1 April 2016
EMA/277124/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dropcys

International non-proprietary name: mercaptamine

Procedure No. EMEA/H/C/004038/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AGEPS:	Central pharmaceutical service of AP-HP (*Assistance Publique – Hôpitaux de Paris*),
ANSM:	Agence nationale de sécurité du médicament et des produits de santé (French Regulatory Agency)
BAK:	benzalkonium chloride
CCCS:	corneal cystine crystal score
cGMP:	cyclic Guanosine Monophosphate
CHMP:	Committee for Medicinal Products for Human Use
CM:	Confocal Microscopy
CVI:	Crystal Volume Index
EMA:	European Medicines Agency
ERA:	Environmental Risk Assessment
GLP:	Good Laboratory Practice
ICH:	International Conference on Harmonisation
IND:	Investigational New Drug
LADR:	Local Adverse Drug Reaction
mg:	milligram
mM:	millimola
NIH:	National Institute of Health
NOAEL:	No-Observed-Adverse-Effect Level
NOEL:	No-Observed-Effect Level
PEC:	Predicted Environmental Concentration
SmPC:	Summary of Product Characteristics
USA:	United States of America

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lucane Pharma submitted on 5 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Dropcys, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

Dropcys, was designated as an orphan medicinal product EU/3/14/1341 on 15 October 2014. Dropcys was designated as an orphan medicinal product in the following indication: Treatment of cystinosis.

The applicant applied for the following indication: prevention and treatment of corneal cystine deposits in patients with cystinosis receiving oral cysteamine therapy. Dropcys should be used from the time of cystinosis diagnosis.

The legal basis for this application refers to:

Article 10a of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by scientific literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 5 November 2014.
- The procedure started on 26 November 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015 (Annex 2).
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 March 2015 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 August 2015 (Annex 4).
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 October 2015.
- During the CHMP meeting on 18 November 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 17 December 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Dropcys.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: David Lyons Co-Rapporteur: Greg Markey

- The applicant submitted written notice to the EMA on 23 December 2015 to request a re-examination of Dropcys CHMP opinion of 17 December 2015.
- During its meeting on 28 January 2016, the CHMP appointed David Lyons as Rapporteur and Greg Markey as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 12 February 2016 (Appendix 2 of Final Opinion). The re-examination procedure started on 13 February 2016.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 11 March 2016 (Annex 6). The Co Rapporteur's Assessment Report was circulated to all CHMP members on 14 March 2016 (Annex 7).
- During the CHMP meeting on 30 March 2016, the detailed grounds for re-examination were addressed

by the applicant during an oral explanation before the CHMP.

- During the meeting on 01 April 2016, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Introduction

Problem statement

Cystinosis is a rare autosomal recessive disease caused by systemic intracellular cystine accumulation. Cystine accumulates within cellular lysosomes and eventually forms crystals in multiple tissues and organs. The responsible gene (CTNS) encodes a 367 amino acid transmembrane protein, cystinosin, which is a lysosomal membrane transporter for cystine. In cystinosis, mutation of the CTNS gene results in defective carrier protein, thereby causing accumulation of lysosomal cystine. Cystinosis affects approximately 0.15 in 10,000 people in the European Union (EU), equivalent to a total of approximately 7,600 people.

The most common form of the disease is infantile cystinosis, presenting with renal tubular Fanconi syndrome, growth retardation, and renal failure. Renal transplantation and systemic treatment with mercaptamine hydrochloride has improved the life expectancy of the affected children. Late-onset cystinosis is much less common. The age of onset ranges from 2 to 26 years, although it is most common in early adolescence. Benign cystinosis is an extremely rare adult-onset condition, which is usually diagnosed during ophthalmic examination and does not present with kidney damage.

First ophthalmic symptoms of cystinosis involve mainly cornea, conjunctiva and retina. Ophthalmic complications include posterior synechiae, blepharospasm, reduced visual acuity, photophobia due to corneal crystal accumulation and/or punctate keratitis, corneal erosions and retinal degeneration leading in some cases to blindness (Gahl et al 1986, Dufier et al 1987, Richler et al 1991, Gahl et al 2000, and Brodin-Sartorius et al 2012). These complications can interfere with the patients' ability to drive, read and work. Patients with the benign form of cystinosis also show crystals in the cornea on slit-lamp biomicroscopy but are usually asymptomatic (Cogan at al 1957).

Systemically administered mercaptamine cannot penetrate the avascular cornea. Therefore, additional topical treatment is needed. In current clinical practice, eye drops used to dissolve cystine crystal deposits in the cornea contain mercaptamine at concentrations varying from 0.1% to 1.13% and are prepared *ex tempore* at the hospitals. Eye drops are instilled from 3 times a day up to every hour when the patient is awake. Corneal transplantation has been used in cases of intractable symptoms and gives relatively good optical results, although there is a risk of recurrent infiltration of the graft by cysteine crystals.

About the product

Dropcys contains 0.1% mercaptamine (also referred to as cysteamine in this report) and is provided in a sterile vial containing white lyophilized powder for reconstitution with 5 ml isotonic sodium chloride 0.9% (w/v). It is intended to be administered at least 5 times per day or every waking hour for maximum efficacy.

Type of Application and aspects on development

This application has been submitted in accordance with Article 10a of Directive 2001/83/EC - well-established medicinal use supported by scientific literature. According to Article 10a of Directive 2001/83/EC, it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific

literature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The requirements of Article 10a application are discussed below:

a) Factors which have been taken into account for the well-established use

- Time over which the substance has been used

In this application, the Applicant referred to several publications dating back to 1991 referring to the use of mercaptamine for the prevention and treatment of corneal cystine deposits in patients with cystinosis. These publications included prospective clinical studies (Kaiser-Kupfer *et al.,* 1987a, Kaiser-Kupfer *et al.,* 1990, Labbé *et al.,* 2014), retrospective cohort studies (Dureau *et al.,* 2003, Broyer *et al.,* 1994, Broyer *et al.,* 1995) as well as individual clinical case studies (Jones et al., 1991, Graaf et al., 1992, Khan et al., 2004, Tavares et al., 2009). Moreover, the Applicant confirmed that mercaptamine 0.1% eye drops have been used in France under a compassionate use program from 1995 until 2013 when it was replaced by a mercaptamine eye drop formulation of higher concentration. The therapeutic value of topical mercaptamine for the treatment of corneal cystine deposits was studied by several academic groups over the years.

- Quantitative aspects of use of the substance

As cystinosis is a rare condition, the number of patients using mercaptamine eye drops is low. This was accepted by the CHMP. Although, it is difficult to assess the exact number of patients treated with hospital preparations, some assumptions could be made. It was estimated by the Applicant that between 1995 and 2013 approximately 100 patients in France received 0.1% mercaptamine eye drops, based on the product sales. Moreover, several patients reported in the literature received mercaptamine eye drops at varying concentrations.

- The degree of scientific interest in the use of the substance (reflected in the published scientific literature)

The Applicant has provided detailed information supported by a number of scientific publications showing that mercaptamine has been extensively studied as reported in the literature since the early 1990s. However, the papers relating to the 0.1% concentration, in particular for the formulation identical to Dropcys, were relatively few. The CHMP noted during the evaluation that the results of the studies in which formulations with a different composition or a different strength have been administered, could not be extrapolated to Dropcys without doubt.

The usefulness of mercaptamine in the treatment of cystinosis is well recognized among clinical experts in the EU and confirmed in the clinical treatment guidelines and consensus papers published by the clinical experts in the field of cystinosis (Ariceta *et al*., 2015, Emma *et al*., 2014).

- Coherence of scientific assessments

The scientific literature provides a consistent view that a treatment with mercaptamine eye drops is necessary to dissolve crystals and alleviate symptoms in patients with cystinosis at all ages.

Despite limitations observed in some of the studies evaluated (retrospective analysis with lack of uniformity in the assessments across studies), they provide sufficient overview of the efficacy and safety profile of mercaptamine eye drops when used as a treatment of corneal cystine crystals. However, as addressed later, various concentrations and formulations have been used in the clinical practice to date.

Overall, this application is based on a literature review of non-clinical and clinical data, supported by more than twenty years of clinical practice with the use of mercaptamine in eye formulations of different concentrations. The CHMP therefore concludes that within the recognised limitation of a rare condition, mercaptamine as a substance use has been a well-established medicinal use within the EU for more than 10 years.

b) The CHMP considers that the documentation submitted by the Applicant includes a review of the relevant literature. The documentation, both favourable and unfavourable has been communicated.

c) Due to the rarity of the disease, attention has been paid to any missing information and the applicant has provided justifications to justify the absence of results of non-clinical and clinical studies.

d) Patients reported in the scientific literature have received ophthalmic preparations of mercaptamine at different concentrations (0.1%, 0.2%, 0.3%, and 0.5%). Moreover, there was a variety in the formulations administered in different studies. As demonstrated in the Tsilou *et al* 2003 study, differences in the formulation (preservatives, excipients, buffers) may have an impact on the efficacy outcome. The influence of changes in the formulation on the ocular permeability and on the efficacy of medicinal products hinders the extrapolation of bibliographical data with different formulations to Dropcys. It is also not possible to assume that the efficacy data obtained with higher concentration of mercaptamine can be extrapolated to 0.1% concentration and the formulation proposed by the Applicant. This has been discussed further in this report.

e) Mercaptamine eye drops are expected to be used together with previously authorised mercaptamine oral formulation. The efficacy and safety profile of the oral formulation has some but limited relevance for the topical use. No ophthalmic preparations of mercaptamine have been authorized in the EU to date.

2.2. Quality aspects

2.2.1. Introduction

DROPCYS finished product is formulated as a hydrochloride salt of mercaptamine and is provided in a sterile, single-use amber glass vial. Each 5 mg vial contains a white lyophilised powder for ophthalmic administration after reconstitution. Dropcys is provided with separate single-dose transparent low-density polytethylene (LDPE) containers of 0.9% sodium chloride for reconstitution of the lyophilized powder and droppers for the dispensing of the eye drop solution.

The dosage form is defined as powder and solvent for instillation solution for intraocular use.

Other ingredients are dextran 40, ascorbic acid, benzalkonium chloride and hydrochloric acid.

2.2.2. Active Substance

General information

The chemical name of the active substance, mercaptamine hydrochloride, is 2-aminoethanethiol hydrochloride or β-mercaptoethylamine hydrochloride corresponding to the molecular formula C_2H_7NS, HCl. It has the relative molecular mass of 113.6 g/mol and the structure is given in Figure 1.

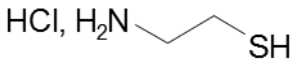


Figure 1 Structure of Mercaptamine hydrochloride

Mercaptamine hydrochloride is a hygroscopic white crystalline powder. It is soluble in water and alcohol and insoluble in methylene chloride. It is sensitive to excess heat (above 60°C) and is reactive with oxidising agents and moisture. Mercaptamine hydrochloride has no chiral centre. Polymorphism has not been observed.

Mercaptamine hydrochloride does not have a monograph in the Ph. Eur.

Manufacture, characterisation and process controls

The manufacturer has provided the information in form of Active Substance Master File (ASMF). Letter of access to the proprietary ASMF has been signed by the supplier.

The synthesis of mercaptamine hydrochloride from the starting material consists of three chemical transformation steps.

Satisfactorily detailed description of the synthesis of the starting material and the active substance has been provided in the restricted part of the ASMF.

The information about the quality of the starting materials, reagents, solvents and auxiliary materials is correctly established. Both in-process controls and intermediate controls are suitable to obtain the quality defined.

The structure of mercaptamine hydrochloride has been confirmed by NRM, IR, elemental analyses and mass spectrometry. Potential impurities have been satisfactorily discussed.

The active substance is packed in 50mL type II glass vials closed with bromobutyl stoppers coated with Teflon and sealed with aluminium capsules.

