EU RISK MANAGEMENT PLAN

for

CYSTADROPS

(Mercaptamine hydrochloride)

RMP version to be assessed as part of this application:	Version number: 2.2
Data lock point for this RMP:	18 August 2024
Date of final sign off:	13 February 2025
Rationale for submitting an updated RMP:	Extension of indication to include patients aged from 6 months to 2 years of age
Summary of significant changes in this RMP:	Extension of indication to include patients aged from 6 months to 2 years of age and update with the termination of SCOB2 (CYT-C2-001) study Change in milestone of Study CYT-DS-001: End of data collection and frequency of study progress report updated
Other RMP versions under evaluation:	Not applicable.
Details of the currently approved RMP:	RMP Version 2.0, dated 28 March 2022.

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LIST OF ABBREVIATIONS

Abbreviation	Wording definition
ADR	Adverse Drug Reaction
ATU	Autorisation Temporaire d'Utilisation
BAK	Benzalkonium chloride
CH	Cysteamine hydrochloride
CHOC	Cysteamine hydrochloride for nephropathic cystinosis
DLP	Data lock point
EDLS	Ehlers-Danlos Like Syndrome
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
MedDRA	Medical Dictionary for Regulatory Activities
NPU	Named Patient Use
OCT-1	Adaptive dose regimen of Cystadrops for corneal crystal deposits
PASS	Post-Authorisation Safety Study
PL	Package Leaflet
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RRD	Recordati Rare Diseases
SD	Standard Deviation
SmPC	Summary of Product Characteristics

PART I: PRODUCT OVERVIEW

An overview of the product is provided in Table 1.

Table 1: Product overview

Active substance (International Non-proprietary Name or common name)	Mercaptamine hydrochloride.
Pharmacotherapeutic group (Anatomical Therapeutic Chemical Code)	Ophthalmologicals (S01XA21).
Marketing Authorisation Holder	Recordati Rare Diseases (RRD).
Medical products to which this Risk Management Plan (RMP) refers	One.
Invented name in the European Economic Area (EEA)	Cystadrops®.
Marketing authorisation procedure	Centralised.
Brief description of the product	Chemical class: Other ophthalmologicals.
	Summary of mode of action: Cystadrops acts topically by dissolving cystine crystals in the cornea. It converts cystine to cysteine and cysteine-mercaptamine mixed disulphide, both of which can pass through the lysosomal membrane without a functional carrier and are then eliminated from the cells. The continuous accumulation of free cystine in lysosomes eventually results in intracellular crystal formulation throughout the body. While oral administration of mercaptamine reduces intracellular cystine accumulation in non-corneal tissues, systemically administered mercaptamine does not reach the cornea and has consequently no effect on corneal cystine deposits.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	https://www.ema.europa.eu/en/medicines/human/EPAR/cystadrops
Indication in the EEA	Current: Treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.
	Proposed: Treatment of corneal cystine crystal deposits in adults and children from 6 months of age with cystinosis.
Dosage in the EEA	Current: Cystadrops is available as 3.8 mg/mL eye drops solution and is administered ocularly. The recommended dose is 1 drop in each eye, 4 times daily during waking hours. The recommended interval between each instillation is 4 hours. The dose can be decreased progressively (to a minimum total daily dose of 1 drop in each eye) depending on the results of ophthalmic examination (such as, corneal crystal cystine deposits, photophobia).
	Proposed: Not applicable.
Pharmaceutical form and strengths	Current: Viscous eye drops solution. Each mL of Cystadrops contains mercaptamine hydrochloride equivalent to 3.8 mg mercaptamine (cysteamine). Cystadrops is packaged in 10 mL amber glass vials filled with 5 mL of solution.
	Proposed: Not applicable.
Is the product subject to additional monitoring in the European Union (EU)?	No

EEA=European Economic Area; EU=European Union; RMP=Risk Management Plan; RRD=Recordati Rare Diseases.

PART II: SAFETY SPECIFICATION

PART II: Module SI - Epidemiology of the Indication and Target Population

SI.1 Corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis

SI.1.1 Incidence

Cystinosis is an ultra-rare (ultra-orphan) disease, with low incidence and prevalence rates globally [Langman et al, 2012; Nesterova and Gahl, 2012; Regulation (EU) No 536/2014, 2014; Richter et al, 2018]. Epidemiological studies of cystinosis are sparse, and recent data on the prevalence and incidence of the disease are limited. Incidence rates of cystinosis in various European countries and Australia are presented in Table 2 [Emma et al, 2014; Elmonem et al, 2016]. Higher incidence rates of cystinosis have been reported in selected populations around the world as a result of the extent of consanguinity within specific communities [Nesterova and Gahl, 2013; Elmonem et al, 2016].

Table 2: Incidence of cystinosis

Country	Incidence (Proportion of live births)	Reference
Australia	1:192 000	[Elmonem et al, 2016]
Denmark	1:115 000	[Elmonem et al, 2016]
France	1:167 000	[Elmonem et al, 2016]
Germany	1:179 000	[Elmonem et al, 2016]
Sweden	1:260 000	[Elmonem et al, 2016]
Selected populations	**Incidence (Proportion of live births)**	**Reference**
Saguenay-Lac-St-Jean, Quebec, Canada	1:62 500	[De Braekeleer, 1991]
Pakistani sub-population, West Midlands, United Kingdom	1:3600	[Hutchesson et al, 1998]

Data specifically reporting on the incidence of nephropathic cystinosis, as opposed to cystinosis more generally, is particularly uncommon. The estimated worldwide incidence of nephropathic cystinosis is 1 in 100 000 to 200 000 live births. Since the introduction of cysteamine therapy, the life expectancy of nephropathic cystinosis patients in developed countries has extended beyond 50 years [Nesterova and Gahl, 2013].

SI.1.2 Prevalence

The prevalence of cystinosis is extremely low, affecting only an estimated 2000 individuals worldwide [Doyle and Werner-Lin, 2015].

SI.1.3 Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Cystinosis is an inherited autosomal recessive storage disease. The adult nonnephropathic, or ocular, cystinosis is characterised by photophobia due to cystine crystal deposits in the cornea and conjunctiva; this form of cystinosis rarely presents before adulthood [Elmonem et al, 2016].

SI.1.4 The main existing treatment options

The primary treatment for cystinosis is oral cysteamine, which acts as a cystine depleting agent and can therefore address cystine accumulation in lysosomes. Treatment with cysteamine reduces progression towards kidney failure. It is more effective if initiated early, before the age of 2 years, when renal function is still intact or little affected. Life-long treatment with cysteamine allows control of renal and non-renal manifestations of the disease. However, oral cysteamine has no therapeutic effect on corneal crystal deposits because of the lack of corneal vascularisation.

In order to dissolve cystine crystals in the cornea, patients need to be treated with topical eye drops containing cysteamine. Currently, ophthalmic formulations are mainly prepared by local pharmacies at hospitals in charge of the management of cystinosis patients. Many different ophthalmic hospital formulations are available in Europe; no product is consistently used. Topical eye drop preparations include different chemical forms of cysteamine (hydrochloride or phosphate) and their concentration varies from 0.10% to 1.13% following local pharmacy practice. The posology is also variable, with the number of instillations as high as 1 every waking hour, which can lead to poor patient compliance.

In Europe, no other licensed ophthalmic formulation of cysteamine is available. In the United States, the Food and Drug Administration approved Cystaran™, a topical cysteamine ophthalmic solution (cysteamine 0.44%, corresponding to cysteamine hydrochloride [CH] 0.65%) for the treatment of corneal cystine crystal accumulation in patients with cystinosis in October 2012 [Huynh et al, 2013]. In France, the only available hospital preparation was a cysteamine hydrochloride 0.10% (CH 0.10%) solution, which was supplied by L'Agence Générale des Equipements et Produits de Santé, Assistance Publique – Hôpitaux de Paris.

SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Cystinosis is an inherited autosomal recessive storage disease characterised by defective cystinosin, the trans-membrane transport protein of cystine out of lysosomes. In cystinosis, free cystine accumulates continuously in lysosomes, eventually resulting in intracellular crystal formulation throughout the body, but tissues vary in their cellular response to this excessive storage. The corneal manifestation of cystinosis (seen by slit-lamp) is a pathognomonic clinical sign [Tsilou et al, 2007]. It is observed very early in life (as soon as 3 months) and is constant after 1 year. Corneal crystals present a myriad of needle-shaped, highly

reflective opacities which may lead to photophobia, ulcerative keratopathy and oedema of the corneal stroma.
There are 3 clinical phenotypes of cystinosis. Approximately 95% of patients have nephropathic infantile cystinosis, also known as infantile cystinosis, which is the most severe form. Children with cystinosis are normal at birth but present with severe medical problems between 6 and 12 months of age. Later-onset forms account for approximately 5% of all cases of cystinosis [Elmonem et al, 2016]. The intermediate (or late-onset) form of nephropathic cystinosis has all the clinical symptoms of infantile cystinosis, but appears in children aged 12 to 15 years. Adult-type nonnephropathic, or ocular, cystinosis is characterised by photophobia due to cystine crystal deposits in the cornea and conjunctiva; this form of cystinosis rarely presents before adulthood [Elmonem et al, 2016]. There are no associated systemic manifestations.

