (n=29; 26 non-serious, 3 serious) and rash (n=18, all non-serious).

Potential Risk	Ehlers-Danlos-like syndrome (EDS)
	The most serious events were cerebrovascular accident (n=3), device occlusion (n=3), hypotension (n=2), multiple fractures (n=2) and muscle spasms (n=2). All other serious events were reported only once. The following reports were identified which could be indicative for Ehlers-Danlos like syndrome, in most cases only one symptom was present: – 5 reports on skin striae – 2 reports on skin lesions – 1 report on nodular rash – 1 report on haemangioma of skin - possible angioma, dorsally on the right elbow – 1 report on contusion (LLT Bruising of leg) and rash papular – Several reports contained musculoskeletal events in relation to PROCYSBI treatment, however, these were isolated symptoms without e.g. involvement of skin, thus, too unspecific to diagnose Ehlers-Danlos like syndrome. – Since Ehlers-Danlos like syndrome has been associated with cerebral ischemia and marked vasculopathy all embolic and thrombotic reports were reviewed. In none of these case reports (2 reports on cerebrovascular accident, 1 report on pulmonary thrombosis, 1 report on cerebrovascular accident and multiple fractures) there was strong evidence for suspicion of Ehlers-Danlos like syndrome. The 169 case reports pertaining to this risk occurred with a frequency of 0.31 in relation to subjects (n=533) exposed to PROCYSBI.
Seriousness/outcomes	Clinical trials: The outcome of the 45 events (identified via search strategy) pertaining to the risk Ehlers-Danlos-like syndrome was reported as recovered/resolved (n=27), recovered/resolving with sequel (n=12), not recovered/not resolved (n=4), unknown (n=1) and fatal (n=1). Post-marketing: The outcome of the 217 events (identified via search strategy) pertaining to the risk Ehlers-Danlos-like syndrome was reported as fatal (n=2), not recovered/not resolved (n=38), recovered/resolved (n=38), recovering/resolving (n=24) and unknown (n=115).
Severity and nature of risk	Unknown
Background incidence/prevalence	Unknown
Risk groups or risk factors	Use of doses higher than 1.95g/m ² /day

Potential Risk	Ehlers-Danlos-like syndrome (EDS)
Potential mechanisms	Unknown
Preventability	– Warning in SmPC and PIL. – Physicians should routinely monitor the skin and bones of patients receiving cysteamine. – Self-examination of the skin by the patient or the parents should also be advised. If any similar skin or bone abnormalities appear, it is recommended to decrease the dose of cysteamine. The use of doses higher than 1.95g/m²/day is not recommended.
Impact on individual patient	Quality of life deteriorates
Potential public health impact of safety concern	Unknown
Evidence source	Clinical evidence in the literature
MedDRA terms	For Ehlers-Danlos like syndrome no pathognomic events could be identified in the scientific literature. As described in the “Direct Healthcare Professional Communication on the association of cysteamine (Cystagon) and Ehlers-Danlos like syndrome” skin biopsies were performed in few patients; histologic examinations showed abnormalities of collagen and elastin fibers as well as angioendotheliomatosis. The features of the reported cases are similar to some of the abnormalities observed in connective tissue disorders such as Ehlers-Danlos syndrome. Connective tissue disorders may affect all organ systems, but mainly the skin, the musculoskeletal and the vascular system are affected, therefore, the following SOC/SMQ are reviewed for possible cases /clusters of symptoms: – SOC Skin and subcutaneous tissue disorders – SOC Musculoskeletal and connective tissue disorders – SOC Vascular disorders – SMQ Embolic and thrombotic events (with all Sub-SMQs)

SVII.1.4 Identified and potential interactions

SVII.1.4.1 Overview of potential for interactions

As demonstrated in rats and humans, absorption of cysteamine is significantly greater at the level of the duodenum, where there is a greater density of organic cation transporter than in the rest of gastrointestinal tract.

- Eudragit L30D55 is used as enteric coating with dissolution above pH 5.5. Drugs that raise the gastrointestinal pH (anti-acid medications) may lead to an earlier release of cysteamine from PROCYSBI capsules. However, nine RP103-04 subjects who stopped using PPIs during the RP103-03 study restarted PPI therapy on a daily basis for the later study. This has not had any impact on control



of WBC cystine levels or the RP103 dose. An increase in RP103 dose would have occurred, had the PPIs impacted RP103 absorption. In fact, doses decreased over time in over half of the patients who have been taking PPIs regularly in the long-term extension study. This does not support the hypothesis of a drug interaction. Results from an interaction studies (RP103-HLTA-009 and RP103 15-001) between RP103 and omeprazole, a proton pump inhibitor, confirms the lack of impact of PPIs on cysteamine pharmacokinetics when RP103 was administered i with orange juice (an acidic drink) or with water.

- The results of *in vitro* metabolism and transporter studies showed that cysteamine bitartrate is a substrate of P-glycoprotein and that it is likely an inducer of CYP1A2 or CYP3A4, and possibly CYP2B6.

SVII.1.4.2 Important identified and potential interactions

No drug-drug interaction is considered as an important identified or potential risk.

SVII.1.5 Pharmacological class effects

Cysteamine is alone in its pharmacological class. It has been assigned ATC code A16AA04.

SVII.1.5.1 Pharmacological class risks already included as important identified or potential risks

Not applicable

SVII.1.5.2 Important pharmacological class effects not discussed above

See Table 30 below.