Specification

The active substance specification for mercaptamine hydrochloride includes tests for appearance, solubility, identification (IR, HPLC and reaction of chlorides), appearance of solution, pH, water content (KF), related substances and impurities (HPLC), assay (HPLC), residual solvents (GC) and microbial quality. The analytical

methods used for testing the drug substance have been properly described. The analytical methods used for testing the active substance have been properly described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data presented for three commercial scale batches confirms consistency and uniformity of the manufacturing process.

Stability

Stability data was presented on three batches and on three batches at scale multiplied by 3 when stored in the intended commercial package for up-to 24 months under long term conditions (25 °C, 60% RH), up to 6 months under accelerated conditions (40 °C, 75% RH) and up to 24 months at 4 °C – 8 °C.

The following parameters were tested: appearance, solubility, identification, appearance of solution, pH, water content, impurities, assay and residual solvents. The specifications for the stability study were those of the routine testing of the active substance. The analytical methods used were the same as for release and were stability indicating.

The obtained results on all batches comply with the acceptance criteria after 6 months of storage in ICH conditions at 40 °C, 24 months of storage at 25 °C and 24 months of storage at 4 °C – 8 °C. A forced degradation study showed that mercaptamine hydrochloride is not photosensitive and is acid stable. Degradation is observed under basic and oxidative conditions. It is stable when exposed to heat (if protected from air) at a temperature not higher than 60°C, above this temperature the mercaptamine crystals melt.

The results justify the proposed re-test period of 2 years when stored below 25°C in the intended packaging.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is supplied as a sterile, lyophilized powder into a 10 mL amber glass vial closed with a rubber stopper and a cap, and a 5 mL transparent low-density polyethylene (LDPE) vial of solvent, Sodium Chloride, closed with a perforating cap. The description of the product is acceptable.

The eye drop product has been developed to provide 5 mg of cysteamine hydrochloride per glass vial and is formulated with ascorbic acid, benzalkonium chloride, dextran 40 and hydrochloric acid. The lyophilised formulation is a powder for the preparation of eye drops supplied in a sterile form to be dissolved in 0.9 % sodium chloride at the time of administration. The final pH after reconstitution is between 3.4 and 4.0. This lyophilised powder form was developed for now over 25 years ago by AGEPS, the central pharmacy of Assistance Publique Hôpitaux de Paris, France, to permit to increase the shelf life of the product.

Characteristics of the active substance and excipients were clearly stated. Excipients used are common for this kind of dosage form and the lack of compatibility studies of the excipients with the active substance have been justified by the stability data presented.

All the excipients are described in the European Pharmacopeia and are analysed according to the current edition of the European Pharmacopeia monographs. Specifications of each excipient are detailed and the

certificates of analysis (provided by the manufacturer of the finished product) were presented. Since the excipients are controlled according to European Pharmacopoeia, validation and justification of specifications are not required.

The low pH of the eye drops (3.4 - 4.0) could be contributing to reported eye disorders (slight pain sensation during instillation, irritation, redness, discomfort, itching, blurring). The rationale for the target pH and buffer capacity of the product has not been satisfactorily discussed in relation to the reported adverse effects of the product. Data to support the choice of the final pH has not been provided.

Adding benzalkonium chloride and ascorbic acid accompanied with the low pH of the reconstituted solution could be highly irritating for the eyes. In comparison to currently authorised ophthalmic preparations, the mentioned excipients used in the finished product formulation are in the higher range of concentrations previously seen. This means that patients who are chronically and continuously exposed could potentially experience additional adverse events.

In this context, suitable experimental data has not been provided for the optimisation of ascorbic acid content. The stabilising effect of antioxidant must be assessed in the finished product in conditions which simulate actual use by measuring the extent of degradation in the finished product, with and without the antioxidant.

Furthermore, a full report of the preservative efficacy test has not been provided. The lower limit of preservative able to obtain the antimicrobial effect has not been demonstrated. In order to prove that the microbiological quality of the eye drop solution is maintained after the attachment of the applicator by the patient and during the treatment at patient´s home, the use of the product should be simulated in practice, which could justify the benzalkonium chloride (BAK) level in the preparation.

The proposed container closure system assembly and usage in the patient's home setting involves several steps that each one poses risk of contamination and can prove difficult to handle. The patient should remove the protective overwrap of both bottles, mix the contents, stir the lyophilisate with the added NaCl 0.9% solvent in order to obtain a ready-to-use solution and thereafter attach the dropper applicator onto the glass bottle (see Figure 3 for a schematic illustration).

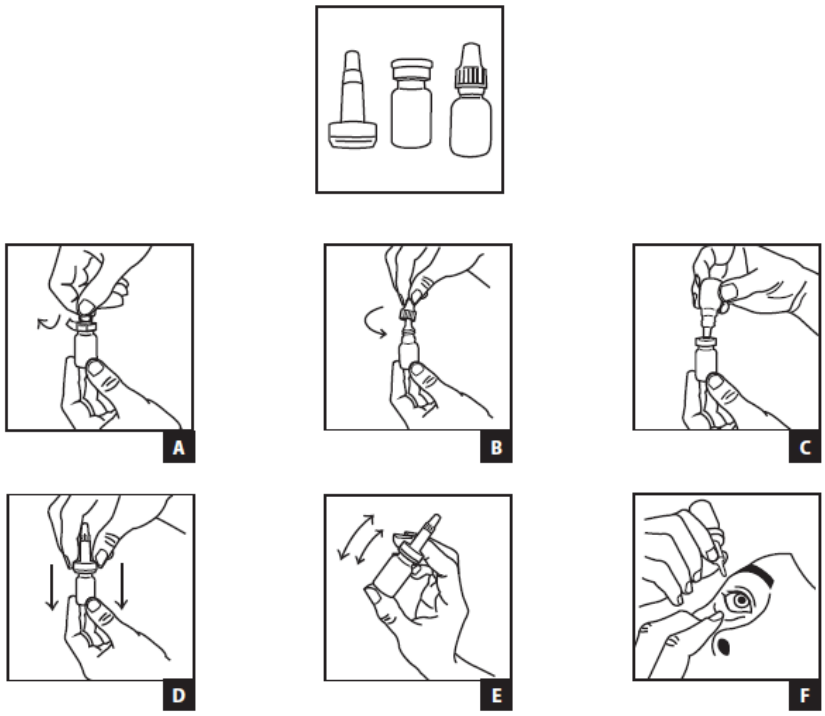


Figure 3 Schematic illustration of the Container Closure System assembly

A usability study evaluating the mounting of the applicator and the dropping step has been provided and the handling instruction was updated including further instructions of the difficulties identified. However, the process of assembly of the container could still prove difficult for some patients or carers and pose a potential risk of contamination of the product. Further developments to the container closure system to improve usability of the product and to mitigate the risk of contamination would have been preferred.

Manufacture of the product and process controls

The manufacturing method of Dropcys is a non-standard method of manufacturing of a medicinal product for ophthalmic use that typically is terminally sterilised. The manufacturing of Dropcys is based on aseptic processing of a lyophilisate including manufacturing steps such as sterilisation of vials and stoppers, manufacturing of the solution, filling, lyophilisation, stoppering and capping. No intermediates are considered in the manufacturing of the finished product.

The commercial batch size for the lyophilised powder has been clearly defined. Critical steps and their control parameters are clearly established and are considered adequate. The lyophilisation cycle could is considered as appropriate based on the evaluation of the process according to the manufacturing validation report.

Process validation protocol and results on validation of three industrial size batches of lyophilisate were included in the dossier. All results comply with the specification. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Gamma-sterilisation of droppers is performed in line with ISO 13485 Standard Requirements. The target dose is in line with Ph. Eur. A validation report of the sterilisation process has been provided.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for: appearance, appearance after reconstitution (visible particles), pH, osmolality, residual moisture (KF), identification (TLC, HPLC), purity and impurities (HPLC), assay (HPLC), residual solvents (GC), antimicrobial preservation efficacy and sterility. Analytical procedures are adequately described. Validation has been performed according to ICH guidelines. Information on reference standards is sufficient and acceptable.

The proposed limits for impurities are in line with ICH Q3B.

Satisfactory analytical results from powder batches have been presented. Batch analysis results are provided for four batches at the intended commercial batch size confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data following the ICH guidelines were provided from three commercial scaled batches of the lyophilised finished product stored under long term conditions in its intended commercial containers at 25 °C/60RH for up to 24 months and at 5 °C for up to 24 months.

The following parameters were tested: appearance, appearance on reconstitution (visible particles), pH, residual moisture, purity and impurities, antimicrobial preservation efficacy and sterility. The specifications for the stability study were those of the routine testing of the finished product. The analytical methods used were the same as for release and were stability indicating.

In summary, all the stability data presented show that throughout the duration of the stability study at 5±3°C and 25°C/60% RH storage conditions, all parameters remained within specifications established for the finished product.

The available stability data supports the proposed shelf-life of 24 months for the lyophilised finished product when stored below 25°C.

Compatibility of the reconstituted product has been evaluated by a study to determine its stability with the complete dropper system. It has been determined that the reconstituted product is stable for all parameters after 7 days of reconstitution with 0,9 % sodium chloride and stored at 5 ºC ± 3 ºC and 3 days at 22 ºC ± 3 ºC. However, according to the SPC, “the recommended dose is 1 drop in each eye every hour that you are awake for optimal efficacy or at least 5 times a day”. In-use stability corresponding in-use specification, obtained for each day of the study (i.e. D1, D2, D3, D4, D5 and D6) has not been provided.

Finished product – Solvent

The manufacturing of the solvent is performed in a Blow-Fill-Seal filling machine. The 0.9% sodium chloride solution is prepared in Class C area and sterile filtered into Class A area where it is filled under aseptic conditions on a sterile blow-fill-seal machine into unit dose vials each containing 5 mL solution. Figure 5

gives a schematic presentation of the blow-fill-seal principles. The plastic containers are formed, filled and sealed online in the same machine. A plastic tube is extruded from melted granulate followed by a plastic/forming process (blow-moulding) where after a filling unit fills the sterile product into the container. The filling unit is then raised and the upper part is tightly sealed and the mould opens to release the filled container.

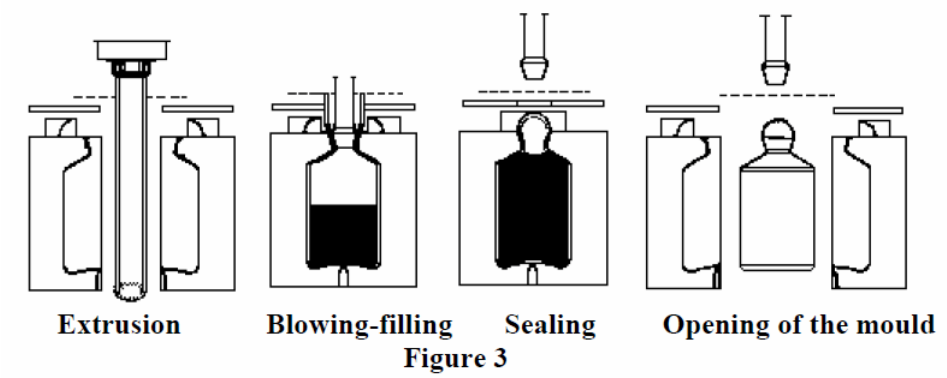


Figure 5 Blow-Fill-Seal manufacturing principles

A process validation was performed on three batches of solvent on a similar Blow-Fill-Seal filling machine to the current used and on one batch packaged in single bottles of 5 mL and manufactured with the current blow-fill-seal machine. Results obtained on all batches are similar but complete validation results on two additional batches manufactured with the current machine should be submitted. Therefore the CHMP recommended that the Applicant commits to submit a variation for the new machine as soon as the Marketing Authorisation will be granted, and requested all validation results to be submitted in this variation application.

The finished product release specifications are appropriate for this kind of dosage form and include tests for: appearance, identification, pH, osmolality, delivered volume, sterility and assay of chlorides (potentiometric titration). Analytical procedures are adequately described. Validation of non Ph. Eur. methods has been performed according to ICH guidelines.