For the most common, severe form of cystinosis (nephropathic infantile cystinosis), the onset of the disease is marked by renal tubular damage at around 6 to 12 months of age. Unless specific cystine-depleting therapy is initiated early in life, the renal disease extends rapidly to glomerular tissue leading to end stage renal failure before the age of 10 years. However, prognosis of the disease has been dramatically improved both by cystine-depleting therapy and by renal transplantation, meaning that nephropathic cystinosis has been transformed from an exclusively paediatric disease to one affecting adults up to 50 years old. The intermediate (or late-onset) form of nephropathic cystinosis appears in children aged 12 to 15 years. Adult type non-nephropathic, or ocular, cystinosis is characterised only by cystine crystal deposits in the cornea and conjunctiva.

Unless cystine-depletion therapy by cysteamine is initiated early in life, renal glomerular damage becomes apparent by 2 to 5 years of age and results in endstage renal failure before 10 years of age. Renal transplantation and the availability of the cystine-depleting medical therapy, cysteamine, have radically altered the natural history of cystinosis. Cystinosis is a good example of a “paediatric” disease where patients now survive into adolescence and adulthood. These individuals have complex, multisystem problems that require ongoing care including corneal cystine deposits and the resulting ophthalmic complications. Corneal cystine crystal deposits lead to photophobia, ulcerative keratopathy and stroma oedema thereby affecting visual acuity.

SI.1.6 Important co-morbidities

Important co-morbidities found in the target population include the following:

- Renal impairment leading to transplant or death
- Impaired growth
- Ophthalmic cystine crystals leading to photophobia and blindness
- Thyroid problems
- Diabetes mellitus
- Gastrointestinal problems
- Liver disease
- Central nervous system problems
- Hypophosphatemic rickets

- Increased urination
- Thirst
- Dehydration
- Acidosis
- Muscle deterioration
- Inability to swallow
- Impaired sweating
- Laboratory findings: hypokalaemia, hypophosphatemia

Important concomitant medications used in the target population (for the relevant indication) are summarised in Table 3.

Table 3: Concomitant medications in the target population

Indication	Concomitant medications
Thyroid replacement therapy	Levothyroxine
Gastrointestinal symptoms	Proton pump inhibitors
Immunosuppression (after transplant)	Tacrolimus, mycophenolate, cyclosporine, sirolimus, azathioprine, prednisone
Impaired growth	Growth hormone
Blood acidosis	Sodium citrate
Hypokalaemia	Calcium supplement
Hypophosphataemia	Potassium supplement
Diabetes	Insulin, metformin

Part II: Module SII - Non-clinical Part of the Safety Specification

A summary of key non-clinical findings and their relevance to humans is outlined in Table 4.

Table 4: Key non-clinical safety findings and relevance to human use

Findings	Relevance to human usage
Toxicity:	
• **Embryo and developmental toxicity**	
The only data available relates to orally delivered cysteamine [WRC, 1966]. There were no adverse effects on reproductive performance with respect to conception and early embryonic development. However, in a development toxicity study, cysteamine was shown to be teratogenic in rats at doses equal or greater than 100 mg/kg/day [Beckman et al, 1998]. This teratogenic dose is equivalent to 0.6 g/m^2/day in the rat, which is less than half the recommended clinical maintenance dose of oral cysteamine (1.30 g/m^2/day).	When administering Cystadrops, the teratogenic risk should be considered.
Safety pharmacology:	
• **Fertility**	
The data available relates to orally delivered cysteamine. A reduction of fertility was observed in rats at 375 mg/kg/day, a dose at which body weight gain was retarded. At this dose, weight gain and survival of the offspring during lactation was also reduced. High doses of cysteamine impair the ability of lactating mothers to feed their pups. Single doses of the drug inhibit prolactin secretion in animals.	When administering Cystadrops, the fertility, teratogenic and lactation-related risks should be considered.
• **Local tolerability**	
The Iris Pharma Study O06F0106 aimed to evaluate the ocular tolerance of Cystadrops after multiple daily instillations (3, 6 and 9) for 3 months in young albino rabbits. With 3 or 6 instillations, there was slight to moderate conjunctival redness in all animals, and other conjunctival effects in some animals. A slight transient cornea and iritis reaction in 1 animal with 3 instillations. With 9 instillations, there was moderate to severe conjunctival redness in all animals, and other slight or moderate conjunctival, cornea and iritis effects in some animals. Animals were sacrificed after 2 weeks of treatment, as treatment 9 times a day was not well tolerated; 5 animals (4 males and 1 female) from this group had anomalies on their liver. The Iris Pharma Study O06F28312 compared the ocular tolerance of 2 formulations of Cystadrops for either 1 or 3 months: a former formulation, and a new formulation. The new formulation contained carboxymethylcellulose sodium at 2.43% (instead of 5.20% in the former formulation), and involved a new manufacturing process (carboxymethylcellulose sodium sterilised by ethylene oxide rather than autoclaving). Use of both formulations for 1 month induced some slight conjunctival effects, slight vascularisation of the cornea, aqueous flare for many animals and iris hyperhemia for few animals. Similar ocular effects were observed for 3 months. The severity of the ocular signs was similar between both groups over the second and third months with more animals presenting ocular signs from the new formulation group. The incidence of microscopic findings was lower in the new formulation group. For both treatments, there were fewer ocular microscopic findings after 3 months of treatment compared with after only 1 month. Two animals in the Cystadrops former formulation group presented with abnormal kidneys after 1 or 3 months of treatment. With the Cystadrops new formulation, 1 animal showed inflammation of the abdominal area and intestine which was not related to treatment. Two animals died (1 sacrificed and 1 found dead on Day 40 without abnormal clinical signs); neither of the deaths were considered related to treatment.	When administering Cystadrops, ocular and conjunctival risks should be considered.

Review of the non-clinical data for Cystadrops concluded that the risk of local reactions as well as fertility, teratogenic and lactation-related risks, should be considered when administering the product. Therefore, Section 4.6 of the Summary of Product Characteristics (SmPC) for Cystadrops notes 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. Of note, Severe eye irritation, Punctate keratopathy and/or toxic ulcerative keratopathy (due to benzalkonium chloride [BAK]), Corneal neovascularisation and Ocular manifestations of Ehlers-Danlos like syndrome (EDLS) are classified as important identified or potential risks for Cystadrops.

Part II: Module SIII - Clinical Trial Exposure

The clinical development programme for Cystadrops included 3 RRD sponsored clinical trials, with a total of 44 subjects enrolled:

- A Phase 3 study (cysteamine hydrochloride for nephropathic cystinosis [CHOC])
- A Phase 1 to 2a study (adaptive dose regimen of Cystadrops for corneal crystal deposits [OCT-1])
- A Phase 3 study (CYT-C2-001: open-label, single-arm, multicenter study to assess the safety of Cystadrops in pediatric cystinosis patients aged from 6 months to less than 2 years) [SCOB2]

A cumulative summary of subject exposure to Cystadrops from clinical trials since the Development International Birth Date of Cystadrops (29 February 2008) is presented in Table 5. A cumulative summary of subject exposure in completed trials according to age and gender is presented in Table 6 and Table 7, respectively.

Table 5: Cumulative subject exposure to Cystadrops from completed clinical trials

Study	Mercaptamine hydrochloride 0.55%	Comparator CH 0.10%	Total
OCT-1	8	Not applicable	**8**[a]
CHOC	15	17	**31**[b]
SCOB2	5	Not applicable	**5**
Total	**28**	**17**	**44**[b]

CH=cysteamine hydrochloride; CHOC=cysteamine hydrochloride for nephropathic cystinosis; OCT1=adaptive dose regimen of Cystadrops for corneal crystal deposits.[a] Subjects in the OCT-1 study acted as their own control.
[b] One patient (CH arm) was lost to follow-up after randomisation and has been excluded from the subject total.

Table 6: Cumulative subject exposure to Cystadrops from completed clinical trials by age

Age range[a]	Number of subjects
Adult	8
Children (aged 12 to 17 years)	6
Children (aged 2 to 12 years)	9
Children (aged <2 years)	5
Total	**28**

[a] Age at entry into the clinical trial.

Table 7: Cumulative subject exposure to Cystadrops from completed clinical trials by gender

Gender	Number of subjects
Male	11
Female	17
Total	**28**

Doses and duration of treatment

The dosage in the CHOC study was 1 drop in each eye 4 times a day for 90 days. The theoretical duration of treatment was between 86 and 94 days, with a dose regimen of 4 drops per day for a theoretical total of 344 to 376 instillations. The actual mean (standard deviation [SD]) duration of treatment intake was

86.3 (19.9) days and the mean number of days on treatment was 83.0 (19.1). Themean (SD) number of administered instillations was 316 (83.9).