Table 7 Adverse reactions - listed in the Cystagon SmPC (possible relationship to cysteamine)

System Organ Class	ADR	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SmPC Cystagon,)	Comment
Investigations	Liver function tests abnormal	Not reported	Common	
Blood and lymphatic system disorders	Leukopenia	Not reported	Uncommon	
Nervous system disorders	Headache	8.9%	Common	
	Encephalopathy	Not reported	Common	
	Somnolence	Not reported	Uncommon	
	Convulsions	Not reported	Uncommon	
Gastrointestinal disorders	Vomiting	10%	Very common	
	Nausea	16.6%	Very common	
	Diarrhoea	12.2%	Very common	
	Abdominal pain	6.6%	Common	
	Breath odour	Not reported	Common	
	Dyspepsia	Not reported	Common	
	Gastroenteritis	Not reported	Common	
	Gastrointestinal ulcer	Not reported	Uncommon	
Renal and urinary disorders	Nephrotic syndrome	Not reported	Uncommon	
Skin and cutaneous tissue disorders	Skin odour abnormal	Not reported	Common	
	Rash	Not reported	Common	
	Hair colour changes	Not reported	Uncommon	
	Skin striae	Not reported	Uncommon	
	Skin fragility	Not reported	Uncommon	
Musculoskeletal and connective tissue disorders	Joint hyperextension	Not reported	Uncommon	
	Leg pain	Not reported	Uncommon	
	Genu valgum	Not reported	Uncommon	
	Osteopenia	Not reported	Uncommon	
	Compression fracture	Not reported	Uncommon	
	Scoliosis	Not reported	Uncommon	
Metabolism and nutrition disorders	Anorexia	Not reported	Very common	
	Lethargy	Not reported	Very common	
	Pyrexia	Not reported	Very common	

System Organ Class	ADR	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (SmPC Cystagon,)	Comment
General disorders and administration site conditions	Asthenia	Not reported	Common	
Immune system disorders	Anaphylactic reaction	1.1%	Uncommon	Reported in one volunteer
Psychiatric disorders	Nervousness	2.2%	Uncommon	
	Hallucination	Not reported	Uncommon	

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The list of safety concerns included in the previous version (v 7.3) of the RMP have been revised, re-evaluated and re-classified based on the definition of important identified/potential risks and missing information given in the GVP Module V (Rev.2) and contains the new classification. Following second day 180 joint CHMP and PRAC assessment report the aforementioned revised version (v 7.4) has been further revised to accommodate the Agency's request for removal of Encephalopathy and Ehlers- Danlos-like syndrome from the summary of safety concerns.

Summary of safety concerns	
Important identified risks	Leukopenia
Important potential risks	• Teratogenicity • Fibrosing colonopathy •
Missing information	• Somatostatin level reduction and associated hormonal, behavioural or cognitive consequences

The following important identified risks have been removed from the list of safety concerns as they are no longer considered as important identified risks and missing information:

Removed identified risks:

Gastrointestinal (GI) symptoms (vomiting, nausea, diarrhoea, abdominal pain).

GI symptoms are known side effects of the PROCYSBI treatment and were frequently observed in clinical trials and post marketing data. Additionally, GI related symptoms are well characterized and adequately addressed in the various product labelling such as European Union (EU) Summary of Product Characteristics (SmPC). These GI symptoms are currently being monitored via routine pharmacovigilance (PV) activities as listed in the EU RMP.

Based on the results from the company-sponsored clinical trials (cumulatively treating 165 patients, and reporting 75 events), as well as, post marketing data (cumulatively treating 835 patients, and reporting 1143 events), many of the *GI symptoms* were found to be related to various bacterial or viral infections, and/or other disorders, such as nervous system disorders, or metabolism and nutrition disorders; thus are not

considered relevant as an important risk. As for the other GI events of interest, the most frequently reported events were vomiting and diarrhoea (clinical studies) and vomiting, nausea, diarrhoea, abdominal pain upper, and abdominal discomfort (post marketing data). No new safety signals or new trends were identified in relation to the risk of GI related symptoms from clinical or post-marketing cases.

Additionally, the appropriate risk minimization measures are well known to the specialist caring for patients with nephropathic cystinosis. Moreover, these are listed events and adequately described in the SmPC. Therefore, *GI symptoms* are not considered an important identified risk and no further evaluation is needed in the PV plan. However, all reports describing *GI symptoms* will continue to be monitored through routine pharmacovigilance activities.

Removed potential risks:

Encephalopathy and Ehlers- Danlos-like syndrome currently included as important potential risks in the RMP are considered sufficiently characterized, identified and adequately listed in sections 4.4 and 4.8 of the SmPC. Therefore, these 2 safety concerns no longer meet the criteria for inclusion as important potential risks in the RMP as per GVP V rev 2.

Removed missing information:

Patients with heart disease:

Cardiac related events may occur in patients with a long-term history of uncontrolled nephropathic cystinosis, and in presence of comorbid conditions. Additionally, as noted by scientific literature it is important to lower cellular cystine levels early thus prevent future organ damage.

Events for *patients with underlying heart disease* has been rarely observed in clinical trials and uncommonly seen in post marketing setting. Progression of renal impairment is associated with compromised cardiovascular functions. There has been no evidence to suggest association between PROCYSBI and *heart disease*. The European Union (EU) Summary of Product Characteristics (SmPC) provides specific recommendation that the treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis for a proper management of this disease.

Patients with heart disease are currently being monitored via routine pharmacovigilance (PV) activities as listed in the EU RMP. No new safety signals or trends were identified in relation to the safety concern of *patients with heart disease* from clinical, post marketing cases, or scientific literature. Therefore, the MAH removed *patients with heart disease* as missing information from the EU RMP. However, all reports describing *patients with heart disease* will continue to be monitored through routine pharmacovigilance activities.

Patients with inflammatory bowel disease or resection of the small intestine:

Inflammatory Bowel Disease (IBD) may occur in patients with a long-term history of uncontrolled nephropathic cystinosis, and in presence of comorbid conditions. Additionally, as noted by scientific literature it is important to lower cellular cystine levels early thus prevent organ damage and improve quality and longevity of patients with cystinosis.

Events for *patients with inflammatory bowel disease or resection of the small intestine* have been rarely observed in clinical trials and in the post marketing setting. Additionally, there are no data to suggest that the safety profile of PROCYSBI among cystinosis patients with underlying IBD or resection of the small intestine to be different than among cystinosis patients without underlying IBD or resection of the small intestine. The European Union (EU) Summary of Product Characteristics (SmPC) listing specific

recommendation that the treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis for proper management of this disease.