Satisfactory analytical results from solvent batches have been presented.

Stability data results were presented in the dossier. All the results comply with the stability specifications after 24 months storage at 25 °C / 60%RH and 30 °C / 65%RH. The stability data support the shelf-life of 24 months at 25 °C / 60% for the product Sodium chloride 0.9% 5 ml solution.

Adventitious agents

No excipients of human or animal origin are used in the manufacturing process of the lyophilised finished product and solvent.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a

satisfactory manner.

However there are major quality issues in relation to the finished product that have not been resolved by the time of opinion. Specifically, the development of the formulation has not been appropriately justified with regard to the levels of benzalkonium chloride, ascorbic acid, the target pH and buffer capacity of the product. The resulting impact on ocular safety has not been adequately justified in relation to the intended use of the product which is to be used mainly in the treatment of paediatric population for a chronic disease in a very frequent schedule of administration. In addition, no in-use stability data were provided to support the proposed posology and shelf-life after reconstitution. Finally, the maintenance of microbiological quality of the product during the course of treatment has not been established.

All of these issues should be resolved in order to consider the quality of the product satisfactory.

It is also considered that the risk of microbial contamination and other potential problems on usability e.g. assembly of the container, could be reduced with further improvements on the container closure system.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the quality of the product is not considered to be acceptable at the time of opinion and therefore the marketing authorisation application for Dropcys is considered currently not approvable from the quality point of view since major objections still remain that preclude a recommendation for a positive opinion.

At the time of Opinion the quality issues precluding a positive recommendation are:

- the development of the formulation was not appropriately justified with regard to the levels of benzalkonium chloride (BAK), ascorbic acid, target pH and buffer capacity of the product.
- no in-use stability data were provided to support the proposed posology and shelf-life determination after reconstitution.
- moreover the maintenance of microbiological quality of the product during the course of treatment was not established.

2.2.6. Recommendation(s) for future quality development

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical dossier submitted in support of this application was based on the review of relevant published data on the pharmacology and toxicology of mercaptamine following systemic and ophthalmic administration.

2.3.2. Pharmacology

The potential effect of mercaptamine hydrochloride in the treatment of ocular cystinosis was evaluated in CTNS -/- knock-out mice using *in vivo* confocal microscopy (Simpson *et al*, 2011). Five mice received 4 drops/day of a 0.55% mercaptamine solution for 4 week and were compared to untreated $CTNS^{-/-}$ mice. The quantitative assessment of cystine crystal content in the cornea was measured by calculating a percent Crystal Volume Index (CVI).

The results indicated that eyes treated with mercaptamine drops showed significantly less crystal accumulation compared to control eyes ($p<0.001$) with only a 15% increase in treated eyes ($p=ns$) compared to 173% increase ($p<0.04$) in untreated eyes.

According to ICH S7A guideline 'safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low'. As these conditions were met for Dropcys, no safety pharmacology studies were submitted.

No pharmacodynamic drug interactions studies were submitted which was acceptable.

2.3.3. Pharmacokinetics

No information relating to mercaptamine distribution, metabolism and excretion has been provided. This was accepted by the CHMP taking into account the expected negligible absorption of mercaptamine following ocular administration, as discussed in Clinical Pharmacology section.

2.3.4. Toxicology

Systemic toxicity

The results of single dose toxicity studies with mercaptamine hydrochloride performed in rodents show that the gastrointestinal tract was the main target organ. The results of one chronic toxicity study in monkeys and 9-week study in rabbits showed effects on bone marrow. However, these effects were not confirmed in other studies.

Some publications (Stich *et al.,*1978, Inoue *et al., 1985)* reported that mercaptamine induces chromosomal aberrations in eukaryotic cell lines. However, this was not confirmed in other studies (Speit *et al.,*1982). Therefore, mercaptamine is not considered to be genotoxic. No carcinogenicity studies were submitted.

Mercaptamine administration in rats, at dose of 375 mg/kg/day, resulted in a reduction of fertility and delayed weight gain. Embryo-fetotoxic effects, such as resorption and abortion, were observed in rats receiving a mercaptamine dose of 100 mg/kg/day and in rabbits receiving 50 mg/kg/day. Mercaptamine was also shown to be teratogenic in rats at doses equal or greater than 100 mg/kg/day.

Mercaptamine administered to neonatal rats at 100 mg/kg/day for 6 to 10 days produced permanent cataracts (Truong *et al*. 1987). It was also reported in rats that mercaptamine dose of 375 mg/kg/day delayed weight gain and decreased survival of offspring during suckling period.

The toxicological findings described above were not considered relevant for ocular administration of mercaptamine since the systemic exposure is anticipated to be low.

Local tolerance

An *in vitro* study (Shin *et al.,* 2011) on human corneal endothelial cells and three ocular tolerance studies with repeated instillation of mercaptamine hydrochloride eye drops (Kaiser-Kupfer *et al.,* 1987; Jain *et al.,* 1988; Bozdag *et al.,* 2008) have been submitted by the applicant.

The results of the *in vitro* study showed that mercaptamine (0–20 mM) suppressed peripheral blood mononuclear cells (PBMC) proliferation, in a dose-dependent manner ($p<0.001$), as well as the levels of TGF-β1 and IL-6 via reactive oxygen species formation. The results suggested that mercaptamine could suppress inflammation associated with PBMCs to corneal endothelial cells (Shin *et al.,* 2011).

In the *in vivo* studies, different concentrations of mercaptamine (0.1%, 0.11%, 0.5%, 0.55%, 1%, 2%, 5% and 10%) were applied to albino rabbits´ eyes for 10 days to 3 months. With high concentrations of mercaptamine (1% or more), mild to moderate hyperaemia and thickening of both eyelids (reversible within 7-10 days), marked to moderate cellular infiltration and mild neovascularization in the peripheral cornea, were observed. No signs of toxicity in the conjunctiva or cornea were found with lower mercaptamine concentrations (Kaiser-Kupfer *et al.,* 1987; Jain *et al.,* 1988; Bozdag *et al.,* 2008).

No local tolerance studies have been conducted with the formulation intended for marketing. This has been justified by the extent of clinical exposure of this formulation.

Toxicology of excipients

The excipients used in Dropcys are all commonly used in eye drops formulations and are considered acceptable in principle. Taking into account the irritant nature of BAK, it cannot be excluded that the continued administration of Dropcys would not cause eye irritation. This topic has been discussed further in Clinical Safety section of this report.

Impurities

The impurities in the drug substance were controlled adequately. Cystamine dihydrochloride, a degradation product of mercaptamine hydrochloride, is very easily formed by oxidation. Therefore, the cystamine specification limit has been set at 1%, which exceeds ICH Q3A (R2) threshold of 0.15%. This level was considered acceptable based on the high safety margin established in a study performed in rabbits (Iwata et al 1998). Taking into account these data and the fact that the specification for this impurity is set at the same level in Cystagon, cystamine dihydrochloride can be considered qualified NMT 1.0%.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has submitted an environmental risk assessment in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). The *n*-octanol/water partition coefficient, as determined by the shake flask method, was below the threshold of 4.5. The PECsurfacewater value was below the action limit of 0.01 µg/L.

Based on the data presented below, the CHMP concluded that the use of mercaptamine hydrochloride for the treatment of corneal cystine deposits is unlikely to have a significant impact on the environment and no Phase II environmental fate and effect analysis are warranted.

Table 1. Summary of main study results

Substance (INN/Invented Name): Mercaptamine Hydrochloride			
CAS-number (if available): 156-57-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-2.706	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-2.706	Not B
	BCF		
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		
PBT-statement :	Not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	3.6×10^{-3}	µg/L	> 0.01 threshold N

2.3.6. Discussion on non-clinical aspects

Mercaptamine is a known active substance that has been used in the clinic for several decades. The pharmacodynamic effects are well described in the scientific literature and support the claim that mercaptamine eye drops could have an effect on the corneal cysteine crystals deposits in cystinosis.

The optimal concentration and application frequency of mercaptamine eye drops were not explored from the non-clinical point of view. Instead, references to clinical evidence (Kaiser-Kupfer *et al*., 1990, Tavares *et al*., 2009, Labbé *et al*., 2014) have been provided, as discussed in the Clinical Pharmacology and Efficacy section in this report.

The range of toxicology data presented in the literature was considered limited. However, the CHMP accepted the absence of the missing information, as this was an application for an active substance in well-established use and since supplementary clinical data from the provided literature references were available to characterise the overall safety profile of the product (see section 2.6.).

No data regarding antigenicity, immunotoxicity, dependence and metabolites have been provided. The absence of these data was considered acceptable, taking into account the intended topical use of Dropcys.

The non-clinical local tolerance of the proposed product should have been evaluated in accordance with the relevant guideline CPMP/SWP/2145/00. However, a formulation identical to Dropcys has been used in clinical practice in France for 25 years, as documented in the retrospective studies from Necker's hospital (Broyer *et al.,* 1994, Broyer *et al.,* 1995 and Dureau *et al.,* 2003) and the baseline data of the prospective evaluations from Quinze-Vingts' hospital (Labbé *et al.,* 2014). Based on these studies, the CHMP considered that local

tolerance has been verified in the clinical setting, and therefore considered the absence of non-clinical studies justified.

Finally, the environmental risk assessment showed that Dropcys was unlikely to present a risk to the environment as the values for log K_{ow} and PECsurfacewater were below the thresholds of concern.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical dossier submitted in support of this application was considered acceptable.

2.4. Clinical aspects

2.4.1. Introduction

The clinical section of this application was based entirely on data available in the published literature.

2.4.2. Pharmacokinetics

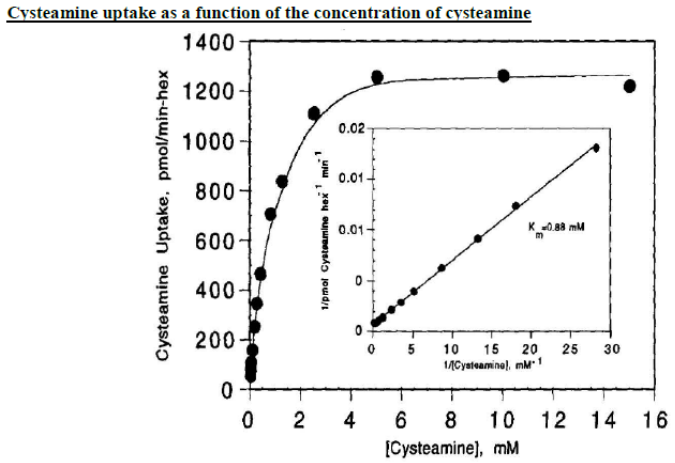
The penetration of topical mercaptamine into the aqueous humour was studied in forty patients undergoing cataract surgery (Hsuan *et al*., 1996). Though administered in high concentrations (50 and 100 mmol/L) every half hour for up to 8 hours, there was no detectable concentration (< 0.1 mmol/L) of free thiols (corresponding to mercaptamine) in the samples of aqueous humour when compared to the control group, at any time points.

No additional data on systemic absorption of mercaptamine applied topically to the eye have been provided. Dropcys is intended to be used in patients with cystinosis receiving oral mercaptamine therapy. The total daily ophthalmic dose is less than 2% of the recommended oral daily dose of mercaptamine; thus, the systemic exposure following ophthalmic administration is expected to be negligible compared to oral administration (Davies *et al.,* 2000, Bodor *et al.,* 2005, Buchan *et al.,* 2010). The CHMP agreed with this conclusion.

Mercaptamine uptake

The uptake of mercaptamine by lysosomes from human skin fibroblasts was investigated to characterize the lysosome specific transport system (Pisoni *et al.,* 1995). A Michaelis-Menten plot of the initial rate of mercaptamine uptake as a function of its concentration showed that the lysosomal uptake of mercaptamine was a saturable process at pH=7 and 37 °C (Figure 1 below).