In OCT-1, the median number of instillations per day at the start of Cystadrops treatment was 4; however, dose adjustments with progressive dose decrease were permitted up to Month 48. The mean (SD) duration of treatment with Cystadrops was 59.8 (0.21) months (range: 59.5 to 60.1 months).

The dosage in the SCOB2 study was 1 drop in each eye four times a day for 90 days. The median number of instillations per day was 4 times, and the mean (SD) overall exposure to Cystadrops was 91.6 (5.5) days.

Part II: Module SIV - Populations Not Studied in Clinical Trials

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

Important exclusion criteria in the pivotal clinical studies across the development programme are included in
Table 8.

Table 8: Exclusion criteria in pivotal clinical studies

Criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale if not
Patients who were pregnant and breast-feeding	Studies in animals have shown reproductive toxicity, including teratogenesis, following systemic administration and excretion of oral cysteamine in breast milk.	No; the recommended total daily ocular dose of cysteamine is no more than 0.4% of the highest recommended oral dose of cysteamine base (Cystagon) for the treatment of cystinosis. An effect related to the systemic absorption of cysteamine administered by the ocular route is not expected.
Patients with: • Uncontrolled hepatic disorder • Cardiovascular disease • Neurologic disease • Cancer • History or presence of alcohol abuse or drug addiction	These patients were excluded from the clinical development programme to minimise the impact of concomitant illnesses or conditions on the results gained in the clinical trials.	No; the recommended total daily ocular dose of cysteamine is no more than 0.4% of the highest recommended oral dose of cysteamine base (Cystagon) for the treatment of cystinosis. Therefore, with the reduced systemic exposure with Cystadrops, use in these patients is not considered to be clinically relevant to be considered as missing information.

SIV.2 Limitations to detect adverse drug reactions in the clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare/uncommon adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Limitations in special populations are summarised in Table 9.

Table 9: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Based on review of all available data, the safety profile in this patient population is not expected to differ from the known safety profile of Cystadrops. Therefore, use during pregnancy or breastfeeding does not constitute a safety concern. However, it is advised in 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. Cysteamine excretion in human's milk is unknown; however, due to the results of animal studies in breast-feeding mothers and neonates, women taking oral cysteamine should not breastfeed. In addition, it is noted that no data on the effect of cysteamine on human fertility are available; however, studies in animals have shown a reduction on fertility. The SmPC for Cystadrops also notes that the recommended total daily ocular dose of cysteamine is no more than approximately 0.4% of the highest recommended dose of oral cysteamine in any age group. Systemic exposure of cysteamine following ocular administration is therefore lower than following oral administration, and no effects during pregnancy and breast-feeding, or on fertility are anticipated, since systemic exposure to cysteamine is negligible. In addition, the SmPC for Cystadrops does not include any wording to indicate the need for any dose adjustment in this patient population.
Fertility	
Breastfeeding women	
Patients with ocular co-morbidities	Included in the clinical development programme; limited data were collected during RRD clinical trials for patients suffering other ocular co-morbidities. These co-morbidities included chalazion, corneal neovascularisation, ocular dryness, hordeolum and keratoplasty. Based on review of all available data, the safety profile in this patient population is not expected to differ from the known safety profile of Cystadrops. Therefore, use in patients with ocular co-morbidities does not constitute a safety concern. The SmPC for Cystadrops also does not include any wording to indicate the need for any dose adjustment in this patient population.
Patients with other relevant comorbidities: • Patients with hepatic impairment • Patients with renal 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. Based on review of all available data, the safety profile in this patient population is not expected to differ from the known safety profile of Cystadrops. Therefore, use in patients with other relevant comorbidities does not constitute a safety concern. The SmPC for Cystadrops also does not include any wording to indicate the need for any dose adjustment in this patient population.

Type of special population	Exposure
Patients >50 years of age	Included in the clinical development programme; a single patient >50 years of age (62 years) was included in the CHOC study. Based on review of all available data, the safety profile in this patient population is not expected to differ from the known safety profile of Cystadrops. Therefore, use in patients >50 years of age does not constitute a safety concern. Cystadrops is indicated for use in adults and children from 2 years of age and the SmPC for Cystadrops does not include any wording to indicate the need for any dose adjustment in this patient population.
Patients <6 months of age	Not included in the clinical development programme. The safety and efficacy of Cystadrops in children aged <6 months has not been established. No data are available; therefore, Cystadrops is not indicated for use in children <6 months of age.
Patients receiving concomitant treatment with ophthalmic products containing BAK	Not included in the clinical development programme. Based on review of all available data, the safety profile in this patient population is not expected to differ from the known safety profile of Cystadrops. Therefore, use in patients receiving concomitant treatment with ophthalmic products containing BAK does not constitute a safety concern. The SmPC for Cystadrops also does not include any wording to indicate the need for any dose adjustment in this patient population.
Population with relevant different ethnic origin	Not applicable; no ethnicities were excluded from the clinical development programme (the majority of patients are assumed to be Caucasian as data was collected in Europe).
Subpopulations carrying relevant genetic polymorphisms	Not applicable; these patients were not included in the clinical development programme and were not studied outside of the clinical development programme.

BAK=benzalkonium chloride; CHOC=cysteamine hydrochloride for nephropathic cystinosis; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.

Part II: Module SV - Post-authorisation Experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

In the Cystadrops 3.8 mg/mL eye drops solution (5 mL solution in a 10 mL amber glass bottle), each mL contains CH equivalent to 3.8 mg of cysteamine. One drop is 0.05 mL; therefore, each drop contains 0.19 mg cysteamine (3.8 mg/20). The recommended dose is 1 drop in each eye, 4 times a day during waking hours which corresponds to 8 drops/day/patient equating to 1.52 mg/day/patient (0.19 mg x 8 drops).

Taking the above information into account, the cumulative patient exposure to Cystadrops in treatment-years has been estimated below.

SV.1.2 Exposure

Cystadrops is currently licensed in 44 countries worldwide and distributed under Named Patient Use (NPU) in 24 countries worldwide. The 2 NPU programmes for Cystadrops (1 previously completed and 1 ongoing) include the following:

- A Temporary Authorisation for Use (ATU) programme for the use of Cystadrops in the treatment of corneal cystine crystal deposits in cystinosis patients (adults and children aged >2 years old), which started in September 2013. The ATU programme was completed on 23 September 2017.

- An NPU programme for the use of Cystadrops in the treatment of corneal cystine crystal deposits in patients with cystinosis, which started in October 2011.

A cumulative summary of patient exposure by age and gender (ATU programme) is presented in Table 10 and Table 11 respectively. Exposure details are unavailable for other countries.

Table 10: Cumulative patient exposure to Cystadrops by age – ATU

Age range	Number of subjects
Adult	64
Children (aged 12 to 17 years)	25
Children (aged 2 to 12 years)	41
Children (aged <2 years)	0
Total	**130**

ATU=Temporary Authorisation for Use.

Table 11: Cumulative patient exposure to Cystadrops by gender – ATU

Gender	Number of subjects
Male	64
Female	66
Total	**130**

ATU=Temporary Authorisation for Use.

In the ATU programme, the most commonly prescribed dosage at enrolment was 4 instillations per day (in approximately 65% of patients), followed by 3 instillations per day (in 22% of patients). At the follow-up visit, an overall decrease in instillation frequency was observed (4 instillations per day in 55% of patients and 3 instillations per day in 24% of patients), in accordance with the permitted dose adjustment depending on results of eye examination (as per Section 4.2 of the current SmPC).

Cumulative sales of Cystadrops from the International Birth Date up to the DLP of this RMP, including post-marketing sales data (including from post-marketing studies) and sales for the NPU programme are presented in Table 12.

Table 12: Cumulative sales of Cystadrops by region up to 18 August 2024

Region	Quantity sold
APAC	3 151
US + Canada	49 775
Europe	143 263
LAC	10 794
MENA	58 782
TOTAL	**265 765**

APAC (Asia Pacific): Brunei Dar-es-S, Hong Kong, India, Japan, Malaysia, Pakistan, Singapore, South Korea;
Europe: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Russia., Serbia, Slovakia, Spain, Sweden, Switzerland, UK;
LAC (Latin America and Caribbean): Argentina, Brazil, Colombia, Mexico, Uruguay;
MENA (Middle East North Africa): Algeria, Bahrain, Egypt, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Rwanda, Saudi Arabia, Syria, Tunisia, Turkey, United Arab Emirates;

Cumulatively, a total of 265 765 bottles of Cystadrops were sold for NPU and post-marketing use. Therefore, cumulatively, a total quantity of approximately 5 049 535 mg of cysteamine was sold (265 765 bottles x 5 mL x 3.8 mg). As 1 day of treatment with cysteamine corresponds to 1.52 mg/day/patient, cumulatively, a total of 3 322 063 patient-days (5 049 535mg/1.52 mg) and hence, 9 102 patient-years (3 322 063 days/365 days) are estimated.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for misuse for illegal purposes

No potential for misuse of Cystadrops for illegal purposes (e.g. as a recreational drug) is expected.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of safety concerns in the initial Risk Management Plan submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the Risk Management Plan

Risks that are not considered important for inclusion in the list of safety concerns are described in Table 13.