Patients with inflammatory bowel disease or resection of the small intestine are currently being monitored via routine pharmacovigilance (PV) activities as listed in the European Risk Management Plan (EU RMP). Upon review of the available data, no new safety signals or new trends were identified in relation to the risk of *patients with inflammatory bowel disease or resection of the small intestine* from clinical, post marketing cases, or scientific literature. No new studies have been initiated or planned with PROCYSBI.

Additionally, appropriate risk minimizations measures are known to the specialist caring for patients with nephropathic cystinosis. There are no associated additional risk minimization measures or pharmacovigilance activities addressing this risk. Therefore, the MAH removed *patients with inflammatory bowel disease or resection of the small intestine* as missing information from the EU RMP. All reports describing *patients with inflammatory bowel disease or resection of the small intestine* will continue to be monitored through routine pharmacovigilance activities. No additional risk management/minimization activities are considered necessary for this product.

In-vivo studies lacking to confirm whether cysteamine bitartrate is an inducer of CYP1A2, CYP3A4, CYP2B6, and to characterize this effect if confirmed:

PROCYSBI is a delayed release formulation of cysteamine bitartrate and is indicated for the treatment of proven nephropathic cystinosis. The product was first approved in April 2013 in both Europe and the United States. Since the first approval until 28 February 2021, a total of 835 patients globally have been treated with PROCYSBI.

On December 2015, during the review of the European Union Risk Management Plan (EU RMP), whether cysteamine bitartrate is an inducer of VYP1A2, CYP3A4 or CYP2B6 was considered as a Missing Information and was added to the EU RMP version 6.0. If confirmed, this effect needs to be characterized. Other than Warnings and Precautions (W&P) in the EU Summary of Product Characteristics (EU SmPC) and routine pharmacovigilance activities, no additional risk mitigation measure is planned or performed to address this missing information.

Pharmacokinetic and clinical information:

No in vivo studies are planned to investigate the potential inducing properties of cysteamine bitartrate, because cysteamine bitartrate is unlikely to cause clinically relevant induction of CYP1A2, CYP3A4, or CYP2B6 based on the following two reasons.

First, the results from the in vitro induction study of cysteamine bitartrate should not be considered positive for enzyme induction (11RAPTP1). Cysteamine bitartrate did not induce the enzyme activity of CYP1A2, CYP2B6, or CYP3A4 at any tested concentration (7, 70, and 700 µM). Although cysteamine increased the mRNA levels of CYP1A2, CYP2B6, and CYP3A4 in some donors, the increase was not consistent across subjects and more importantly, the increase was not concentration-dependent (Table 1), which didn't meet the criteria of positive induction in the EMA guidance, i.e., "a more than 100% increase in mRNA and the increase is concentration dependent".

Table 1: Induction of CYP3A4/2B6/1A2 mRNA by cysteamine bitartrate

	Fold of induction relative to vehicle (solvent) control								
	CYP3A4			CYP2B6			CYP1A2		
Donor	1	2	3	1	2	3	1	2	3
Positive control	75	207	132	3.1	20	12	4.8	36	10
Cysteamine bitartrate 7 µM	1.7	3.3	4.6	2.7	0.63	1.4	2.1	4.6	1.3

Cysteamine bitartrate 70 μ M	2.4	7.0	13	0.5	1.0	1.8	2.6	7.7	1.3
Cysteamine bitartrate 700 μ M	1.4	1.0	1.8	3.6	4.7	2.5	4.8	4.5	1.6

Note: Positive control: rifampicin for CYP3A4, Phenobarbital for CYP2B6, and β -naphthoflavone for CYP1A2
Source data: Tables 13, 14, and 15 from report 11RAPTP1

Secondly, available clinical data do not indicate CYP induction by cysteamine bitartrate. To date, there has been no evidence to suggest reduced efficacy of sirolimus and tacrolimus (sensitive CYP3A4 substrates) leading to increased risk for transplant rejection in patients receiving PROCYSBI treatment.

Conclusion:

Available pharmacokinetic data would not suggest that PROCYSBI is a CYP inducer. Post-marketing experience does not raise a signal indicative of CYP induction by PROCYSBI. Therefore, the MAH removed *In-vivo studies lacking to confirm whether cysteamine bitartrate is an inducer of CYP1A2, CYP3A4, CYP2B6, and to characterize this effect if confirmed* as missing information from the EU RMP. The current product label EU SmPC and routine pharmacovigilance activities are deemed sufficient. All reports describing *Patients with inflammatory bowel disease or resection of the small intestine* will continue to be monitored through routine pharmacovigilance activities.

SVII.3 Details of important identified risks, important potential risks and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Note: Cases for evaluation of post-marketing data included reports from literature, spontaneous and solicited sources, independent of seriousness or causality. Case reports from the non-company sponsored studies were not included in this analysis.

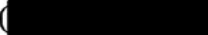
Important identified risk: Leukopenia	
Potential mechanisms	The mechanism of cysteamine-induced leukopenia is unknown. The exact mechanisms for drug-induced neutropenia or agranulocytosis are not well established. Non-immune and cell-mediated immune mechanisms are discussed depending on the culprit drugs, and host genetic traits may play a role (Tesfa et al., 2009).
Evidence source and strength of evidence	Clinical evidence in literature Post marketing data: Cumulatively, 9 relevant case reports (including 10 events, 6 serious and 4 non-serious) pertaining to this risk have been received among approximately the 809 patients exposed to PROCYSBI in the post-marketing setting. The following PTs were included: White blood cell count decreased (n=5), Leukopenia (n=3), Agranulocytosis (n=1), Pancytopenia (n=1). In 2 cases, WBC results were reported in context of PROCYSBI dosing and likely refer to WBC cystine levels, a parameter used for monitoring and dose titration in patients treated with PROCYSBI. These 2 cases are therefore not considered for this risk. Five cases were confounded by immunosuppressive therapy in the post-transplant setting.