Figure 1. Cysteamine uptake as a function of concentration



Consequently, the Applicant stated that the concentration of the eye drops formulation proposed in this marketing application (8.8 mmol/L) is optimal for the maximal uptake into lysosomes from cultured fibroblasts and that the lysosomes from corneal keratinocytes are expected to behave similarly.

Justification of the proposed formulation

An instilled drug mainly penetrates the eye by absorption across the cornea from the precorneal tear film. The conjunctival cul-de-sac normally contains about 7 to 9 µL of tears; and with a physiologic turnover rate of 0.1 to 0.15 min-1 the rate of tear flow is about 1 µL/min. The maximum volume of fluid that can be contained in the cul-de-sac without overflow is about 30 µL (the mean drop volume of Dropcys). The increased volume of fluid in the cul-de-sac is quickly delivered into the lachrymal drainage system by the pumping action of the canaliculi associated with the blink movement. Moreover when the dosage volume is sufficiently small, bioavailability can be improved by a factor of ~4 for drugs with low corneal permeability (Keister 1991). Therefore, the Applicant stated that increasing the drop volume for mercaptamine hydrochloride would not be beneficial.

The precorneal tear film is a 7-9 µm thick stagnant fluid layer spread over the corneal epithelium, therefore its mixing with the marginal tear fluid after drugs' instillation takes place only by blink movements, which at the same time carry the drug away from the conjunctival sac. Because of the above mechanism, tear film saturation with the instilled drug is incomplete. For example, after instillation of fluorescein solution, the initial tear concentration increased slightly on increasing the instilled volume from 5 to 20 µL, but further volume increase failed to raise the degree of saturation over a 46% level of the instilled drug concentration.

Solution drainage may be decreased with increased solution viscosity, and addition of viscous vehicles (e.g. methylcellulose) has been used in an attempt to raise the initial tear film saturation. This has been achieved when kinematic viscosity increases up to 15 to 20 centistokes (cSt). Dynamic viscosity of 12 to 15 mPa. was considered optimal for ophthalmic delivery (Buchan *et al.,* 2010).

2.4.3. Pharmacodynamics

Mechanism of action

Mercaptamine passes through plasma and lysosomal membranes and, because of its weak amino (NH2) base, concentrates within acidic lysosomes. Within the lysosome, the thiol (SH) group of mercaptamine reacts with cystine to form cysteine and a cysteine-mercaptamine mixed disulphide. This complex crosses the lysosomal membrane *via* the lysine transporter, towards the cytoplasm, where it then separates into mercaptamine and cysteine. Cystine is thus eliminated from cells.

Primary pharmacology

The primary pharmacodynamic action of mercaptamine has been characterised in several studies.

Cultured skin fibroblasts from patients with nephropathic cystinosis and normal individuals were incubated with labelled cystine, and granule-rich fractions (i.e. lysosomal fractions) obtained from cells disrupted by sonication were added to tubes containing the test reagents for 30 minutes. The rate of depletion of free cystine by mercaptamine and the effect of concentration are shown in Figure 2 below: 90% of the original intracellular cystine content was depleted within 1 hour by both 1 mmol/L and 0.1 mmol/L mercaptamine, and 50% of the cystine depletion occurred in the first 15 minutes after addition of 0.1 mmol/L mercaptamine to the culture medium.

Figure 2. Effect of various cysteamine concentrations on cystine content

Effect of various cysteamine concentrations on cystine content of cystinotic fibroblasts

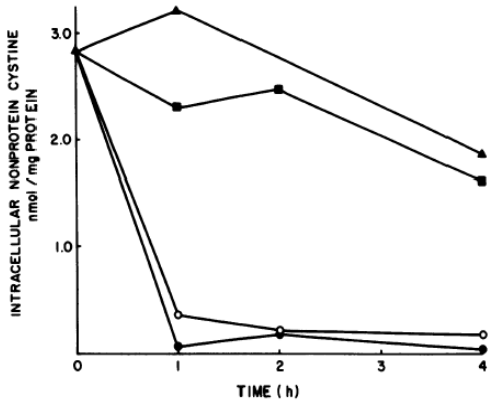


FIGURE 1 The effect of cysteamine on the intracellular nonprotein cystine content of cystinotic fibroblasts in cystine-deficient medium. 1.0 mM ●, 0.10 mM ○, 0.01 mM ■, control ▲.

A similar cystine-depleting effect was observed with cysteamine in polymorphous-nuclear cell, leukocytes, muscle cells, and in cornea epithelium cells (Kaiser-Kupfer 1987a). In addition, *in vitro*, corneal stromal cells from a patient with nephropathic cystinosis were substantially depleted of cystine by mercaptamine.

In vivo, oral cysteamine readily depletes peripheral leukocytes of 90% of their endogenous cystine content and has proven efficacy in maintaining renal function and normalizing growth rates in children with cystinosis.

2.4.4. Discussion on clinical pharmacology

In vitro and *in vivo* data indicate that mercaptamine acts as a cystine-depleting agent reducing cystine crystal accumulation.

The pharmacokinetics of cysteamine after oral administration has been well characterised but this information has been found not relevant for the ophthalmic administration. Since nephropatic cystinosis patients receive cysteamine also by the oral route, it represents the main source of exposure to the product in these patients. Even if only topical mercaptamine was administered, the total daily ophthalmic dose would represent less than 2% of the recommended oral daily dose. Thus, no safety concerns derived from the systemic exposure after ocular instillation are expected. No additional pharmacokinetic data were considered necessary.

The Applicant has provided a pharmacokinetic rationale for the suitability of the selected formulation regarding drop volume, drug concentration and viscosity of the ophthalmic solution. This theoretical argumentation was acknowledged. However, other aspects of the formulation, such as the content of benzalkonium chloride, high acidity of the solution and the necessity for a frequent daily dosing were not addressed and will be discussed later in this report.

2.4.5. Conclusions on clinical pharmacology

The documentation on clinical pharmacology submitted in support of this application was adequate.

2.5. Clinical efficacy

The Applicant has submitted publications of the following studies for demonstration of efficacy of mercaptamine hydrochloride 0.1% eye drops:

- two prospective studies (Kaiser-Kupfer *et al.,* 1987a, Kaiser-Kupfer *et al.,* 1990).
- three retrospective studies (Dureau *et al.,* 2003, Broyer *et al.,* 1994, Broyer *et al.,* 1995).

In addition, a number of studies and case reports evaluating mercaptamine hydrochloride eye drops at different concentrations were submitted as supportive documentation.

Only the studies conducted in France, i.e. Broyer 1994, Broyer 1995, Dureau 2003 as well as the supportive study by Labbé 2014, have included data on the AGEPS formulation containing 0.1% mercaptamine and 0.02% BAK, which is identical to the Dropcys formulation.

The Kaiser-Kupfer studies were conducted with 0,1% mercaptamine formulated in saline, with no BAK added.

Table 2: Main studies with 0.1% mercaptamine hydrochloride eyedrops

Ref	Design	Patients	Treatment Duration	Results
Kaiser-Kupfer 1987	Prospective double-masked, eye-randomized, placebo-controlled	2 pts with nephropatic cystinosis 1M, 21 mth 1F, 20 mth	0.1% mercaptamine in one eye Normal saline in the other eye One drop hourly while awake 5 months 4 months	Slit-lamp biomicroscopy: Decreased crystal deposition in the treated eye
Kaiser-Kupfer 1990	Prospective double-masked, eye-randomized, placebo-controlled trial	29 pts with nephropathic cystinosis 25 pts analysed 18 patients 2-42 mths, 11 patients 4-31 years	0.1% mercaptamine eye drops, Normal saline in the other eye One drop hourly while awake Followed up to 39 mths	7 patients (2 mth-19 y) treated with 0.1% 5 pts (2 mth-2 y) reduced corneal deposits
Dureau 2003	Retrospective, open label cohort (1980-2000)	29 pts with nephropathic cystinosis (7 mth-26y)	Mercaptamine eyedrops* 6 times per day Follow-up undetermined for each patient	Corneal deposits Visual acuity Photophobia Retinopathy
Broyer 1994	Retrospective, open label cohort (1980-1994)	10 pts treated 4 pts (5-10 y) 6 pts (10-14 y) 24 pts untreated 7 pts (5-10 y) 17 pts (10-14 y)	Mercaptamine eyedrops*	Corneal deposits, Photophobia Retinopathy Improvement in patients treated
Broyer 1995	Retrospective, open label cohort (1980-2000)	23 pts treated (10-25 y) 18 pts untreated (10-25 y)	Mercaptamine eyedrops*	Corneal deposits, Photophobia Retinopathy Improvement in patients treated

*No mention is made to the concentration of the topical formulation administered. It is assumed that patients were treated with 0.1% given that it was the topical formulation available in France at the period of time described in the paper

Table 3: Supportive studies with 0.2% and 0.3% mercaptamine hydrochloride eyedrops

Ref	Design	Patients	Treatment Duration	Results
Bradbury 1991	Double masked, randomized*, placebo-controlled	6 patients 5 pts treated (8y,13y,9y,10y,16y) (1 withdrew 2wk after starting)	Topical mercaptamine 0.2% 0.9% sodium chloride (EDTA) 6 times/day 6 months 5 patients on oral mercaptamine	VA: 3 pts↑ VA in the treated eye CS: 3 pts↑ CS in the treated eye Crystal density score All patients improved photophobia, pain and blepharospasm in the eye receiving topical mercaptamine. S
MacDonald 1990	Not specified Placebo-controlled	4 patients (3F/1M) 33 mth-21 y	Topical mercaptamine 0.3% 0.9% sodium chloride 4 times/day 7 months 2 patients on oral mercaptamine	VA : No difference between groups Number of crystals in cornea : No difference between groups

*Patients were randomized to receive topical mercaptamine 0.2% in one eye and normal saline in the other eye as a control

Table 4: Supportive studies with 0.5 % mercaptamine hydrochloride eyedrops

Ref.	Methods	Patients		Efficacy Results	
		Treated (gender; age)	Compliant	Reduced crystals score (CS)	Endpoint of ≥1 decrease in CS
Blanksma 1996	Open, both eyes PO4-cysteamine 5/d 1 year Photophobia Visual acuity Corneal erosion	3 (2F/1M; 13y, 15y, 30y)	3	NA	NA
Iwata 1998	DB randomized 0.5% cysteamine 1/h; 8-20 months Symptoms CS	12 (6F/6M; 3-29y)	11	8	6
Gahl 2000	Retrospective 0.55% cysteamine HClCS	10 (1-32y)	10	10	8
Tsilou 2003	Multicenter 0.55% cysteamine HCl DB randomized *vs.* other 0.55% formulation (all eyes treated) 1/h Evaluation every 3 months	16 (9F/7M; 2-11y); 1 dropout	15	NIH 11 Sigma Tau 3 global result 14/30	NIH 7 Sigma Tau 1 global result 8/30
Soliman 2009	Retrospective 0.55% cysteamine HCl At least 3 m cysteamine eyedrops and follow-up CS	16 (8F/8M; 10-112 m) 11 followed up for the eye	poor	2	1
Labbé 2014	Open, both eyes 3-5 instillations/d 0.55% cysteamine HCl Treatment for 48 m Gel formulation Evaluation after 1, 3, 6 12, 24 36 and 48 months	8 (8-21y)	8	Number of responders NA Mean reduction from 2.91±0.13 to 2.75±0.32	NA

Table 5: Supportive individual case reports

Ref.	Patients (gender; age)	Treatment	Method (time of evaluation)	Results
Jones 1991	1 F, 2y	0.5% cysteamine Hourly; 3 months	Slit-lamp (3m; 6m)	Photophobia reduced Substantial (but incomplete) clearance of crystals in cornea after 3 months No adverse event
Gräf 1992	1 M, 2y	0.5% cysteamine HCl right eye 0.1% cysteamine HCl left eye 6-8 times a day; 38 weeks	Slit-lamp (6m; 9m)	Start clearance of crystals after 4 wks in right eight; total clearance after 26 wks Start clearance of crystals after 2 wks in left eye; total clearance after 12 wks
Khan 2004	1 M, 8y	0.5% cysteamine bitartrate 5 times a day; 8 months	Slit-lamp (8m)	Photophobia reduced from 1st month Visual acuity 20/30 Corneal crystals density score 1.5 (over 3)
Tavares 2009	1 F, 20y	0.1136% cysteamine HCl 10 times a day; 1 year	Slit-lamp IVCM (0; 3; 6; 12m)	Photophobia reduced at 3m and nil at 1y Visual acuity 20/20 Reduced crystals density from 3 m, stable until 1y No adverse event

2.5.1. Dose response studies

No dose response study has been reported in the scientific literature regarding the topical use of mercaptamine in ocular cystinosis.