Table 13: Risks not considered important

Risk not considered important	Justification for non-inclusion in list of safety concerns
Known risks that do not impact the risk-benefit profile	
Instillation site pain	The frequency for Instillation site pain is listed as common in the SmPC and Package Leaflet (PL) for Cystadrops. Although Instillation site pain is listed as an undesirable effect in Section 4.8 of the SmPC for Cystadrops, cumulatively (up to the DLP of 30 April 2021), no adverse drug reactions (ADRs) of Instillation site pain were experienced by patients in clinical trials or have been reported from post-marketing sources. The information in the SmPC and PL is considered sufficient and therefore further characterisation and additional risk minimisation measures are not considered necessary; this risk can sufficiently be monitored through routine pharmacovigilance activities.
Instillation site discomfort	The frequency for Instillation site discomfort is listed as very common in the SmPC and PL for Cystadrops. Although Instillation site discomfort is listed as an undesirable effect in Section 4.8 of the SmPC for Cystadrops, cumulatively (up to the DLP of 30 April 2021), no ADRs of Instillation site discomfortwere experienced by patients in clinical trials. In addition, the 5 ADRs of Instillation site discomfort that have been reported from post-marketing sources (up to the DLP of 30 April 2021) were all non-serious; 2 of these ADRs resolved (ADR outcome was unknown for the remaining 3 ADRs). The information in the SmPC and PL is considered sufficient and therefore further characterisation and additional risk minimisation measures are not considered necessary; this risk can sufficiently be monitored through routine pharmacovigilance activities.

ADR=adverse drug reaction; DLP=data lock point; PL=Package Leaflet; SmPC=Summary of Product Characteristics.
Source: Post-marketing data and the SmPC and PL for Cystadrops.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the Risk Management Plan

The rationale for considering the important identified and potential risks and missing information to impact the risk-benefit balance of Cystadrops is presented in Table 14, Table 15, and Table 16, respectively.

Table 14: Justification for risk-benefit impact of important identified risks

Important identified risk	Justification for risk-benefit impact
1. Severe eye irritation	Section 4.4 of the SmPC for Cystadrops states that 'Cystadrops contains benzalkonium chloride which may cause eye irritation'. Section 4.8 of SmPC for Cystadrops also notes that Eye irritation is among the most common adverse reactions for Cystadrops. Cumulatively (up to the DLP of 30 April 2021), a total of 280 ADRs (all non-serious) pertaining to severe eye irritation have been identified from RRD's safety database. Severe eye irritation can lead to poor compliance to treatment. Therefore, it is considered that there is sufficient evidence to classify severe eye irritation as an important identified risk for Cystadrops.

ADR=adverse drug reaction; DLP=data lock point; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.
Source: NPU programmes, post-marketing data, clinical trials, a non-RRD-sponsored study and the SmPC for Cystadrops.

Table 15: Justification for risk-benefit impact of important potential risks

Important potential risk	Justification for risk-benefit impact
1. Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	Section 4.4 of the SmPC for Cystadrops states that 'Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Monitoring is required'. Cumulatively (up to the DLP of 30 April 2021), a total of 4 case reports describing 10 ADRs (9 serious, 1 non-serious) pertaining to punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) have been identified from RRD's safety database. Superficial punctate keratopathy may cause the sensation of having a foreign body in the eye, blurred vision, dry eyes, photophobia, burning sensations and watery eyes. Therefore, punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) is considered as an important potential risk for Cystadrops.
2. Corneal neovascularisation	In general, corneal neovascularisation can lead to a profound decline in vision. The abnormal vessels block light, cause corneal scarring, compromises visual acuity, and possibly leads to inflammation and oedema. Cumulatively (up to the DLP of 30 April 2021), 2 case reports describing a single serious ADR each of Corneal neovascularisation have been identified from RRD's safety database. Therefore, corneal neovascularisation is considered as an important potential risk for Cystadrops.

Important potential risk	Justification for risk-benefit impact
3. Ocular manifestations of EDLS	Tsilou et al (2002) discussed the age-related prevalence of anterior segment complications in cystinosis patients. Of 10 renal transplant recipients, a 19-year-old patient with nephropathic cystinosis had pupillary block glaucoma that was attributed to iris thickening and decreased motility. In 172 cystinosis patients, a 38-year-old woman and 29-year-old man developed a phthisical eye due to posterior synechiae and angle-closure glaucoma [Tsilou et al, 2002]. In both eyes of a 33-year-old dead patient, donated for pathology, microscopic examination disclosed retinal detachment [Tsilou et al, 2007]. Cumulatively (up to the DLP of 30 April 2021), 1 case report describing a single serious ADR pertaining to ocular manifestations of EDLS has been identified from RRD's safety database. Section 4.8 of the SmPC for Cystadrops states that ocular hyperaemia is among the most common adverse reactions in patients using Cystadrops. Also, ocular manifestations of EDLS can lead to visual impairment. Therefore, ocular manifestations of EDLS is considered as an important potential risk for Cystadrops.
4. Increased risk of infection and medication error due to device assembly failure	Ocular infection can lead to various degrees of visual impairment and, in the worst case, to vision loss. Medication error due to device assembly failure can lead to corneal cystine crystal deposits accumulation and worsening of ocular cystinosis symptoms. Cumulatively (up to the DLP of 30 April 2021), a total of 40 case reports describing 49 ADRs (3 serious, 46 non serious) pertaining to Increased risk of infection and medication error due to device assembly failure have been identified from RRD's safety database. Therefore, increased risk of infection and medication error due to device assembly failure is considered as an important potential risk for Cystadrops.

ADR=adverse drug reaction; BAK=benzalkonium chloride; DLP=data lock point; EDLS=Ehlers-Danlos like syndrome; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.
Source: NPU programmes, post-marketing data, clinical trials, a non-RRD-sponsored study and the SmPC for Cystadrops.

Table 16: Justification for risk-benefit impact of missing information

Missing information	Justification for risk-benefit impact
1. Long-term safety	There is limited information on the long-term safety of Cystadrops. Therefore, the anticipated risk of the long-term use of Cystadrops remains to be further investigated and is considered missing information. The anticipated risk of long-term use of Cystadrops will be further investigated through an open label, longitudinal postauthorisation safety study (PASS) to assess and characterise the longterm safety of Cystadrops in paediatric and adult patients with cystinosis, who were followed-up for 5 years. The countries to be included are the United Kingdom, Italy, France, the Netherlands and Germany (with an estimated inclusion of 70 patients). Data collection started in January 2020; the end of data collection is estimated to be in first quarter of 2028.

PASS=post-authorisation safety study.

SVII.2 New safety concerns and reclassification with a submission of an updated Risk Management Plan

Not applicable

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

Characterisation of the important identified risk for Cystadrops is presented in Table 17 (Severe eye irritation). Characterisation of the important potential risks is presented in Table 18 (Punctate keratopathy and/or toxic ulcerative keratopathy [due to BAK]), Table 19 (Corneal neovascularisation), Table 20 (Ocular manifestations of EDLS), and Table 21 (Increased risk of infection and medication error due to device assembly failure).