Important identified risk: Leukopenia	
	Two remaining cases including the relevant PTs Pancytopenia and Leukopenia provided only limited information on the events and lacked details on diagnostic work-up.
Characterisation of risk	In the general population, seriousness of leucopenia depends on the severity of the reduction in WBC counts ranging from mild and asymptomatic to severe and complicated leukopenia. The risk of serious infection is known to increase as the ANC falls to the severely neutropenic range ($< 500/\mu\text{L}$). With appropriate management using pre-established procedures, with intravenous broad-spectrum antibiotic therapy and hematopoietic growth factors, the mortality rate is currently around 5% (Andr�s and Maloisel, 2008). In idiosyncratic situations the excess 1-year mortality is reported to be mostly explained by the underlying disease state (van Staa et al., 2003).
Risk factors and risk groups	Mostly transplanted patients. It should be taken into account that a high portion of nephropathic cystinosis patients develop end stage renal disease and undergo kidney transplantation, thus receive immunosuppressive agents which may be causative of bone marrow suppression and leukopenia. Of note, patients who have renal insufficiency or bacteraemia at the time of presentation have a significantly higher mortality (Julia et al., 1991)
Preventability	- Warning in SmPC and PIL (blood count monitoring) - Frequent monitoring of clinical state - Regular monitoring of blood count Of note event is unpredictable but occurs preferably in the beginning of the treatment (van Staa et al., 2003)
Impact on the risk benefit balance of the product	Increase of infection, possible fatal outcome. Increase of hospitalization, risk of hospital acquired infection.
Public health impact	Increase of hospitalization costs, costs of additional care, decrease of ability to work.
MedDRA terms	SMQ Haematopoietic leukopenia (narrow) SMQ Agranulocytosis (narrow)

Important potential risk: Teratogenicity	
Potential mechanisms	Resorptions and post-implantation losses.
Evidence source and strength of evidence	<u>Evidence source:</u> non-clinical data. <u>Strength of evidence:</u> Animal studies have shown embryo foetotoxic effects, including teratogenesis.
Characterisation of risk	<u>Clinical trials:</u> One SAE of PT Abortion spontaneous in a [REDACTED] female was received. The patient's underlying cystinosis is associated with renal impairment and may lead to End Stage Renal Disease (ESRD), requiring

Important potential risk: Teratogenicity	
	dialysis. Despite several reminders the patient did not take contraceptive measures and underwent regular dialysis. The outcomes of pregnancy in patients with ESRD on dialysis are considered to be extremely poor and maternal complications include miscarriage, premature rupture of membranes and pre-term birth (Manisco et al., 2015). With the patient's underlying illness as reasonable explanation the sponsor assessed the causality for miscarriage as not related to RP103, in line with the investigator. Excluding healthy subjects (none of the SAEs occurred in healthy subjects), 165 patients were treated with PROCYSBI (RP103) during clinical trials. Of the patients treated, 1 report of an SAE (PT Abortion spontaneous) pertaining to this risk was identified. <u>Post-marketing:</u> No ICSR on teratogenicity was received. Five case reports of PT exposure during pregnancy were received. Among these five reports, one reported pregnancy outcome as normal new-born and the remaining four were unknown. As no case report pertaining to this risk was identified, no frequency was determined.
Risk factors and risk groups	First trimester of pregnancy.
Preventability	Warnings and Precautions section in RSI and the patient medication information. The RSI advises of using contraceptive measures during PROCYSBI treatment.
Impact on the risk benefit balance of the product	Case reports received on exposure during pregnancy did not provide evidence of a teratogenic effect of PROCYSBI. No impact on the risk-benefit balance was identified.
Public health impact	Considerable.
MedDRA terms	Pregnancy and neonatal topics (SMQ broad).

Important potential risk: Fibrosing colonopathy	
Potential mechanisms	Fibrosing colonopathy has been associated with Eudragit, one of the ingredients of PROCYSBI delayed-release capsules. Reported cases of fibrosing colonopathy with Eudragit were almost exclusively limited to young aged cystic fibrosis patients, who received pancreatic enzyme supplements at extreme doses, which were beyond published recommendations for these preparations. The case control study conducted in the US reported that "the strength, coating, and manufacturer of the products used were not associated with the risk of fibrosing colonopathy", however, it cannot be excluded that high dosages of Eudragit L 30 D-55 /L 100-55 may contribute to the pathogenesis of fibrosing colonopathy. Moreover, the non-clinical studies have not been able to reproduce this pathology in animals. Fibrosing colonopathy could appear only after a long-term, chronic treatment of patients.
Evidence source and strength of evidence	<u>Evidence source:</u> scientific literature.

Important potential risk: Fibrosing colonopathy	
	Strength of evidence: Eudragit L30 D-55, the ingredient in the enteric coating of cysteamine in RP103, is a methacrylic acid polymer composed with two surfactants, sodium lauryl sulfate and polysorbate 80. Animal studies have shown that methacrylic acid induces submucosal fibrosis (van Velzen et al., 1996) and there has been, to date, a single report describing the incidence of fibrosing colonopathy in a child that was associated with the ingestion of Eudragit-coated mesalazine for the treatment of ulcerative pancolitis (Prieto et al., 2009). Since a causal link could not be conclusively ruled out for methacrylic acid in this case report, the authors advised caution for the monitoring of related events due the relatively small number of patients exposed to Eudragit-coated drugs. Although rare, a dose-dependent lipase-induced fibrosing colonopathy has been reported in young children with cystic fibrosis treated with very high doses of pancreatic enzyme replacement therapy containing Eudragit (Smyth, 1996). Because the majority (53 to 100 percent) of the children in whom fibrosing colonopathy has been observed were taking high-strength pancreatic-enzyme products, the safety of the high-strength preparations was questioned. Based on a study of 14 cases of fibrosing colonopathy in the United Kingdom, the committee concluded that the risk was associated with high-strength products. The possibility of occurrence of fibrosing colonopathy even with lower doses has not been ruled out.
Characterisation of risk	Clinical trials: No clinical case report of fibrosing colonopathy was identified in the clinical trial dataset: Three serious case reports were detected via a broader search of gastrointestinal AEs in the safety database and reviewed for potential fibrosing colonopathy. The search included AEs from the SOC Gastrointestinal disorders which appeared 1 year after starting PROCYSBI treatment and which seemed to be resistant to treatment. The 3 case reports included 3 serious AEs which belonged to the search strategy. The AEs were the PTs Constipation, Gastroenteritis and Vomiting (each n=1). None of the case reports indicated fibrosing colonopathy as cause for the events. As no case report pertaining to this risk was identified, no frequency was determined. Post-marketing: The total of 2 medically confirmed reports (1 serious and 1 non serious) with fibrosing colonopathy were retrieved from post marketing database. The serious case report () of unconfirmed fibrosing colonopathy was reported in the patient who had faecal incontinence and diarrhoea one year after introduction of PROCYSBI. The physician considered fibrosing colonopathy as cause and referred the patient to a gastroenterologist for examination. The outcome of the examination was not provided and no confirmation of fibrosing colonopathy as cause for the events was received. The outcome of the events was unknown.