The Applicant stated that there is no pharmacokinetic rationale for a higher concentration of mercaptamine hydrochloride than 0.1% (8.8 mmol/L) in eye drops, given the saturable uptake of mercaptamine into the lysosome and the saturable tear-film concentration.

The compliance with a repeated (hourly) administration of eye drops was the only factor shown to be consistently correlated with treatment success (Kaiser-Kupfer *et al*., 1990, Tavares *et al*., 2009, Labbé *et al*., 2014). Because mercaptamine does not penetrate internal eye chambers (Hsuan *et al*., 1996), the objective of local treatment is a progressive clearing of corneal mercaptamine crystals. Treatment must be continued with the same frequency of instillations to clear the gene-deficient cells as they migrate towards the corneal surface (Katz *et al*., 1987a).

2.5.2. Main studies

- ***Kaiser-Kupfer et al., 1987a***

This was a double-blind, eye-randomized study conducted to evaluate 0.1% mercaptamine hydrochloride eye drops vs. placebo.

Study participants: Two young children (1 male aged 21 months; 1 female aged 20 months) with nephropatic cystinosis, whose corneas contained visible crystals on slit-lamp biomicroscopy. The diagnosis of nephropatic cystinosis was confirmed by a raised leukocyte cystine level. Both patients were receiving oral mercaptamine treatment (60 and 70 mg/kg/day, respectively).

Treatments: Fresh bottles of eye drops were used every five days to reduce the risk of contamination.

- One drop of mercaptamine in normal saline was placed in one randomly selected eye, hourly while the subject was awake.
- Normal saline was placed in the other eye according to the same schedule.

Outcomes/endpoints: Findings were documented photographically and confirmed on slit-lamp biomicroscopy by three or four independent ophthalmologists who were unaware of the identity of the mercaptamine-treated eye.

Results**:**

Baseline data:

- Patient 1: On initial ophthalmic examination at 14 months of age, sparse corneal crystals were evident on stereophotography. The crystals were evident in both eyes on slit-lamp biomicroscopy as well as photography when the patient was enrolled at 21 months of age
- Patient 2: Slit-lamp biomicroscopical examination at the age of 13 months revealed bilateral and symmetrical corneal crystal deposition. Corneal crystal accumulation progressed in both eyes between the ages of 13 months and 19 months, one month before mercaptamine treatment started.

Outcomes and estimation: After 1 month of treatment, clinical impression of decreased crystal deposition was noted. After 5 and 4 months of treatment, respectively, mercaptamine eye drops significantly reduced the crystal deposits in the cornea whereas the number of crystals in the untreated eye was not markedly reduced.

- ***Kaiser-Kupfer et al., 1990***

This was a double-masked, eye-randomized, placebo-controlled trial with 0.1% (10 mmol/L) mercaptamine eye drops.

Study participants: Children and adults with nephropathic cystinosis confirmed by a typical clinical presentation and a leukocyte cystine concentration greater than 3 nmol half-cystine per milligram of protein (normal < 0.2nmol) and treated with oral mercaptamine. 2 children from the previous study (Kaiser-Kupfer et al., 1987a) were included in the evaluation.

Treatments: Patients received one drop of 0.1% mercaptamine hydrochloride eye drops in one randomly selected eye and one drop of saline in the other eye. The treatment was administered every hour while the subject was awake. Fresh bottles were used every 5 days to reduce the risk of contamination.

During the study, mercaptamine concentration was changed to 0.5% and patients initially treated with 0.1% eye drops were switched to 0.5% eye drops. A group of new patients received 0.5% formulation only.

Outcomes/endpoints: Ophthalmological examination by slit-lamp biomicroscopy and photography; every 3-4 months.

A corneal density score (CS) was constructed on arbitrary units ranging from 0 to 3 with 0.125 increments based on a library of standard transparencies ranked in order of increasing density.

The patients were assessed by 3 different ophthalmologists masked to therapy and 3 different photographic observers. The observations included density of corneal crystals in each eye, corneal density score (CS), differences in corneal scores between the eyes and from one visit to the other

The endpoint was considered to be reached and code was broken when there was a unanimously agreed difference in the CS between the 2 eyes at that visit and a decrease in the better eye from the previous visit. Compliance to treatment was rated from 1 (poor) to 4 (excellent), based on 4 pediatricians' estimation.

Statistical methods: Two-tailed Student´s t-test vs. the likelihood of correctly choosing the treated eye by chance.

Results

Baseline data: Twenty-nine patients aged 2 months to 31 years were entered into the study. Four patients dropped out of the study: 2 died of unrelated causes, a 31-year old male discontinued after 1 month and a 6-year old boy was excluded for worsening of clinical condition precluding continuation in the study.

Eighteen patients were younger than 42 months and 11 patients were aged 4 to 31 years.

Group 1 (children younger than 4 years), included patients 1 through 16. Patients 1 through 5 received 0.1% mercaptamine eye drops. Patients 6 through 11, initially treated with 0.1% mercaptamine eye drops, did not show improvement and were switched to 0.5% eye drops in the randomized, treated eye. Patients 12 through 16 were recruited directly into the 0.5% mercaptamine regimen.

Group 2 (patients 4 to 23 years of age), included patients 17 through 25. Patients 17 through 21 received 0.1% mercaptamine eye drops; patients 19 through 21 were subsequently switched to 0.5% mercaptamine in the randomized, treated eye. Patients 22 through 25 were randomized directly to receive 0.5% mercaptamine.

Data are presented on 25 patients who were enrolled and followed up for their response to mercaptamine eye drop therapy between November 1985 and September 1989. The results are summarized in the Table 6 below:

Table 6 Individual patients' results

Patients With Cystinosis Receiving Cysteamine Eye Drops

Patient/Sex	Initial Age, y-mo	Time to End Point, mo*	Duration of Follow-up, mo	Compliance Score
		Group 1		
1/M	0-2	24†	...	1
2/F	1-2	14	...	3
3/F	1-8	4	...	3
4/M	1-9	5	...	4
5/M	2-7	7	...	4
6/F	1-5	34/3‡	...	2
7/F	1-5	16/4‡	...	3
8/F	1-11	...	30	1
9/F	1-0	...	20	1
10/F	1-1	...	21	1
11/M	1-2	...	24	1
12/M	0-11	...	4	4
13/M	1-11	...	0	NK§
14/F	2-6	4	...	4
15/M	2-0	...	0	NK§
16/F	3-6	...	0	NK§
		Group 2		
17/M	15-10	...	39	2
18/M	19-11	...	39	2
19/M	4-2	...	14	2
20/M	21-0	...	3	1
21/M	23-0	...	3	1
22/F	14-3	...	1	4
23/F	16-10	9	...	4
24/M	17-0	...	0	NK§
25/F	21-9	6	...	4

*The end point denotes the time at which the randomization code was broken. In those patients not reaching the end point, the duration of follow-up is given. The compliance score is described in the "Patients and Methods" section.

†Corneal crystals did not appear until 14 months of age.

‡The number to the right is the number of months receiving 0.5% cysteamine.

§NK indicates not known; insufficient information to gauge compliance.

Outcomes and estimation: Endpoint of fewer crystals in treated vs. untreated eye as measured by CS was reached in 10 out of 25 patients ($p<0.002$). Median time to endpoint was 8 months, ranging between 4 and 37 months in Group 1 and between 6 and 9 months in Group 2; follow-up ranged between 0 and 30 months in Group 1 and 39 months in Group 2. In 10 patients who reached the endpoint, 5 were receiving 0.1%, 3 0.5%, one was for 34 months on 0.1% and 3 on 0.5% and one was for 16 months on 0.1% and 4 on 0.5%.

In only one out of 10 who was reported as fully compliant, the endpoint was not reached; conversely in only 2 out of 10 patients who reached the endpoint compliance was either rated 1 or 2.

Group 1: Of 16 children, 8 responded to 0.1% or 0.5% mercaptamine therapy with a marked decrease in crystal density in the treated eye.

Group 2: 2 out of 9 patients reached the end point at 9 and 6 months, respectively. Of these patients not reaching the end point, the duration of follow-up ranged from 0 months (not yet seen following randomization) to 39 months. An analysis of the compliance score of all patients indicated better compliance, on average, for those reaching the end point compared with those not reaching the end point.

- ***Dureau et al., 2003***

This was a retrospective study in patients with nephropatic cystinosis. All patients had received oral mercaptamine (50 mg/kg/d) and topical mercaptamine (6 times per day) since the time of diagnosis.

Corneal crystals infiltration was assessed on a 0 to 3 severity score corresponding to a number of crystals/mm^2 slit-lamp beam (Grade 1: 1-10 crystals; Grade 2: 10-50 crystals; Grade 3: > 50 crystals) and epithelium, stroma and endothelium infiltration were rated according to age.

In addition to corneal infiltration, the following parameters were evaluated:

- visual acuity: Best-corrected Visual Acuity
- photophobia: severity of photophobia was graded according patient´s estimation as 0 (no photophobia), 1 (photophobia limited to bright light), 2 (photophobia limited to room light) or 3 (photophobia limited to dim light)
- presence of peripheral or macular retinopathy.

Results: A total of 29 treated nephropathic cystinosis patients were reported as being followed annually. Age-range at the time of examination was 7 months to 26 years. Despite the fact that 10 patients were examined once, 10 from 2 to 5 times, and 9 more than five times, the study did not provide results of evolution over time.

Corneal infiltration: All patients had epithelial infiltration at all stages of the evolution, beginning in the peripheral cornea. The infiltration progresses from the surface toward the depth of the cornea, and from the periphery toward the center.

Photophobia: By 10 years of age, most of the patients complained of photophobia. Severe photophobia (grade 3) occurred only after 15 years of age and required symptomatic treatment (lubricant or tinted glasses).

Visual acuity: There was a decrease in visual acuity with time but most of the patients had relatively good vision (>20/40) until age 20. Poor visual acuities (<20/60) were noted only after 20 years of age.

Retinopathy: The authors observed a total of 14 of 29 patients without retinopathy, 3 cases of maculopathy and 3 instances of impairment on electroretinogram.

- ***Broyer et al., 1994***

Two groups of patients were followed up at the Enfants Malades Hospital:

1. Seventeen children, now aged 3 and a half years to 15 years, were treated with mercaptamine from the age of 10 to 33 months for a period of 17 to 184 months between August 1980 and March 1994.

2. Ten children, now aged 15 to 21 years, were treated later on with mercaptamine from the age of 51 to 88 months for the same length of time, with all children having reached the stage of kidney failure.

A control group comprised of 26 patients who had never received mercaptamine.

In all cases, the diagnosis was reached as a result of a cystine assay in the leukocytes according to the method using a protein that binds to cystine.

In this series of patients treated with oral mercaptamine before the age of 33 months, 7 also received the mercaptamine eye drops from an age between 5 and 10 years. Photophobia, corneal deposits and retinopathy were estimated from an index of 0 to 4 as shown in the Table below. The exact method of the index evaluation was not described. The visual acuity was graded down from 10 being the maximum score.

The comparison with a group of patients who had never received neither oral mercaptamine nor local mercaptamine shows a significant difference in favour of these treatments, with the biggest benefit being observed for retinopathy.