Table 17: Important identified risk – Severe eye irritation

Important identified risk	Severe eye irritation
Medical Dictionary for Regulatory Activities (MedDRA) terms	Preferred Terms (PTs): Eye pain, Vision blurred, Eye irritation, Ocular hyperaemia, Eye pruritus, Lacrimation increased, Abnormal sensation in eye, Dry eye, Foreign body sensation in eye, Eyelid oedema, Eyelid irritation, Eye swelling, Eye inflammation, Eye discharge and Swelling of eyelid.
Potential mechanisms	Three potential mechanisms have been described in the literature: • The use of BAK. Benzalkonium chloride, a cationic detergent, is suspected to be cytotoxic to corneal and conjunctival epithelial cells, goblet cells and detergent by disrupting the lipid layer of the tear film, causing tear instability and evaporation, with subsequent epithelial keratopathy and ocular dryness [Baudouin et al, 2010]. Superficial punctate keratopathy may cause burning sensations. • The natural history of the disease with extrusion of cystine crystals through breaks in Bowman's membrane was previously hypothesised to cause chronic irritation of the overlying epithelium [Tsilou et al, 2002]. • The pH of the solution; it is noted that pH falling above the pH range of tears may cause ocular discomfort and stinging [Dalton et al, 2008].
Evidence sources and strength of evidence	Clinical trials, a non-RRD-sponsored study, the NPU programmes, post-marketing data and literature. Cumulatively, a total of 502 ADRs (9 serious, 493 non-serious,) pertaining to severe eye irritation have been identified from RRD's safety database. Eye irritation is listed in the SmPC for Cystadrops. Section 4.8 of SmPC for Cystadrops states that Eye irritation is among the most common adverse reactions for Cystadrops [Cystadrops SmPC and PL, 2020].
Characterisation of the risk	Cystinosis is a rare disease with few epidemiological data. A review of the natural history of the disease was performed by Tsilou et al (2002) and Tsilou et al (2007). The author describes chronic corneal irritation as an ocular manifestation of cystinosis. The incidence of severe eye irritation is unknown. Ocular irritation is listed as an ADR in the SmPC for Cystadrops. Clinical trials

Table 17: Important identified risk – Severe eye irritation

Cumulatively, a total of 80 ADRs pertaining to severe eye irritation were reported for Cystadrops from clinical trials and were as follows:

PT	Number of ADRs	n%
Eye pain	19	76.0
Vision blurred	15	60.0
Eye irritation	15	60.0
Ocular hyperaemia	11	44.0
Eye pruritus	10	40.0
Lacrimation increased	3	12.0
Abnormal sensation in eye	2	8.0
Dry eye	1	4.0
Foreign body sensation in eye	1	4.0
Eyelid oedema	1	4.0
Eyelid irritation	1	4.0
Eye discharge	1	4.0

n: number of patients with at least 1 ADR.
PT: Preferred term

In the OCT-1 study, all ADRs were non-serious and, when reported, the outcome was resolved. In the CHOC study, all ADRs were non-serious and resolved. In SCOB2 study, all ADRs were non serious. Two (2) out of the 3 ADRs were not resolved and the remaining ADR was resolved.

The severity of the ADRs reported in clinical trials were as follows:

Severity	n
Mild	24
Moderate	17
Severe	7 (stinging, burning, blurred vision, lacrimation increased)
Unbearable	3 (burning, stinging)

n: number of patients with at least 1 ADR included in the System Organ Class "Eye disorders".

All ADRs at the time of instillations were transient and none resulted in treatment withdrawal.

Non-RRD-sponsored study
Cumulatively 2 case report describing the 4 non-serious ADRs of Eye irritation (1) and Eye discharge (2), Foreign body sensation in eyes (1) in subjects participating in the Phase 1 Mylan study were identified. All ADRs were mild in severity and resolved.

ATU programme
Cumulatively, a total of 20 case reports describing 34 ADRs pertaining to severe eye irritation with Cystadrops were identified from the ATU programme. The ADRs were as follows:

PT	Number of ADRs
Eye irritation	15
Eye pain	9
Vision blurred	4
Ocular hyperaemia	3

Table 17: Important identified risk – Severe eye irritation

Lacrimation increased	1
Dry eye	1
Eye pruritus	1

All reported ADRs were non-serious at the time of instillations. The outcomes for the ADRs were as follows: resolved (17), not resolved (10) and unknown (7). Severity was not reported for the ADRs.

Other NPU programmes

Cumulatively, a total of 7 case reports describing 12 ADRs pertaining to severe eye irritation with Cystadrops were identified from the other NPU programmes. The ADRs were as follows:

PT	Number of ADRs
Eye irritation	5
Vision blurred	2
Eye swelling	2
Abnormal sensation in the eye	1
Eye pain	1
Ocular hyperaemia	1

All reported ADRs were non-serious. The outcomes for the ADRs were as follows: resolved (8) and unknown (4). The ADR of Eye pain was noted to be severe; severity was not reported for the remaining ADRs.

Post-marketing data

Cumulatively, a total of 242 case reports describing 434 ADRs pertaining to severe eye irritation with Cystadrops were identified from post-marketing spontaneous/solicited sources. The ADRs were as follows:

PT	Number of ADRs
Eye irritation	151
Eye pain	92
Vision blurred	64
Eye discharge	30
Abnormal sensation in eye	28
Ocular hyperaemia	25
Dry eye	13
Eye pruritus	13
Foreign body sensation in eyes	4
Eye swelling	3
Lacrimation increased	3
Swelling of eyelid	3
Eyelid irritation	2
Eye inflammation	2
Eyelid oedema	1

Table 17: Important identified risk – Severe eye irritation

	Nine (9) of the reported events are serious, 425 are non-serious. The outcomes for the ADRs were as follows: resolved (140), resolving (12), recovered with sequelae (2), not resolved (132) and unknown (148). Severity was mild for 44 ADRs, moderate for 12, severe for 5 and not reported for the rest of them. *Impact on individual patient* Severe eye irritation can lead to poor compliance to treatment.
Risk groups or risk factors	Poor compliance is a risk factor for severe eye irritation.
Preventability	Monitoring is required. This recommendation is included in the SmPC for Cystadrops (Section 4.4 [Special warnings and precautions for use]) [Cystadrops SmPC and PL, 2020].
Impact on the risk-benefit balance of the product	The impact of this risk on the benefit-risk balance of Cystadrops is considered acceptable. No significant change to the risk is anticipated during post-marketing use.
Public health impact	No public health impact is anticipated for severe eye irritation associated with the use of Cystadrops.

ADR=adverse drug reaction; ATU=Temporary Authorisation for Use; BAK=benzalkonium chloride; CHOC=cysteamine hydrochloride for nephropathic cystinosis; MedDRA=Medical Dictionary for Regulatory Activities; NPU=Named Patient Use; OCT-1=adaptive dose regimen of Cystadrops for corneal crystal deposits; PL=Package Leaflet; PT=Preferred Term; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.
Source: NPU programmes, post-marketing data, clinical trials, a non-RRD-sponsored study, the SmPC for Cystadrops and literature.

Table 18: Important potential risk – Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)

Important potential risk	**Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)**
MedDRA terms	PTs: Punctate keratitis, Keratitis, Keratopathy, Ulcerative keratitis.
Potential mechanisms	Benzalkonium chloride is suspected to be cytotoxic to corneal and conjunctival epithelial cells, goblet cells and detergent by disrupting the lipid layer of the tear film, causing tear instability and evaporation, with subsequent epithelial keratopathy and ocular dryness [Baudouin et al, 2010].
Evidence sources and strength of evidence	ATU programme, non-RRD-sponsored study, post-marketing data and literature. Cumulatively, a total of 4 case reports describing 10 ADRs (9 serious, 1 non-serious) pertaining to punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) have been identified from RRD's safety database. Section 4 of the SmPC for Cystadrops states that punctuate keratopathy and/or toxic ulcerative keratopathy has been reported in patients using Cystadrops, and that monitoring is required [Cystadrops SmPC and PL, 2020].
Characterisation of the risk	Keratopathy and/or toxic ulcerative keratopathy is a known complication of cystinosis. In 172 patients with cystinosis, superficial punctate keratopathy was observed in 3% of patients aged 0 to 9.9 years, 22% of patients aged 10 to 14.9 years, and in 40% of patients older than 30 years [Tsilou et al, 2002]. Clinical trials (RRD sponsored) Cumulatively, no ADRs pertaining to punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) have been reported from clinical trials.

Table 18: Important potential risk – Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)

	Non-RRD-sponsored study Cumulatively, 5 serious ADRs of Punctate keratitis were reported in 2 subjects participating in the Phase I Mylan study. All ADRs resolved. Severity was not reported for the ADRs. The ADRs were assessed by RRD as possibly related to Cystadrops, 2 of which due to having a close temporal relationship with the product. ATU programme Cumulatively, 1 case report describing the serious ADRs of Keratitis (3) and Ulcerative keratitis (1) was reported with Cystadrops in the ATU programme. No information on the severity of ADRs was reported; therefore, it is not possible to evaluate the severity and the nature of the risk. Of the 3 ADRs of Keratitis, 2 resolved and 1 was not resolved. The outcome of Ulcerative keratitis was unknown. The ADRs were assessed by RRD as probably related to Cystadrops. Other NPU programmes Cumulatively, no ADRs pertaining to punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) have been reported form the NPU programme in other countries. Post-marketing data Cumulatively, 1 case report describing the ADR of Keratitis was identified. The ADR was non-serious and had an unknown outcome. The ADR was assessed by RRD as unrelated to Cystadrops (there was no reasonable possibility for a causal relationship; however, the reporter's causality assessment was not reported). This case reported a type of keratitis which could rather be attributed to the underlying condition of Cystinosis. Impact on individual patient Superficial punctate keratopathy may cause the sensation of having a foreign body in the eye, blurred vision, dry eyes, photophobia, burning sensations and watery eyes.
Risk groups or risk factors	Age is a risk factor, with increased incidence of superficial punctate keratopathy reported in older cystinosis patients. It is suggested that superficial punctate keratopathy develops due to breaks in a thinned Bowman's membrane in combination with the deposition of cystine crystals. Consequently, it can be assumed that untreated patients might be at increased risk of developing superficial punctate keratopathy [Tsilou et al, 2002].
Preventability	Monitoring is required (corneal staining). This recommendation is included in the SmPC for Cystadrops (Section 4.4 [Special warnings and precautions for use]) [Cystadrops SmPC and PL, 2020].
Impact on the risk benefit balance of the product	The impact of this risk on the benefit-risk balance of Cystadrops is considered acceptable. No significant change to the risk is anticipated during post-marketing use.