Important potential risk: Fibrosing colonopathy	
	The other non-serious report [REDACTED] with event verbatim of increasing Diarrhoea/Fibrosing colonopathy was reported in a patient with history of kidney transplant who had aggravated diarrhoea that started 3 years after treatment of PROCYSBI. However, details and diagnostic work-up, as well as verification of the underlying cause of diarrhoea were not provided. The event was not resolved at the time of the latest follow-up report. A broader search of gastrointestinal AEs in the safety database was performed and reviewed for potential fibrosing colonopathy. The search included AEs from the SOC Gastrointestinal disorders which appeared 1 year after starting PROCYSBI treatment and which seemed to be resistant to treatment. The search revealed 15 additional case reports, reporting 26 PTs pertaining to SOC Gastrointestinal disorders, which were reviewed for potential fibrosing colonopathy. Of these 26 events 19 were non-serious and 7 were serious. The most frequent PTs pertaining to the GI tract were: Vomiting (n=7; 3 serious, 4 non-serious), Nausea (n=4; 1 serious, 3 non-serious), Diarrhoea (n=3, 1 serious, 2 non-serious), and Abdominal pain upper (n=3; 1 serious, 2 non-serious). No strong evidence of fibrosing colonopathy as underlying cause for these non-specific gastrointestinal symptoms was found in any of the cases. Cumulatively, 2 reports pertaining to this risk have been received among approximately the 664 patients exposed to PROCYSBI in the post-marketing setting. However, fibrosing colonopathy had not been confirmed.
Risk factors and risk groups	Use of doses higher than the maximum recommended dose of 1.95g/m ² /day; abuse; overdose.
Preventability	The European consensus recommended to remain below a dose of 10,000 IU lipase/kg body weight. The United Kingdom Committee on the Safety of Medicines has also restricted the use of high-strength pancreatic-enzyme products (MCA, 1995). The prescribed dose must be respected (the use of doses higher than 1.95g/m²/day is not recommended). Fibrosing colonopathy is listed under Warnings and Precautions section in RSI and the patient medication information. The RSI states that unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy.
Impact on the risk benefit balance of the product	No case reports of clinically confirmed fibrosing colonopathy were received. No impact on the risk-benefit balance was identified.
Public health impact	Unknown.
MedDRA terms	PT: Fibrosing colonopathy An additional analysis was performed of cases in which gastrointestinal symptoms (all PTs occurring in SOC Gastrointestinal disorders) appeared

Important potential risk: Fibrosing colonopathy	
	1 year after starting PROCYSBI treatment (i.e. onset date at least one year after start of treatment with PROCYSBI) and which seem to be resistant to treatment (i.e. GI events with outcome reported as “recovered” do not support the diagnosis of fibrosing colonopathy and were therefore excluded). For the post-marketing setting, cases were considered for further analysis if both events start date and start date of PROCYSBI treatment were provided.

SVII.3.2. Presentation of missing information

Missing information: Somatostatin level reduction and associated hormonal, behavioural or cognitive consequences	
Evidence source	Recognised as a missing information because experimental administration of delayed-release cysteamine was shown to cause depletion of somatostatin in several animal species. The relevance of these findings to humans is not known, but this phenomenon has not been observed in the clinical trials of RP103 (cysteamine bitartrate).
Anticipated risk / consequence of the missing information	The effects of somatostatin level reduction in humans are still unknown, presumably there may be hormonal, behavioural or cognitive consequences. The safety database search revealed no cases from clinical trials and post-marketing pertaining to this risk.
MedDRA terms and search terms	Database search of the case reports with verbatim of “Somatostatin” in narrative field and/or reporter’s comment field. SOC Psychiatric disorder.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Leukopenia
Important potential risks	• Teratogenicity • Fibrosing colonopathy •
Missing information	• Somatostatin level reduction and associated hormonal, behavioural or cognitive consequences

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Operating model for routine pharmacovigilance is described in the Pharmacovigilance System Master File available upon request.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include the following:

- Individual case safety report collection, evaluation, and submission to the relevant health authorities;
- Continuous surveillance of safety data as defined by the signal management process;
- Review of aggregated safety data during the production of periodic safety reports (e.g. PSUR)

Routine pharmacovigilance activities may also be described in the Pharmacovigilance System Master File as applicable.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for, Teratogenicity, Fibrosing colonopathy,

Specific follow-up questionnaires will be utilized for reports of, teratogenicity, fibrosing colonopathy, in order to better characterize these safety concerns (Annex 4).

Careful documentation of any reports will help understand whether this is a clinically significant problem and whether additional measures for prevention are needed. This will mitigate the risk and help improve patient safety. Also, it will help better understand and characterise the safety concerns and identify specific risk factors

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk minimisation measures

Table Part V.1 Description of routine risk minimisation measures by safety concern

Risk minimisation measures by safety concern

Safety concern 1 (Identified Risk): Leukopenia	
Objective(s) of the risk minimisation measures	To minimise the risk of developing leukopenia and to prevent any complications which may develop if these risk minimisation measures are not followed.
Routine risk minimisation measures	- SmPC section 4.4: Special warnings and precautions for use. - Section 2 of PI: Warning and precautions
	Other routine risk minimisation measures Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.
Additional risk minimisation measure(s)	None

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	A cumulative medical review of spontaneous reports and solicited reports for this specific purpose will be carried out quarterly. Reporting of any findings to regulatory authorities will take place as required, based on the nature and strength of the evidence and its impact on benefit risk assessment.
Criteria for judging the success of the proposed risk minimisation measures	Analysis of causal relationship of reported cases
Planned dates for assessment	Six months is deemed an adequate period to assess the impact of the risk minimisation measures.