Table II. – EVALUATION OF PHOTOPHOBIA, CORNEAL DEPOSITS, RETINOPATHY AND VISUAL SIGHT IN CYSTINOTIC PATIENTS TREATED WITH ORAL CYSTEAMINE AND CYSTEAMINE EYE DROPS (TREATED GROUP) AND COMPARISON WITH A GROUP OF CHILDREN WHO DID NOT RECEIVE THESE TREATMENTS (UNTREATED GROUP)

AGE (YEARS)	5-10		10-14	
Photophobia				
treated	n = 4	1	n = 6	0,8
untreated	n = 7	1	n = 8	2,3
Corneal deposits				
treated	n = 4	1	n = 6	1,1
untreated	n = 7	1,6	n = 6	3
Retinopathy				
treated	n = 4	0,5	n = 5	0,2
untreated	n = 6	0,8	n = 17	1
Visual sight				
treated	n = 4	7,2	n = 6	9,3
untreated	n = 6	7,6	n = 8	7,2

- ***Broyer et al., 1995***

Ocular complications: In order to judge the efficacy of mercaptamine eye drops, the set of recent data on 40 patients aged 10 to 25 years, correctly followed-up, were recovered and compared those who used mercaptamine eye drops with those who did not. An index of 0 to 4 was attributed for photophobia and for the quantity of corneal deposits. The results are provided in the table below. The methods of index evaluation were not provided.

Table 7 Ocular symptoms in patients receiving (cysteamine+) or not (cysteamine -) cysteamine eye drops. Symptoms are graded from 0 to 4 and visual acuity in 1/10.

	Cystéamine +		Cystéamine -	
	n	m	n	m
Photophobia (0 to 4)	23	1,6*	17	2,6*
Corneal deposits (0 to 4)	21	2,6	17	3,0
Visual acuity (0 to 10)	21	8,6**	18	5,7**

*: p < 0,01 ; **: p > 0,001.

Analysis performed across trials (pooled analyses and meta-analysis)

Treatment compliance

Problem of treatment adherence is of particular importance with this life-long treatment. Most of the studies which have specifically addressed the compliance issue (mainly the NIH studies) showed that these were usually linked to the high frequency of topical administration and not to the ocular tolerability as can be concluded from the poor (even poorer) compliance to systemic treatment by cysteamine as well (Iwata *et al.,* 1998, Table below).

Compliance to →	ophthalmic mercaptamine (N pts)	systemic mercaptamine (N pts)
Good	8	4
Fair	2	5
Poor	1	4
Not available	3	1
Total	14	14

As observed in Kaiser-Kupfer *et al*., 1990, there was a high variability in the treatment compliance (half of patients showed poor compliance) which could negatively interfere with the efficacy results.

Supportive studies

- *Bradbury* et al., *1991*

Six patients with nephropathic cystinosis were randomised to receive topical cysteamine 0.2% six times a day in one eye and normal saline in the other eye as a control. All patients had corneal cystine crystals and all but one was receiving oral cysteamine.

At each monthly visit the following parameters were measured:

- Visual acuity (Snellen's Chart)

- Contrast sensitivity (Vistech contrast sensitivity)
- Slit-Lamp Biomicroscopy (number of corneal crystals was scored on an arbitrary scale of 0 to 4 plus of crystals on 0.5 increments)
- Subjective assessment of photophobia, pain, blepharospasm and visual acuity for each eye.

Results: One patient withdrew two weeks after treatment was started. All patients showed a subjective improvement in visual symptoms (photophobia, pain and blepharospasm) in the eye receiving topical cysteamine. There was also a small improvement in visual symptoms in the eye receiving topical sodium chloride 0.9% in 4 out of 5 cases.

There were no substantial increases in visual acuity for any patient in the study although 3 patients showed a slight improvement in visual acuity in the treated compared with the untreated eye. Contrast sensitivity improved in 3 patients in the treated eye.

After 6 months of treatment all patients showed some improvement on slit-lamp examination in the crystal density rated on a 0 to 4 score (with 0.5 increments) though only 2 out of 5 patients reached a decrease in score of at least 1 (the endpoint as previously defined). The remaining three patients showed a 0.5 score reduction. No changes were observed in the untreated eyes.

The authors reported problems related to the adherence to the treatment (difficulties due to photophobia and blepharospasm and the unwillingness of teachers to administer the drops whilst the subjects were at school). As a conclusion, they recommended administering cysteamine eye drops at the 0.5% concentration at least six times a day to obtain the quickest improvement in visual function.

- *MacDonald* et al., *1990*

Four patients (33 mth-21 y) affected by nephropatic cystinosis. The two youngest patients were receiving oral cysteamine at the initiation of the study. All patients had corneal cystine crystal deposition involving all levels of the cornea and two patients had retinal crystals.

Topical 0.3% cysteamine drops were instilled into one eye four times a day and normal saline into the other eye as a control. The cysteamine eye drops were prepared with a pH of 4.6 to 5.3 and osmolarity of 330-340 mOsm.

Three observers independently ranked the clinical appearance of corneal crystals in the two eyes as better, worse, or the same throughout the study period. Patients were examined at the initiation of therapy and at two monthly intervals, for 7 months, with photographic documentation at the termination of the therapy. Compliance was excellent.

After 7 months of therapy, there was no difference in the visual acuity of the treated and untreated eyes. The observers could not clinically detect any appreciable difference in the number of crystals seen in the corneas of the treated and untreated eyes.

Limited information on efficacy was provided in this study. A subjective impression of evolution (better, equal, worse) was selected as scale of the effect.

The old age of patients, a limited drug penetration and the low frequency of drug administration were considered as reasons for the lack of response. A more frequent administration was recommended by the authors.

- *Blanksma* et al., *1996*

Three patients with nephropathic cystinosis receiving oral cysteamine therapy were given 5mMol/l cysteamine eyedrops (preserved by BAK 0.01%) in both eyes five times a day.

Visual acuity was tested with Snellen charts, photophobia and corneal erosions were estimated and glare was measured at the start of the therapy and after six and twelve months.

The visual acuity did not alter significantly. At six months follow-up, the corneal punctuate erosions disappeared completely in all patients. All patients experienced a reduction of the photophobia. At six and twelve months two of the three patients showed a significant improvement of the glare.

This study provides very limited support for the claimed indication as corneal deposits were not measured.

- *Iwata* et al., *1998*

This study compared the efficacy of cystamine and mercaptamine with respect to cystine crystal dissolution. One eye of 14 patients with cystinosis was randomized to either cystamine or mercaptamine, 0.5%, with 0.01% BAK; the companion eye was treated with the alternate preparation. Patients and/or their parents were instructed to take the eye drops every hour while awake. The patients were followed at 6-8 month intervals.

At baseline, photophobia, pain or foreign body sensation was registered. Haziness of the cornea and the presence and degree of crystals in the cornea were assessed. Visual acuity was measured with ETDRS charts (picture optotype visual acuity cards for younger patients).

Corneal crystals were observed with slit lamp biomicroscopy and photographed. A density score was assigned to each slide based on 13 standard slides. They were graded from “0” (clarity at the center) to “3.00” (the greatest recognizable crystal density), using increments of 0.25 units. This system was used by two independent and masked graders. The average of the two scores was used for analysis.

Results: Fourteen patients (8F/6M) underwent a baseline evaluation. Two patients chose not to enter the protocol. Photophobia of various degrees was reported by 11 of the 14 patients. No patients reported acute eye pain. At the baseline visit, grading of corneal crystals were 2.75 or greater in all patients in both eyes, except for one 3 year-old patient.

Twelve patients were enrolled in the protocol. One patient exited the study. The period of randomized treatment for the remaining patients ranged 8-20 mths (mean 15 mth, >12 mth in 10 patients).

Subjective improvement of photophobia and/or discomfort was reported in 5 of the 6 patients who showed a significant reduction in crystal score. The best corrected visual acuity at the end of the randomized treatment showed an improvement of five letters or more compared with the baseline in 3 patients.

Table 8. Summary of Topical Cystamine vs Cysteamine in Cystinosis Patients.

Patient	Age (y)/sex	Duration of study (months)	Crystal-density score		Eye treated with cysteamine	Improvement of symptoms[a]	Compliance	
			Baseline OD/OS	End of study OD/OS			Eye drops[b]	Oral cysteamine[c]
1	25/M	20	3.00/3.00	3.00/3.00	OS	+	+++	+
2	11/M	17	3.00/3.00	0.25/2.875	OD	++	+++	+++
3	7/M	16	3.00/2.75	2.50/0.125	OS	++	+++	++++
4	3/F	19	3.00/3.00	2.875/3.00	OD	No symptoms	DCD	++
5	29/M	15	3.00/3.00	1.75/3.00	OD	+	+++	+++
6	5/F	16	3.00/3.00	0.00/3.00	OD	No symptoms	+++	++
7	7/F	16	3.00/3.00	3.00/1.625	OS	++	+++	++
8	3/F	14	2.125/2.375	1.875/2.25	OS	−	++	+
9	28/F	0	2.875/2.875	NA	NA	NA	NA	?
10	25/M	12	3.00/3.00	3.00/2.00	OS	++	++	++
11	18/F	12	3.00/3.00	3.00/3.00	OD	+	+++	++
12	23/M	11	3.00/3.00	3.00/3.00	OD	−	+	+
13	16/F	0	2.75/2.75	NA	NA	NA	NA	+++
14	13/F	8	3.00/3.00	3.00/3.00	OD	−	+++	+

[a] Improvement of symptoms: −, none or questionable; +, moderate, ++, significant; NA, not available.
[b] Eye drops compliance: +, 1 to 4 times per day; ++, 5 to 7; +++, 8 or more; DCD, discontinued.
[c] Oral cysteamine compliance: +, poor; ++, fair; +++, good; ++++, excellent; ?, unknown.

- *Gahl* et al., *2000*

A cohort of 10 patients (1 year-32 years, 6 patients older than 10 years) was treated with 0.5% cysteamine eye drops (both eyes) and followed up for at least for one year. The density of crystals in the central cornea was evaluated semiquantitatively by comparison with a library of slit-lamp photographs of corneas containing cystine crystals at different densities. Scores ranged from 0 (clear) to 3.00 (packed with crystals), with increments of 0.25.

Patients from the age of 1, with a corneal cystine crystal score (CCCS) of 0.25, to 32 years, with a CCCS of 3.00, all showed a reduction in their CCCS after 8 to 41 months of cysteamine eye drops treatment. In each of these 10 cases, the final CCCS was either 0 or 0.25, and the reduction in CCCS was sustained for each patient, with follow-up for more than 1 year in every case. The patients used the eyedrops 10 times per day on average (range 6-12) during the treatment period.

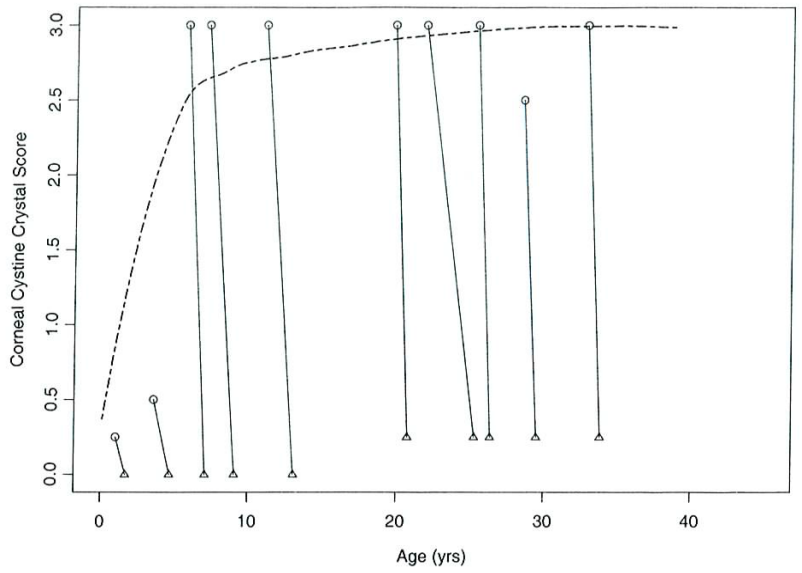


FIG. 6. Effects of cysteamine eyedrop therapy on CCCS. For each of 10 patients with nephropathic cystinosis, the CCCS before treatment (open circles) and after treatment (open triangles) with 0.55% cysteamine eyedrops is shown superimposed on a plot of the natural history of corneal crystal accumulation in nephropathic cystinosis (dashed line). Regardless of age (1–32 years) and initial CCCS (0.25–3.00), cysteamine eyedrop treatment for 8 to 41 months lowered the CCCS to 0 or 0.25 unit.