Table 18: Important potential risk – Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)

Public health impact	No public health impact is anticipated for punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) associated with the use of Cystadrops.

ADR=adverse drug reaction; ATU=Temporary Authorisation for Use; BAK=benzalkonium chloride; MedDRA=Medical Dictionary for Regulatory Activities; NPU=Named Patient Use; PL=Package Leaflet; PT=Preferred Term; RRD=Recordati Rare Disease; SmPC=Summary of Product Characteristics.
Source: ATU programme, a non-RRD-sponsored study, post-marketing data, the SmPC for Cystadrops and literature.

Table 19: Important potential risk – Corneal neovascularisation

Important potential risk	**Corneal neovascularisation**
MedDRA terms	PT: Corneal neovascularisation.
Potential mechanisms	The extrusion of cystine crystals through breaks in the Bowman's membrane was previously hypothesised to cause chronic irritation of the overlying epithelium. This chronic corneal irritation in association with dry eyes in cystinosis could be the mechanism behind the band keratopathy and peripheral corneal neovascularisation [Tsilou et al, 2002].
Evidence sources and strength of evidence	Clinical trials, post-marketing data and literature. Cumulatively, 7 case reports all describing a single serious ADR of Corneal neovascularisation have been identified from RRD's safety database.
Characterisation of the risk	Of 172 patients with cystinosis followed up at the National Institute of Health between 1976 and 2000, peripheral corneal neovascularisation was observed in 5% of patients aged 15 to 19.9 years, and in 53% in patients older than 30 years [Tsilou et al, 2002]. <u>Clinical trials</u> Cumulatively, 1 case report describing the ADR of Corneal neovascularisation was received from the OCT-1 trial. The ADR was serious and moderate in severity; ADR outcome was not resolved. The ADR was assessed by RRD as possibly related. Corneal neovascularisation is a known complication of cystinosis; therefore, the causal role of Cystadrops in this ADR cannot be established with certainty. A 95% confidence interval also cannot be calculated. <u>NPU programmes (ATU programme and other NPU programmes)</u> Cumulatively, no ADRs pertaining to corneal neovascularisation have been reported from the NPU/ATU programmes. <u>Post-marketing data</u> Cumulatively, 6 case reports describing serious events of corneal neovascularisation were identified, including 4 created retrospectively from the medical history of the patients included in CYT-DS-001 PASS. The events of corneal neovascularization were assessed by RRD as possible/reasonably possible to Cystadrops in two cases and unassessable in the remaining four cases due to insufficient information. Of these six cases, two patients received less than recommended dose which can have contributed to the development of a corneal neovascularization due to the underlying cystinosis. <u>Impact on individual patient</u> In general, corneal neovascularisation can lead to a profound decline in vision. The abnormal vessels block light, cause corneal scarring,

Table 19: Important potential risk – Corneal neovascularisation

	compromises visual acuity, and possibly leads to inflammation and oedema.
Risk groups or risk factors	Age is a risk factor, with peripheral corneal neovascularisation reported in just over half of cystinosis patients older than 30 years [Tsilou et al, 2002]. As the suggested mechanism behind the development of peripheral corneal neovascularisation is chronic corneal irritation by cystine crystals (subsequently triggering the release of neovascular or ischemic factors leading to neovascularisation), it can be assumed that untreated patients might have higher probability for development of peripheral corneal neovascularisation.
Preventability	Based on the suggested mechanism of peripheral corneal neovascularisation development and knowing that topical cysteamine can delay and even reduce the deposition of crystals in the cornea, it can be assumed that treatment with topical cysteamine contribute to delay or even prevent this ocular complication. Monitoring should be implemented.
Impact on the risk-benefit balance of the product	The impact of this risk on the benefit-risk balance of Cystadrops is considered acceptable. No significant change to the risk is anticipated during post-marketing use.
Public health impact	No public health impact is anticipated for corneal neovascularisation associated with the use of Cystadrops.

ADR=adverse drug reaction; ATU=Temporary Authorisation for Use; MedDRA=Medical Dictionary for Regulatory Activities; NPU=Named Patient Use; OCT-1=Adaptive dose regimen of Cystadrops for corneal crystal deposits; PT=Preferred Term; RRD=Recordati Rare Diseases.
Source: Clinical trials, post-marketing data and literature.

Table 20: Important potential risk – Ocular manifestations of EDLS

Important potential risk	**Ocular manifestations of EDLS**
MedDRA terms	High Level Term: Glaucomas (excl congenital). PTs: Corneal hypertrophy, Corneal diameter increased, Lens dislocation, Keratoconus, Corneal diameter decreased, Myopia, Pathologic myopia, Impaired healing, Retinal detachment, Scleral discolouration.
Potential mechanisms	According to Besouw et al (2011), copper deficiency can cause decreased activity of lysyl oxidase, the enzyme that generates the aldehydes required for collagen cross-linking. Thus, copper supplementation might prevent oral cysteamine interference with collagen cross-linking and resulting in disorders similar to that of EDLS [Besouw et al, 2013].
Evidence sources and strength of evidence	Literature and post-marketing data. Cumulatively, 5 case report describing 5 ADR pertaining to ocular manifestations of EDLS have been identified from RRD's safety database.
Characterisation of the risk	Tsilou et al (2002) discussed the age-related prevalence of anterior segment complications in cystinosis patients. Of 10 renal transplant recipients, a 19-year-old patient with nephropathic cystinosis had pupillary block glaucoma that was attributed to iris thickening and decreased motility. In 172 cystinosis patients, a 38-year-old woman and 29-year-old man developed a phthisical eye due to posterior synechiae and angle-closure glaucoma [Tsilou et al, 2002]. In both eyes of a 33-year-old dead patient, donated for pathology, microscopic examination disclosed retinal detachment [Tsilou et al, 2007]. Clinical trials

Table 20: Important potential risk – Ocular manifestations of EDLS

	Cumulatively, no ADRs pertaining to ocular manifestations of EDLS have been reported in clinical trials. NPU programmes (ATU and in other countries) Cumulatively, no ADRs pertaining to ocular manifestations of EDLS have been reported from the NPU/ATU programmes. Post-marketing data Cumulatively, 5 cases describing the following 5 events pertaining to ocular manifestations of EDLS were retrieved: impaired healing, Glaucoma, Angle closure glaucoma, Retinal detachment and Scleral discolouration (n=1 each). All events were serious, except one. The outcomes were recovering (n=1), not recovered (n=2), and unknown for the remaining events. However, none of these events were assessed as suggestive of ocular manifestation of EDLS following Cystadrops therapy Impact on individual patient The following specific symptoms are considered to be important: megalocornea/glaucoma, ectopia lentis, unusual myopia worsening, confirmed keratoconus, microcornea, impaired corneal wound healing, retinal detachment and blue sclera. Ocular manifestations of EDLS can lead to visual impairment.
Risk groups or risk factors	No ocular manifestations of EDLS were reported with cysteamine eye drop solution. A small subset of 6 cystinosis patients reported oral cysteamine toxicity with a suspicion of potential interference between cross-linking of collagen fibres. These patients also demonstrated copper deficiency (a potential risk factor) [Besouw et al, 2011].
Preventability	Monitoring is required.
Impact on the risk-benefit balance of the product	The impact of this risk on the benefit-risk balance of Cystadrops is considered acceptable. No significant change to the risk is anticipated during post-marketing use.
Public health impact	No public health impact is anticipated for ocular manifestations of EDLS associated with the use of Cystadrops.

ADR=adverse drug reaction; EDLS=Ehlers-Danlos like syndrome; MedDRA=Medical Dictionary for Regulatory Activities; NPU=Named Patient Use; PL=Package Leaflet; PT=Preferred Term; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.
Source: Literature, post-marketing data and SmPC for Cystadrops.

Table 21: Important potential risk – Increased risk of infection and medication error due to device assembly failure

Important potential risk	**Increased risk of infection and medication error due to device assembly failure**
MedDRA terms	The methodology and the MedDRA terms search for this important potential risk were revised to present the data with more consistency. The objective of this evaluation is to evidence any case of device assembly failure/issue where an infection and/or a medication error (e.g., missed doses) might have occurred.