Effectiveness of risk minimisation measures	
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The implementation of routine risk minimization measures is expected to reduce the frequency of leukopenia leading to decreased rate of acquired infections.
Comment	None.

Safety concern 2 (Potential Risk): Teratogenicity	
Objective(s) of the risk minimisation measures	To minimise the risk of teratogenicity and to prevent any complications which may develop if these risk minimisation measures are not followed.
Routine risk minimisation measures	- The SmPC section 4.3 states that PROCYSBI is contraindicated in patients who are breast-feeding. - Warning in section 4.6 of the SmPC that 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. - Recommendation in section 4.6 of the SmPC that PROCYSBI should not be used during pregnancy, particularly during the first trimester, unless clearly necessary. - Section 5.3 presents preclinical data regarding teratogenic effects.
	There is only one SmPC for this single formulation product.
	Other routine risk minimisation measures Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.
Additional risk minimisation measure(s)	None

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	A cumulative medical review of spontaneous reports and solicited reports for this specific purpose will be carried out quarterly. Reporting of

Effectiveness of risk minimisation measures	
	any findings to regulatory authorities will take place as required, based on the nature and strength of the evidence and its impact on benefit risk assessment.
Criteria for judging the success of the proposed risk minimisation measures	Do not expect to see any cases with exposure during pregnancy unless it is intentional by the patient.
Planned dates for assessment	Six months is deemed an adequate period to assess the impact of the risk minimisation measures.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

Safety concern 3 (Potential Risk): Fibrosing colonopathy	
Objective(s) of the risk minimisation measures	To minimise the possible risk of fibrosing colonopathy by following the proposed risk minimisation measures.
Routine risk minimisation measures	Warning in section 4.4 of SmPC that fibrosing colonopathy has been reported in patients with cystic fibrosis who were treated with high-dose pancreatic enzymes with an enteric coating of methacrylic acid ethyl acrylate copolymer (Eudragit), one of the excipients of PROCYSBI.
	There is only one SmPC for this single formulation product.
	Other routine risk minimisation measures - Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis. - Proactive follow-up to determine any possible cases of fibrosing colonopathy after every 6 months (Regional Appendix 1). - Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all cases of suspected fibrosing colonopathy.
Additional risk minimisation measure(s)	None

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	A cumulative medical review of spontaneous reports and solicited reports for this specific purpose will be carried out quarterly. Reporting of any findings to regulatory authorities will take place as required, based on the nature and strength of the evidence and its impact on benefit risk assessment.
Criteria for judging the success of the proposed risk minimisation measures	Patients with suspected fibrosing colonopathy are identified in very early stages of the disease.
Planned dates for assessment	Six months is deemed an adequate period to assess the impact of the risk minimisation measures.
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	None

V.2. Additional Risk Minimisation Measures

None

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Leukopenia	Routine Risk Minimization Measures: - SmPC section 4.4: Special warnings and precautions for use. - Section 2 of PIL: Warning and precautions <u>Additional Risk Minimization Measures:</u> <u>None</u>	Routine Pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - None Additional pharmacovigilance activities: - None
	•	•
Teratogenicity	Routine risk minimisation measures: Warning in section 4.4 of the SmPC that if a pregnancy is	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	diagnosed or planned, the treatment should be carefully re-considered, and the patient must be advised of the possible teratogenic risk of cysteamine - Recommendation is section 4.6 of the SmPC that PROCYSBI should not be used during pregnancy, particularly during the first trimester, unless clearly necessary. - Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis Additional risk minimisation measures - None	reactions reporting and signal detection: - follow-up form for drug exposure during pregnancy Additional pharmacovigilance activities: - None
Fibrosing colonopathy	Routine risk minimisation measures: - Warning in section 4.4. of the SmPC that FC has been reported in patients with cystic fibrosis who were treated with high-dose pancreatic enzymes with an enteric coating of methacrylic acid ethyl acrylate copolymer (Eudragit), one of the excipients of PROCYSBI. - Section 4.2 of the SmPC clearly states that PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - follow-up form for adverse reaction Additional pharmacovigilance activities: - None
Somatostatin level reduction and associated hormonal, behavioural or	Routine risk minimisation measures: - SmPC section 5.3 - Treatment under supervision of experienced physician Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None



Safety concern	Risk minimisation measures	Pharmacovigilance activities
cognitive consequences	• None	Additional pharmacovigilance activities: • None

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for PROCYSBI (cysteamine bitartrate, also called mercaptamine bitartrate)

This is a summary of the risk management plan (RMP) for PROCYSBI. The RMP details important risks of PROCYSBI, how these risks can be minimised, and how more information will be obtained about PROCYSBI's risks and uncertainties (missing information).

PROCYSBI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PROCYSBI should be used.

This summary of the RMP for PROCYSBI should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of PROCYSBI's RMP.

I. The medicine and what it is used for

PROCYSBI is authorised for the treatment of nephropathic cystinosis (see SmPC for the full indication). It contains cysteamine bitartrate (also called mercaptamine bitartrate) as the active substance and it is given by oral administration.

Further information about the evaluation of PROCYSBI's benefits can be found in PROCYSBI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <https://www.ema.europa.eu/en/medicines/human/EPAR/procysbi>: link to product's EPAR summary landing page on the EMA webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PROCYSBI, together with measures to minimise such risks and the proposed studies for learning more about PROCYSBI's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of PROCYSBI is not yet available, it is listed under 'missing information' below.