- *Tsilou* et al.*, 2003*

A prospective, double masked, eye-randomised trial was conducted to evaluate the efficacy of a new topical cysteamine formulation. Patients with cystinosis aged 2-12 years who had never received topical cysteamine and whose corneal cystine crystal score (CCCS) was ≥ 1.00 were randomised to receive the new formulation in one eye and the standard formulation in the other eye:

- the standard cysteamine formulation (NIH) was a 0.55% cysteamine hydrochloride solution with benzalkonium chloride 0.01%.
- the new formulation (Sigma-Tau Pharmaceuticals) was a 0.55% cysteamine hydrochloride solution with monosodium phosphate 1.85%, disodium EDTA 0.10%, and benzalkonium chloride 0.01%.

Ophthalmic examinations were performed at baseline and every 3 months for 1 year. Study subjects were evaluated for the presence of photophobia and blepharospasm with the examination including best corrected visual acuity (ETDRS charts or picture optotype visual acuity cards), slit lamp biomicroscopy, and slit lamp photography with assignment of a Corneal cystine crystal score (CCCS) by two masked graders. CCCS ranged from “0” (clarity at the centre) to “3.00” (greatest recognizable crystal density) in 0.25 increments. If the graders disagreed, a third grader assessed the photograph.

The primary outcome was the proportion of study subjects with a reduction in CCCS of 1.00 unit or more in the eye treated with the new formulation and in the eye treated with the standard formulation.

Results: A total of 16 subjects were enrolled. Mean age at enrolment was 6 years (median 6 years, age range 2–11 years). All eyes had a baseline CCCS of at least 1.25. One subject prematurely discontinued therapy.

Seven of the eyes receiving the standard formulation (47%) showed an improvement of one unit or more in the CCCS at 1 year, compared to one of the eyes (7%) receiving the new formulation (p=0.04 by Fisher’s

exact test). Considering eyes as paired observations, one study subject showed a one unit or more improvement in both eyes, while six study subjects improved in only the eye receiving the standard formulation, and no study subjects improved in only the eye receiving the new formulation (p=0.031 by McNemar's test for paired observations). Including study subjects with less than a one unit change, a Cochran-Mantel-Haenszel statistic test indicated that the means were significantly different (p=0.003). The median change from baseline to 1 year in CCCS was –0.75 for the standard formulation and 0.0 for the new formulation (p=0.0005 Wilcoxon signed rank). Compliance scores indicated good to excellent compliance.

Table 2 Efficacy study at 1 year: corneal cystine crystal score (CCCS) changes from baseline

	Standard formulation	New formulation
⩾1 unit improvement*	7 (47%)	1 (7%)
<1 unit improvement	4 (27%)	2 (13%)
No change	3 (20%)	7 (47%)
<1 unit worsening	1 (7%)	5 (33%)
⩾1 unit worsening	0 (0%)	0 (0%)
Total	15	15

*p=0.04.

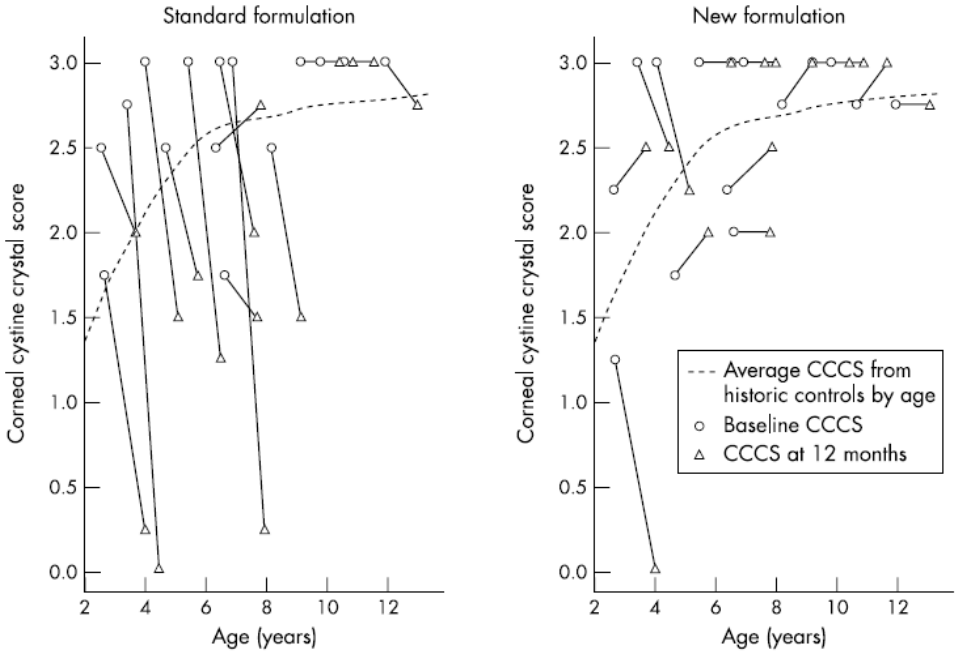


Figure 1 Baseline and follow up corneal cystine crystal score (CSSS) by age and treatment of patients enrolled in efficacy study versus average CCCS for historic controls.[14]

- *Soliman* et al., *2009*

Children with renal Fanconi syndrome and siblings of diagnosed cases were studied for diagnosis of nephropatic cystinosis in Centre of Pediatric Nephrology and Transplantation (Cairo, Egypt). Of 33 screened cases, the diagnosis of nephropatic cystinosis was confirmed in 16 patients (8M/8F, mean age at diagnosis of 52.7 ±39.2 months); 14 had corneal cystine crystals. A total of 11 patients (69%) were > 2 y at the time of diagnosis (7 patients > 5 y)

Ophtalmologic examination included fundus examination for corneal cystine crystals. They were scored as described by Gahl et al. Photophobia was subjectively described as absent, mild, moderate or severe. In addition to oral cysteamine (20-45 mg/kg), mercaptamine eyedrops were provided to all diagnosed cases and CCCS was followed up on a quarterly basis. Cysteamine eyedrops were specifically prepared for the investigators according to the formula described by Gahl et al.

Table 9 Ocular manifestation in patients diagnosed with nephropathic cystinosis.

	No. of cases	%
Photophobia	8	50
Mild	4	25
Moderate	3	18.75
Severe	1	6.25
Cystine Deposits	14	87.5
Corneal crystals	14	87.5
Subconjunctival	1	6.25
Subretinal	1	6.25
Retinal	2	12.5
Retinal pigmentary changes	5	31.25
Cataracts	1	6.25

Results: Follow up data for 6 mths were available for 6 patients. The mean CCCS was 1.81 at diagnosis and after 6 mths (with a decrease of 0.5 in 2 cases and similar increase in 2 others). Scores decreased in 2 other patients by 12 mth. The mean score at 9-12 months was 1.5.

The cysteamine formulation administered (presumably 0.55% concentration) did not significantly reduce corneal deposits after 6 months of treatment. Compliance was generally inadequate and may justify the poor response to the treatment.

- *Labbè* et al., *2014*

This study included eight patients with infantile nephropathic cystinosis, 4 children, 3 adolescents, and 1 adult (mean age at inclusion, 12.1 ± 4.6 years)

At study initiation, all patients received systemic mercaptamine and mercaptamine 0.1% eye drops (AGEPS formulation) at a frequency varying from three times daily to five times daily. After a one month run-in period, patients were switched to mercaptamine 0.55% at the same dose frequency. The dose regimen was adapted at D30 (M1) and D90 (M3) in order to decrease the frequency of instillation.

Table 10 Demographic data

	Result	Median	Range
Number of patients	8	–	–
Gender	M: 2/F: 6	–	–
Age at diagnosis of the disease (months)	17.5 ± 10.8	16	0–38
Duration of the disease at inclusion (years)	6.9 ± 4.9	7	0–19
Age at inclusion (years)	12.1 ± 4.6	12	7–21
Renal graft	Yes: 3	–	–
WBC cystine (nmol 1/2 cystine/mg)	2.6 ± 1.9	2	0.8–5.6
Cysteamine 0.10% (number of eye drops/day)	4.0 ± 0.5	4	3–5

Othalmologic evaluation included an evaluation of pain at instillation (analogic visual scale 0–100 mm), best corrected visual acuity (BCVA), objective evaluation of photophobia (0–5), slit-lamp biomicroscopy analysis,

intraocular pressure (IOP) measurement, and a slit-lamp photograph of the cornea under a standardized protocol.

The density of corneal crystals in the central cornea was assessed according to Gahl's classification. Then, anterior segment OCT (AS-OCT) (the depth of crystal deposition (DCD) in the central cornea and the central corneal thickness) and in vivo confocal microscopy (IVCM) analyses of crystal deposits were also performed.

Visits were performed at D−30, D1 (baseline), D30, D90, M6 then every 6 months during 4 years (M48).

Results: All patients completed the study. The IVCM total score was stable during the run-in period from D−30 (11.38 ± 3.30) toD1 (11.38 ± 2.94). After switching to 0,55% formulation, the IVCM total score decreased from baseline to D90 by a mean of 28.6 ± 17.5% ($p < 0.001$). From D90 to M48, the IVCM total score remained stable and significantly decreased as compared to that at D1 despite a reduced dose regimen from D90. At M48, the mean IVCM total score was 8.13 ± 4.15, decreased by a mean 29.9 ± 26.29% from D1 ($p = 0.001$), with a reduced number of instillations compared to that at D1. The IVCM total score and photophobia were significantly correlated ($p = 0.04$).

The cystinosis corneal crystal score assessed clinically with the slit-lamp (Gahl's score) slightly decreased from D1 (2.94 ± 0.13) to D180 (2.75 ± 0.20) and then remained stable until M48. Photophobia continuously decreased from D1 (2.50 ± 0.89) to M48 (1.63 ± 1.02) with the same trend as the IVCM total score. The DCD decreased from D1 (306 ± 99 μm) toM12 (271 ± 111 μm) and then remained stable until M48. BCVA remained unchanged during the study such as CCT. A trend of increased intraocular pressure from baseline to 48 months (from 11.8 ± 2.5 mm Hg to 14.8 ± 2.3 mm Hg) was observed. Interestingly, the IVCM total score was significantly correlated with DCD ($r = 0.75$, $p < 0.001$) and photophobia ($p = 0.04$).