Table 21: Important potential risk – Increased risk of infection and medication error due to device assembly failure

	First, a search on cases where the following MedDRA PTs were reported was done: Device failure, Device issue, Device material issue, Intentional device misuse, Device use error, Device difficulty to use, Underdose, Circumstance or information capable of leading to medication error, Device fastener issue, Treatment noncompliance, Product administration error, and Inappropriate schedule of product administration. The PT "medication error" was removed and replaced by the narrow SMQ of medication errors as described below. The PT "intentional device misuse" was added. Then, to prevent any loss of cases of interest where the above PTs were not used, all cases belonging to the following extended search criteria were reviewed to identify any possible device assembly failure: - Cases reporting ocular events: High-Level Group Term (HLGT) of Ocular infections, irritations, and inflammations, and the HLT of Eye and Eyelid infections - Cases belonging to the narrow SMQ of medication errors Only cases suspected of being related to device assembly failure were considered in this section. Consequently, all cases and adverse events that were not in relation to any device assembly issue were deleted, as not deemed relevant for the evaluation of this potential risk.
Potential mechanisms	The vial and the dropper must be assembled by the patient. During this process, Cystadrops is in contact with air and can be contaminated by particles. Cystadrops can also be in contact with the hands of the patient which can lead to microbiological contamination of the product and then to eye infection. If the patient fails to assemble the vial and the dropper, they won't be able to take the drops, which can lead to medication error (e.g. missed doses).
Evidence sources and strength of evidence	The NPU programmes, a non-RRD-sponsored study, post-marketing data from the global safety database, clinical trials and literature. Cumulatively, there is no cases reporting device assembly failure, whether associated to an infection or a medication error or not.
Characterisation of the risk	Neither ocular infection in cystinosis patients, nor medication error of Cystadrops has been previously reported in the literature. Information on whether these ADRs described below were due to device assembly failure was not provided. <u>Clinical trials</u> Cumulatively, no events pertaining to increased risk of infection and medication error due to device assembly failure have been reported in clinical trials. <u>Non-RRD-sponsored study</u> Cumulatively, no events pertaining to increased risk of infection and medication error due to device assembly failure have been reported in non-RRD-sponsored study. <u>ATU programme</u> Cumulatively, a total of 10 case reports describing 13 events pertaining to the PTs mentioned above were retrieved. The adverse events were as

Table 21: Important potential risk – Increased risk of infection and medication error due to device assembly failure

follows:

PT	Number of events
Treatment noncompliance	8
Underdose	5

None of these cases reported an issue with the device assembly but rather noncompliance in terms of frequency of administration, leading sometimes to underdose.

NPU programme – other countries
Cumulatively, no adverse events pertaining to increased risk of infection and medication error due to device assembly failure have been reported in other NPU programmes.

Post-marketing data
Cumulatively, a total of 41 case reports describing 47 events pertaining to the specific PTs mentioned above were identified from post-marketing spontaneous/solicited sources. The adverse events were as follows:

PT	Number of events
Treatment noncompliance	26
Inappropriate schedule of product administration	4
Device difficult to use	3
Product administration error	3
Underdose	10
Circumstance or information capable of leading to medication error	1

None of these cases reported an issue with the assembly of the vial and the dropper but rather noncompliance and errors in terms of frequency of administration of the product, sometimes leading to underdose, or issues with the availability of the drug or difficulty to use the product in relation to its glueyness and stickiness. The circumstance capable of leading to an error was the administration of the drug in the freezer.

In addition, a total of 223 cases of ocular events and 27 cases pertaining to the SMQ medication errors were reviewed cumulatively. No cases suspected of being related to device assembly failure were retrieved.

No evidence of treatment-emergent adverse events which could be taken as indicative of infection or medication errors due to device assembly failure was reported with Cystadrops from clinical trials, NPU programmes, post-marketing use or literature.

Impact on individual patient
Ocular infection can lead to various degrees of visual impairment and, in the worst case, to vision loss. Medication error due to device assembly failure can lead to corneal cystine crystal deposits accumulation and

Table 21: Important potential risk – Increased risk of infection and medication error due to device assembly failure

	worsening of ocular cystinosis symptoms.
Risk groups or risk factors	The container closure system consisting of a glass vial and a separate dropper applicator is not optimal from a microbiological and user-friendly view which consequently may lead to a risk of contamination (increased risk of infection) and medication errors. Patients with impaired vision might have some difficulties in assembling the vial and the dropper.
Preventability	Information regarding the user instructions on assembling the device and warning the users about potential microbiological contamination has been included in the [Cystadrops SmPC and PL, 2020].
Impact on the risk-benefit balance of the product	The impact of this risk on the benefit-risk balance of Cystadrops is considered acceptable. No significant change to the risk is anticipated during post-marketing use.
Public health impact	No public health impact is anticipated for increased risk of infection and medication error due to device assembly failure associated with the use of Cystadrops.

ADR=adverse drug reaction; ATU=Temporary Authorisation for Use; MedDRA=Medical Dictionary for Regulatory Activities; NPU=Named Patient Use; OCT-1=adaptive dose regimen of Cystadrops for corneal crystal deposits; PL=Package Leaflet; PT=Preferred Term; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.
Note: The search criteria for this risk were updated to exclude some PTs that are covered by other safety concerns for Cystadrops; therefore, this table has been carefully reviewed and updated in line with this search criteria.
Source: NPU programmes, post-marketing data, clinical trials, a non-RRD-sponsored study, the SmPC for Cystadrops and literature.

SVII.3.2 Presentation of the missing information

Missing information that is considered a safety concern for Cystadrops is described in Table 22 (Missing information – Long-term safety).

Table 22: Missing information – Long-term safety

Missing information	**Long-term safety**
Evidence source	There is limited information on the long-term safety of Cystadrops.
Anticipated risk/consequence of the missing information	The anticipated risk of long-term use of Cystadrops will be further investigated through an open label, longitudinal PASS to assess and characterise the longterm safety of Cystadrops in paediatric and adult patients with cystinosis, who were followed-up for 5 years. The countries to be included are the United Kingdom, Italy, France, the Netherlands and Germany (with an estimated inclusion of 70 patients). Data collection started in January 2020; the end of data collection is estimated to be in first quarter of 2028.

PASS=post-authorisation safety study.

Part II: Module SVIII - Summary of the Safety Concerns

A summary of the safety concerns for Cystadrops is presented in Table 23.

Table 23: Summary of safety concerns

Important identified risks	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to benzalkonium chloride) • Corneal neovascularisation • Ocular manifestations of EDLS • Increased risk of infection and medication error due to device assembly failure
Missing information	• Long term safety

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are considered warranted.

III.2 Additional Pharmacovigilance Activities

Details of the ongoing PASS (Study CYT-DS-001) are presented below.

Study title:
Open-label, longitudinal, post-authorisation safety study to assess the safety of Cystadrops® in paediatric and adult cystinosis patients in long-term use.

Rationale and study objectives:
The objective of this study is to assess and characterise the long-term safety of Cystadrops in paediatric and adult patients with cystinosis, who were followed-up for 5 years. This study has also been designed to collect quality of life data and to assess the benefit of Cystadrops by measuring photophobia and using other ophthalmologic assessments (e.g. corneal cystine crystal score, best corrected visual acuity and crystal thickness).

Study design:
The PASS is a single-arm, open-label, longitudinal, non-interventional multicentre study.

Study sites for the PASS are located in the following countries: France, Germany, Italy and the Netherlands.

Study population:
The study is to include paediatric (≥2 years of age) and adult patients with medically-confirmed cystinosis (there is an estimated inclusion of 70 patients). Patients or their parents/legal guardian also needed to provide evidence of a personally signed and dated informed consent document indicating that the patient or the parent/legal guardian has been informed of all pertinent aspects of the study. Additionally, the patients/parents/legal guardian needed to be willing to comply with regular visits and ophthalmic routine exams.

Patients with contraindications to any of the Cystadrops components, or whom had any medical condition that would interfere with the evaluation of the study objectives, or participated (or were to also participate) in another ophthalmic investigational study were excluded.

Milestones:
Milestones for the PASS are summarised in Table 24.

Table 24: PASS milestones

Milestone	Planned date
Ethics submission	November 2018.
Start of data collection	January 2020.
End of enrolment	December 2021
End of data collection	March 2028.
Study Progress Report	Every 2 years.
Final Report of study results	Approximately <1 year after database lock.

PASS=post-authorisation safety study.

III.3 Summary Table of Additional Pharmacovigilance Activities

Ongoing and additional pharmacovigilance activities are summarised in Table 25.

Table 25: Ongoing and planned additional pharmacovigilance activities

Study title Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Study CYT-DS-001 Open-label, longitudinal post-authorisation safety study to assess safety of Cystadrops® in paediatric and adult cystinosis patients in long-term use. Ongoing	To assess and characterise the long-term safety of Cystadrops in paediatric and adult patients with cystinosis, who were followed-up for 5 years.	• Severe eye irritation • Punctate keratopathy and /or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestation of EDLS • Increased risk of infection and medication error due to device assembly failure • Long-term safety	Ethics submission.	November 2018.
			Start of data collection.	January 2020.
			End of enrolment.	December 2021.
			End of data collection.	March 2028
			Study Progress Report.	Every 2 years
			Final Report of study results.	Approximately <1 year after database lock.