II.A. A List of important risks and missing information

Important risks of PROCYSBI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PROCYSBI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Leukopenia
Important potential risks	• Teratogenicity • Fibrosing colonopathy •
Missing information	• Somatostatin level reduction and associated hormonal, behavioural or cognitive consequences

II.B. Summary of important risks

Important identified risk: Leukopenia	
Evidence for linking the risk to the medicine	<u>Evidence source:</u> scientific literature, available data on immediate-release cysteamine, post-marketing data. <u>Strength of evidence:</u> Cumulatively, 9 relevant case reports (including 10 events, 6 serious and 4 non-serious) pertaining to this risk have been received among approximately the 809 patients exposed to PROCYSBI in the post-marketing setting. The following PTs were included: White blood cell count decreased (n=5), Leukopenia (n=3), Agranulocytosis (n=1), Pancytopenia (n=1). In 2 cases, WBC results were reported in context of PROCYSBI dosing and likely refer to WBC cystine levels, a parameter used for monitoring and dose titration in patients treated with PROCYSBI. These 2 cases are therefore not considered for this risk. Five cases were confounded by immunosuppressive therapy in the post-transplant setting.

Important identified risk: Leukopenia	
	Two remaining cases including the relevant PTs Pancytopenia and Leukopenia provided only limited information on the events and lacked details on diagnostic work-up.
Risk factors and risk groups	Mostly transplanted patients. It should be taken into account that a high portion of nephropathic cystinosis patients develop end stage renal disease and undergo kidney transplantation, thus receive immunosuppressive agents which may be causative of bone marrow suppression and leukopenia. Of note, patients who have renal insufficiency or bacteraemia at the time of presentation have a significantly higher mortality (Julia et al., 1991)
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • PL section 2 • Treatment under supervision of experienced physician Additional risk minimisation measures: • None

Important potential risk: Teratogenicity	
Evidence for linking the risk to the medicine	<u>Evidence source:</u> non-clinical data. <u>Strength of evidence:</u> Animal studies have shown embryo foetotoxic effects, including teratogenesis.
Risk factors and risk groups	First trimester of pregnancy.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3, 4.4, 4.6, 5.3 • Before starting PROCYSBI in a woman of child-bearing potential, pregnancy status should be confirmed. Patients should be advised of the potential risk to a fetus and the importance of ensuring adequate contraception while taking PROCYSBI. • PL section 2 • Treatment under supervision of experienced physician Additional risk minimisation measures: • None

Important potential risk: Fibrosing colonopathy	
Evidence for linking the risk to the medicine	<u>Evidence source:</u> scientific literature. <u>Strength of evidence:</u> Eudragit L30 D-55, the ingredient in the enteric coating of cysteamine in RP103, is a methacrylic acid polymer composed with two surfactants, sodium lauryl sulfate and polysorbate 80. Animal studies have shown that methacrylic acid

Important potential risk: Fibrosing colonopathy	
	induces submucosal fibrosis (van Velzen et al., 1996) and there has been, to date, a single report describing the incidence of fibrosing colonopathy in a child that was associated with the ingestion of Eudragit-coated mesalazine for the treatment of ulcerative pancolitis (Prieto et al., 2009). Since a causal link could not be conclusively ruled out for methacrylic acid in this case report, the authors advised caution for the monitoring of related events due the relatively small number of patients exposed to Eudragit-coated drugs. Although rare, a dose-dependent lipase-induced fibrosing colonopathy has been reported in young children with cystic fibrosis treated with very high doses of pancreatic enzyme replacement therapy containing Eudragit (Smyth, 1996). Because the majority (53 to 100 percent) of the children in whom fibrosing colonopathy has been observed were taking high-strength pancreatic-enzyme products, the safety of the high-strength preparations was questioned. On the basis of a study of 14 cases of fibrosing colonopathy in the United Kingdom, the committee concluded that the risk was associated with high-strength products. The possibility of occurrence of fibrosing colonopathy even with lower doses has not been ruled out.
Risk factors and risk groups	Use of doses higher than the maximum recommended dose of 1.95g/m ² /day; abuse; overdose.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • PL section 2 • Precaution for assessment of unusual abdominal symptoms • Treatment under supervision of experienced physician Additional risk minimisation measures: • None

Missing information: Somatostatin level reduction and associated hormonal, behavioural or cognitive consequences	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 5.3 • Treatment under supervision of experienced physician Additional risk minimisation measures: • None

II C. Post-authorisation development plan

II.C.1. Studies which are conditions of marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of PROCYSBI.

II.C.2. Other studies in post authorisation development plan

There are no studies required for PROCYSBI.

Part VII: Annexes

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Annex 4 - Specific adverse event follow-up forms

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- a. Follow-up Form for Teratogenicity
- b. Follow-up form for Fibrosing colonopathy

a. Follow-up Form for Teratogenicity

I. GENERAL INFORMATION					
☐ Marketed Product					
☐ Non Interventional Study		Protocol No.	Site No.	Subject's No.	
☐ Clinical Trial		Protocol No.	EudraCT No/ IND No. (if applicable)		
		Site No.	Subject's No.		
1. REPORT TYPE ☐ Initial ☐ Follow-up	2. COUNTRY	3. SUBJECT INITIALS (if applicable according to local rules)	4. PREGNANCY REFERRED TO ☐ Subject ☐ Subject's partner	SUBJECT SCREENED ON (if applicable) (dd/mm/yyyy)	
				SUBJECT RANDOMISED ON (if applicable) (dd/mm/yyyy)	
II. MATERNAL DATA (to be referred to pregnant subject or subject's pregnant partner as applicable)					
5. DATE OF BIRTH (dd/mm/yyyy)	7. RACE ☐ White/Caucasian ☐ Black ☐ Hispanic ☐ Native American ☐ Asian ☐ Other:	8. METHOD OF CONTRACEPTION (if required) ☐ Intrauterine system (IUS) ☐ Intrauterine device (IUD) ☐ Hormonal contraception ☐ Barrier methods ☐ Male sterilisation ☐ Other:		9. CONTRACEPTION CORRECTLY USED ☐ Yes ☐ No ☐ Not applicable	
6. AGE (yrs) (specify if other unit)	☐ Not applicable			10. PREGNANCY TEST ☐ Yes ☐ No ☐ Not applicable If Yes, specify date and test results: If No, specify reason:	
		11. DATE OF LAST MENSTRUAL PERIOD (dd/mm/yyyy)		12. EXPECTED DATE OF DELIVERY (dd/mm/yyyy)	
13. MEDICAL/SURGICAL HISTORY AND CONCOMITANT DISEASES (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy e.g. alcohol, smoking, other substance consumption, hypertension, eclampsia, diabetes including gestational, infections during pregnancy, environmental or occupational exposure that may pose a risk factor; use also section 15 if needed)					
14. PREVIOUS OBSTETRIC HISTORY (include details on all previous pregnancies, including abortion or stillbirth; use section 15 if needed)					
	Gestation week	Outcome			
1.					
2.					
3.					
4.					
15. COMMENTS					
16. DRUG INFORMATION (include therapies taken prior or during pregnancy including contraceptives and <u>excluding</u> the product(s) object of this report)					
Trade or generic name	Route	Dosage	Date of administration (dd/mm/yyyy)	Indication	Ongoing