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No imposed post-authorisation efficacy studies are planned for Cystadrops.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Routine risk minimisation measures for Cystadrops are summarised in Table 26.

Table 26: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risk	
Severe eye irritation	Routine risk communication: SmPC Section 4.4 and 4.8. PL Section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 2 of the PL for Cystadrops recommends speaking to a doctor if abnormal eye sensation, stinging or pain in the eye occurs. Section 3 of the PL advises that patients remove excess medicine around the eye with a moist tissue to avoid potential irritation. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.
Important potential risk	
Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	Routine risk communication: SmPC Section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: As BAK has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, Section 4.4 of the SmPC notes that monitoring is required. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.
Corneal neovascularisation	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.

Safety concern	Routine risk minimisation measures
Ocular manifestations of EDLS	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.
Increased risk of infection and medication error due to device assembly	Routine risk communication: SmPC Section 6.6. PL Section 3. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 6.6 of the SmPC and Section 3 of the PL include notes on how to use Cystadrops and advise that patients wash their hands carefully in order to avoid microbiological contamination of the content in the vial. Additionally, for minimisation of medication errors, Section 3 of the PL includes a QR code linked to a video advising how to use Cystadrops. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.
Missing information	
Long-term safety	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

The routine risk minimisation measures described in Section V.1 are considered sufficient to manage the safety concerns of Cystadrops.

V.3 Summary Table of Risk Minimisation Measures

A summary of the risk minimisation measures for Cystadrops are summarised in Table 27.

Table 27: Description of routine risk minimisation measures by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Severe eye irritation	Routine risk minimisation measures: SmPC Section 4.4 and 4.8. PL Section 2 and 4. Section 2 of the PL for Cystadrops recommends speaking to a doctor if abnormal eye sensation, stinging or pain in the eye occurs. Section 3 of the PL advises that patients remove excess medicine around the eye with a moist tissue to avoid potential irritation. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).
Important potential risks		
Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	Routine risk minimisation measures: SmPC Section 4.4. As BAK has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, Section 4.4 of the SmPC notes that monitoring is required. Legal status: Subject to restricted medical prescription on. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Corneal neovascularisation	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription . Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).
Ocular manifestations of EDLS	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).
Increased risk of infection and medication error due to device assembly failure	Routine risk minimisation measures: SmPC Section 6.6. PL Section 3. Section 6.6 of the SmPC and Section 3 of the PL include notes on how to use Cystadrops and advise that patients wash their hands carefully in order to avoid microbiological contamination of the content in the vial. Section 3 of the PL also includes a QR code linked to a video advising how to use Cystadrops. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Long-term safety	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS (Study CYT-DS-001).

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome; PASS=post-authorisation safety study; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of the Risk Management Plan for Cystadrops (mercaptamine hydrochloride)

This is a summary of the Risk Management Plan (RMP) for Cystadrops. The RMP details important risks of Cystadrops, how these risks can be minimised, and how more information will be obtained about Cystadrops' risks and uncertainties (missing information).

Cystadrops' Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Cystadrops should be used.

This summary of the RMP for Cystadrops should be read in the context of all this information including the assessment report of the evaluation and its plainlanguage summary, all which is part of the European Public Assessment Report.

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

VI.1 The Medicine and What it is Used For

Cystadrops is authorised for Corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis (see SmPC for the full indication). It contains mercaptamine hydrochloride as the active substance and it is administered ocularly.

Further information about the evaluation of Cystadrops' benefits can be found in Cystadrops' European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/cystadrops.

VI.2 Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cystadrops, together with measures to minimise such risks and the proposed studies for learning more about Cystadrops' 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 PL 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.

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

VI.2.1 List of important risks and missing information

Important risks of Cystadrops are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Cystadrops. 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	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to benzalkonium chloride) • Corneal neovascularisation • Ocular manifestations of EDLS • Increased risk of infection and medication error due to device assembly failure
Missing information	• Long term safety

BAK=benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.

VI.2.2 Summary of important risks

Summaries of the important risks and missing information for Cystadrops are provided in the following tables.

Important identified risk of severe eye irritation	
Evidence for linking the risk to the medicine	Clinical trials, a non-Recordati Rare Diseases (RRD)-sponsored study, the Named Patient Use (NPU) programmes, post-marketing data and literature. Eye irritation is listed in the SmPC for Cystadrops. Section 4.8 of SmPC for Cystadrops states that Eye irritation is among the most common adverse reactions for Cystadrops.
Risk factors and risk groups	Poor compliance is a risk factor for severe eye irritation.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and 4.8. PL Section 2 and 4. Section 2 of the PL for Cystadrops recommends speaking to a doctor if abnormal eye sensation, stinging or pain in the eye occurs. Section 3 of the PL advises that patients remove excess medicine around the eye with a moist tissue to avoid potential irritation. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.

	Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety study (Study CYT-DS-001).

NPU=Named Patient Use; PL=Package Leaflet; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.

Important potential risk of punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK)	
Evidence for linking the risk to the medicine	The Temporary Authorisation for Use programme, a non-RRD-sponsored study, post-marketing data and literature. Section 4 of the SmPC for Cystadrops states that punctuate keratopathy and/or Toxic ulcerative keratopathy has been reported in patients using Cystadrops, and that monitoring is required.
Risk factors and risk groups	Age is a risk factor, with increased incidence of superficial punctate keratopathy reported in older cystinosis patients. It is suggested that superficial punctate keratopathy develops due to breaks in a thinned Bowman's membrane in combination with the deposition of cystine crystals. Consequently, it can be assumed that untreated patients might be at increased risk of developing superficial punctate keratopathy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. As BAK has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, Section 4.4 of the SmPC notes that monitoring is required. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety study (Study CYT-DS-001).

BAK=benzalkonium chloride; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.

Important potential risk of corneal neovascularisation	
Evidence for linking the risk to the medicine	Clinical trials, post-marketing data and literature.
Risk factors and risk groups	Age is a risk factor, with peripheral corneal neovascularisation reported in just over half of cystinosis patients older than 30 years. As the suggested mechanism behind the development of peripheral corneal neovascularisation is chronic corneal irritation by cystine crystals (subsequently triggering the release of neovascular or ischemic factors leading to neovascularisation), it can be assumed that untreated patients might have higher probability for development of peripheral corneal neovascularisation.
Risk minimisation measures	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis.

	Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety study (Study CYT-DS-001).

Important potential risk of ocular manifestations of EDLS	
Evidence for linking the risk to the medicine	Literature and post-marketing data.
Risk factors and risk groups	No ocular manifestations of EDLS were reported with cysteamine eye drop solution. A small subset of 6 cystinosis patients reported oral cysteamine toxicity with a suspicion of potential interference between cross-linking of collagen fibres. These patients also demonstrated copper deficiency (a potential risk factor).
Risk minimisation measures	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety study (Study CYT-DS-001).

EDLS=Ehlers-Danlos like syndrome; SmPC=Summary of Product Characteristics.

Important potential risk of increased risk of infection and medication error due to device assembly	
Evidence for linking the risk to the medicine	The NPU programmes, a non-RRD-sponsored study, post-marketing data, clinical trials and literature.
Risk factors and risk groups	The container closure system consisting of a glass vial and a separate dropper applicator is not optimal from a microbiological and user-friendly view which consequently may lead to a risk of contamination (increased risk of infection) and medication errors. Patients with impaired vision might have some difficulties in assembling the vial and the dropper.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 6.6. PL Section 3. Section 6.6 of the SmPC and Section 3 of the PL include notes on how to use Cystadrops and advise that patients wash their hands carefully in order to avoid microbiological contamination of the content in the vial. Section 3 of the PL also includes a QR code linked to a video advising how to use Cystadrops. Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety study (Study CYT-DS-001).

NPU=Named Patient Use; PL=Package Leaflet; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.

Missing information of long-term safety	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Treatment should be supervised by a physician experienced in the management of cystinosis. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-authorisation safety study (Study CYT-DS-001).

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

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

VI.2.3.2 Other studies in post-authorisation development plan

Study CYT-DS-001

Purpose of the study: The objective of this post-authorisation safety study is to assess and characterise the long-term safety of Cystadrops in paediatric and adult patients with cystinosis, who were followed up for 5 years. This study has also been designed to collect quality of life data and to assess the benefit of Cystadrops by measuring photophobia and using other ophthalmologic assessments (e.g. corneal cystine crystal score, best visual acuity and crystal thickness).

PART VII : ANNEXES

Annex 4 Specific adverse drug reaction follow-up forms

Annex 6 Details of proposed additional risk minimization activities (if applicable)

Annex 4 Specific adverse drug reaction follow-up forms

Not applicable.

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

Not applicable.