		Dose	Unit	Frequency	From	To	
							☐
							☐
							☐
							☐
							☐
							☐

III. INFORMATION ABOUT THE PRODUCT(S) OBJECT OF THIS REPORT (Include information, if applicable, on run in and rescue medication. In case of subject's partner pregnancy, the information included in this section is to be referred to the intake of the medication by the male subject)

17. Product(s) name	Route	Dosage			Date of administration (dd/mm/yyyy)		Ongoing
		Dose	Dose Unit	Frequency	From	To	
							☐
							☐
							☐
							☐

18. Is the pregnancy caused by an interaction between the product(s) and contraceptives? ☐ Yes ☐ No

IV. PREGNANCY INFORMATION

19. PRENATAL TESTS

19.a Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?

☐ Yes | ☐ No | ☐ Unknown

19.b If yes, please specify test, test date and results:

V. INFORMATION SOURCE

20. INFORMATION ON THE REPORTER (i.e. the person who has filled in the form)

TITLE: _____ NAME: _____

ADDRESS: _____ CITY: _____ COUNTRY: _____

PHONE No. _____ FAX No. _____ e mail: _____

The undersigned declares that to best of my knowledge the information provided in this Pregnancy Report Form is accurate and correct.

Signature: _____ Date (dd/mm/yyyy): _____

VI.	PREGNANCY OUTCOME (additional information can be included in section 29)	
21. IN CASE OF DELIVERY		
21.a DELIVERY	21.b DATE OF DELIVERY (dd/mm/yyyy)	21.c MATERNAL COMPLICATIONS OR PROBLEMS RELATED TO BIRTH (if any):
☐ Normal		
☐ Forceps/Ventouse		

☐ Caesarean Section	☐ Full Term ☐ Preterm If premature newborn Gestational Age: _____ Weeks: _____
22. IN CASE OF ABORTION	
22.a ABORTION ☐ Therapeutic ☐ Voluntary (Elective) ☐ Spontaneous	22.b SPECIFY REASON AND ANY ABNORMALITY OF THE FOETUS (if known)
22.c DATE OF ABORTION (dd/mm/yyyy) At week: _____	
VII. CHILD INFORMATION (additional information can be included in section 29)	
23. NEONATE ☐ Normal ☐ Birth defect ☐ Stillbirth Specify abnormality: _____	24. SEX ☐ Male ☐ Female 25. HEAD CIRCUMFERENCE (cm) _____
26. WEIGHT (kg) _____	27. HEIGHT (cm) _____
28. APGAR SCORES 1 min: _____ 5 mins: _____ 15mins: _____	
29. FOR ADDITIONAL INFORMATION	
29.a Postnatal problems that occurred, e.g. jaundice, respiratory distress, if any	
29.b Other possible causes that could partially or entirely led to the abnormality/birth defect, if any	
29.c Additional comments	
VIII. INFORMATION SOURCE	
30. INFORMATION ON THE REPORTER (i.e. the person who has filled in the form)	
TITLE: _____ NAME: _____	
ADDRESS: _____ CITY: _____ COUNTRY: _____	
PHONE No. _____ FAX No. _____ e mail: _____	
<i>The undersigned declares that to best of my knowledge, the information provided in this Pregnancy Report Form is accurate and correct.</i>	
Signature: _____ Date (dd/mm/yyyy): _____	

b .Follow-up form for Fibrosing colonopathy

Follow up form for suspected ADR after PROCYSBI:

Questionnaire for detailed follow-up of 'possible signs suggestive of fibrosing colonopathy'

For Office use only

Patient Male ☐ Female ☐ Age at AE date _____ occurencetime _____ Hosp / ID No: _____		Adverse _____ _____ _____ Start _____ (dd/mm/yy)	
Has abdominal X-ray and ultrasound been performed? ☐ Yes ☐ No If yes when? _____ (dd/mm/yy)		If so what tests and _____ _____ _____	
Has colonoscopy with/without biopsy been performed? ☐ Yes ☐ No If yes when? _____ (dd/mm/yy)		If yes what tests and _____ _____ _____	
Is there a history of ☐ Abdominal pain ☐ abdominal distension ☐ Excessive constipation		☐ Persistent diarrhoea ☐ Bleeding per rectum ☐ Persistent vomiting	
☐ Gut surgery? if yes what type _____			
Were there any systemic manifestations? ☐ Yes ☐ No			
Please provide more information in box below if you answered Yes to any of these questions			
_____ _____ _____ _____			

Reporting ☐ doctor ☐ pharmacist ☐ other: _____ Name: _____ Address: _____ _____	Contact details (email or phone) _____ _____ _____
--	---



Postcode: _____	Signature _____	Date: _____ (dd/mm/yy)
-----------------	-----------------	------------------------

**Annex 6- Details of proposed additional risk minimisation activities (if applicable)**

Not Applicable