Table 11 Summary of study results

N = 16 eyes	Visits								
	Day −30 M−1	Day 1 M0	Day 30 M1	Day 90 M3	Day 180 M6	Month 12 M12	Month 24 M24	Month 36 M36	Month 48 M48
IVCM total score									
Mean (SD)	11.38 (3.30)	11.38 (2.94)	9.88 (3.18)	8.19 (3.06)	8.63 (3.91)	8.13 (3.63)	7.88 (3.88)	7.50 (3.65)	8.13 (4.15)
Range	6–16	7–18	5–16	4–14	5–18	5–17	3–15	3–14	5–15
CCCS									
Mean (SD)	2.94 (0.11)	2.91 (0.13)	2.88 (0.18)	2.78 (0.22)	2.75 (0.20)	2.81 (0.21)	2.75 (0.29)	2.73 (0.32)	2.75 (0.32)
Range	2.75–3	2.75–3	2.50–3	2.50–3	2.50–3	2.50–3	2.25–3	2.25–3	2.25–3
OCT DCD (μm)									
Mean (SD)	301.4 (105.1)	306.4 (98.9)	296.1 (106.0)	279.2 (109.7)	285.6 (107.2)	271.4 (111.0)	259.1 (121.6)	266.6 (123.0)	265.1 (119.3)
Range	202–545	200–531	210–544	190–527	199–543	185–550	162–561	173–573	173–568
OCT CCT (μm)									
Mean (SD)	538.3 (22.2)	543.1 (28.6)	544.3 (28.9)	537.0 (23.1)	544.3 (24.8)	546.2 (28.2)	549.5 (26.4)	550.6 (26.2)	552.8 (27.3)
Range	510–571	502–580	494–578	504–570	509–582	505–581	506–580	508–577	501–577
Photophobia									
Mean (SD)	2.8 (1.1)	2.5 (0.9)	2.6 (0.8)	2.0 (0.9)	2.2 (1.3)	2.2 (0.8)	1.5 (0.5)	1.4 (0.8)	1.6 (1.0)
Range	1–4	1–4	1–4	1–3	0–4	1–3	1–2	0–3	0–3
VA (logMAR)									
Mean (SD)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)
Range	−0.0–0.4	−0.1–0.3	−0.2–0.3	−0.1–0.3	−0.1–0.3	−0.1–0.3	0.0–0.3	−0.1–0.3	−0.1–0.3
IOP (mm Hg)									
Mean (SD)	10.8 (2.0)	11.8 (2.5)	11.4 (2.4)	12.4 (1.8)	11.5 (3.2)	13.2 (2.1)	14.7 (2.5)	13.9 (2.2)	14.8 (2.3)
Range	8–14	8–16	8–16	9–15	8–16	10–16	11–19	10–18	12–18
CH 0.10% (instillations/day)									
Mean (SD)	4.0 (0.5)	4.0 (0.5)	3.9 (0.8)	3.0 (0.9)	3.0 (0.9)	3.0 (0.9)	2.9 (0.8)	2.9 (0.8)	3.0 (0.9)
Range	3–5	3–5	2–5	1–4	1–4	1–4	1–4	1–4	1–4

CCCS: cystinosis corneal crystal score (Gahl score); DCD: depth of crystal deposition; CCT: central corneal thickness.
VA: visual acuity; IOP: intraocular pressure; CH: cysteamine hydrochloride.

Supportive case reports

Four cases reports have been submitted; two out of them refer to the topical 0.1% eye drops formulation and provide additional, although limited, support for the efficacy of Dropcys.

- *Jones* et al., *1991*

A 2-year-old girl with nephropatic cystinosis with severe crystal deposition within the cornea and conjunctiva and intense photophobia was treated with topical cysteamine 0.5%. Eye drops were instilled into one eye only, hourly during waking hours. After three months the crystals were completely cleared from the axis of the cornea. Clearance was substantial, but not complete, from the peripheral cornea. The decrease in photophobia was evident. The left cornea was unchanged.

- *Graaf* et al., *1992*

A two-year-old boy with infantile nephropathic cystinosis was given mercaptamine eye drops at various concentrations to treat the corneal cystine deposits. Slit-lamp examination revealed fine, disseminated, superficial corneal deposits resembling bronze dust. When administered every two hours into the right eye during waking hours (6 to a maximum 8 drops a day), the 0.1% solution cleared the cystine crystals fully within 26 weeks. In the other eye, use of the 0.5% solution at the same drop instillation frequency resulted in removal of the cystine crystals after 12 weeks.

- *Khan* et al., *2004*

An 8-year-old boy with nephropatic cystinosis was experiencing debilitating photophobia. Uncorrected visual acuity was 20/40 in either eye. Slit-lamp examination has shown multiple intracorneal crystals in both eye with a density score (0.00-3.00 in 0.25 increments) of 3.00. Oral capsule Cystagon was used to prepare a 0.5% ophthalmic solution. The resultant solution of 0.5% was administered 5 times daily. Eight months after initiating topical treatment uncorrected visual acuity was 20/30 in both eyes and the corneal crystal density score was rated as 1.50.

- *Tavares* et al., *2009*

A 20-year-old woman with infantile cystinosis received cysteamine eyedrops (0.11%) 10 times a day (a formulation stable at room temperature). The density of the cystine crystals in the cornea was evaluated using slit lamp biomicroscopy and confocal microscopy. Initial BCVA was 20/30. Biomicroscopy showed crystalline keratopathy, central and peripheral, located in the stroma of both eyes.

By the 3- and the 6-month visit, the patient had substantially fewer complaints of photophobia, but no change in BCVA was seen. Confocal microscopy evidenced a decrease in the amount and density of corneal crystals. By the 12 month of therapy, the patient presented an improvement in BCVA (20/20) and reported almost no photophobia. However, biomicroscopy and confocal microscopy findings were very similar to those observed in the previous visit.

2.5.3. Discussion on clinical efficacy

In support of this application, the applicant provided a summary of relevant data in the scientific literature. Difficulties inherent to the bibliographic nature of the dossier and the limited sized cohorts due to the rarity of the condition, however, made it challenging to evaluate the effect of Dropcys in the treatment and prevention of corneal cystine deposits in patients with cystinosis. Patients reported in the scientific literature have received ophthalmic preparations of mercaptamine at different concentrations (0.1%, 0.2%, 0.3%, and 0.5%). In addition, some of the cohorts described in different papers corresponded to a single reference centre (Kaiser-Kupfer et al., 1987a and 1990; Dureau et al., 2003, Broyer et al., 1994 and 1995), some of them were follow-ups of previously reported cohorts and some investigators participated in several publications. The applicant clarified that a total of 68 nephropatic cystinosis patients have been treated with 0.1% mercaptamine eye drops, 37 of them with the AGEPS formulation identical to Dropcys.

As demonstrated in the Tsilou 2003 study, differences in the formulation (preservatives, excipients, buffers) may have an impact on the efficacy outcome. The influence of changes in the formulation on the ocular permeability and on the efficacy of medicinal products hinders the extrapolation of bibliographical data with different formulations to Dropcys.

In the USA, 0.1% mercaptamine eye drops was initially administered under an Investigational new Drug (IND) program, but in 1990 the formulation was changed to 0.55%. It was acknowledged that the 0.1% strength was frequently used in France until the recent introduction of a 0.5% gel formulation. From the information provided by the Applicant, it was difficult to establish the extent of use of the 0.1% strength across the EU. Indirect data from literature suggested its use in some countries in addition to France but no comprehensive overview of concentrations used in different EU countries has been provided.

Design and conduct of clinical studies

Most papers included data from case series or small retrospective studies. The prospective, randomised studies have been also submitted although the number of included patients was very limited (Kaiser-Kupfer *et.al*., 1990, Bradbury *et al*., 1991, MacDonald *et al.,* 1990, Labbe *et al.,* 2014). Eyes (and not patients) were the randomization unit. Whereas this paired-eye design requires additional adjustments due to clustering effect and makes masking potentially challenging, it was considered to be an acceptable method of optimizing the limited number of patients (Lee *et al.,* 2012; Fan *et al.,* 2011).

Children and adults with nephropatic cystinosis (in a wide age range) receiving treatment with oral mercaptamine have been evaluated in the submitted studies. The majority of patients were children, in line with the natural history of the condition.

The rate of corneal crystal accumulation in cystinosis reflects the severity of the CTNS mutation (Gahl *et al.,* 2000). In this regard, the role of 0.1% mercaptamine eye drops in less severe forms of the condition including the non-nephropatic form in which oral treatment with mercaptamine is not recommended has been considered. However, although patients with a milder form of the disease could potentially benefit from an eye drops preparation of 0.1% mercaptamine, there is insufficient data in this application for claiming the indication. No patients with a milder form of cystinosis seemed to be included in the submitted publications.

Selection of the patients in general has been made according to standard diagnostic criteria (leukocyte cystine concentration and the clinical presentation of the condition). Mercaptamine crystal corneal deposits have been qualified by slit lamp biomicroscopy. In all but one of the studies (Labbé *et al.,* 2014) the effect of topical mercaptamine has also been monitored with this technique. Some other methods have been reported in the scientific literature in order to quantify and analyze crystal deposition (e.g., *in vivo* confocal

microscopy; IVCM). IVCM provides a more sensitive and precise method although a great variability has been reported and it only can be used in patients older than 6 years. In general, slit-lamp examination was found to be acceptable as it constitutes the standard method of diagnosis and follow-up of corneal cystine deposits in clinical practice (Emma 2014).

With respect to the quantification of the density of corneal deposits, several scales based on semi quantitative scores have been used in different papers, the CCCS score built by Gahl (Gahl *et al.,* 2000) being the most widely used. It ranges from 0 to 3 with 0.125 increments (arbitrary units) based on a library of standard transparencies ranked in order of increasing density. A ceiling effect appears to occur in this scale so that after reaching the maximal value, the score seems little sensitive to changes. This plateau probably occurs because of the inability of the observer to distinguish grades of crystal density once the cornea becomes truly packed with crystals (Gahl *et al.,* 2000). This may happen in adult patients as corneal crystal accumulation increases with age. Differences between studies in methods of grading corneal deposits and in the definition of response make reaching sound conclusions on efficacy problematic.

Efficacy data and additional analyses

The analysis of efficacy of mercaptamine 0.1% eye drops mainly relies on the prospective, double-blind, placebo-controlled study by Kaiser-Kupfer (Kaiser-Kupfer *et al.,* 1990), conducted with the NIH formulation (0,1% mercaptamine solution in saline, not containing BAK and therefore different from Dropcys).

During the study, the 0.1% formulation was changed to a higher concentration (0.5%) so that only 7 subjects (5 children, 2 adolescents) were exclusively treated with the intended concentration for Dropcys. The five younger subjects showed a reduction of the density of corneal crystals evident on slit-lamp examination. No response was observed in the two older subjects. Whether the observed differences are the result of baseline differences with regards to corneal crystal density among the subjects or due to the true effect of topical mercaptamine treatment cannot be determined with the available data. The effect size with respect to placebo (control with normal saline eye drops) has not been reported. It is also unknown if the reduction in the corneal density was translated into a clinically relevant effect on the main symptoms (photophobia, pain, visual acuity, visual contrast sensitivity).

The retrospective cohort of patients with cystinosis followed-up at the Enfants Malades Hospital (Paris) and referenced in three publications (Dureau 2003, Broyer 1994 and Broyer 1995) provides some additional support. Although no mention is made of the concentration of the formulation administered, it was assumed that patients were treated with the 0.1% AGEPS formulation given that it was the only topical formulation available in France at that time. Very limited assessment of the efficacy of the treatment with topical mercaptamine eye drops with regards to corneal deposits and symptoms was included but only in the 2 publications from 1994 and 1995. In these retrospective comparisons, patients receiving mercaptamine eye drops had slightly better results compared to untreated patients. No sound conclusions can be drawn from this comparison.

No dose response study was submitted so it is not known if Dropcys contains the optimal concentration of mercaptamine. Limited conclusions can be drawn from indirect comparison of the different strengths (0.1%-0.5%). In general, papers in which mercaptamine 0.5% formulation was used include a greater number of patients and more consistent results compared to the 0.1% formulations. In relation to this point, additional efforts have been made by the Applicant in order to evaluate the efficacy of mercaptamine 0.1% versus 0.5% in the Kaiser-Kupfer 1990 study, analysing the results from patients treated with each concentration (0.1%, 0.5%) and the group of patients who were switched from 0.1% to 0.5%. After excluding several patients

(due to withdrawals, lack of available results, and other reasons) the Applicant eventually considered 20 patients (7, 4 and 9 respectively), to be suitable for inclusion in the analysis. A total of 71% (5/7) of patients treated with 0.1%, 75% (3/4) of those on 0.5% and 22% (2/9) of those patients who switched responded to treatment. Even though these figures may appear similar, the lack of robustness of this analysis prevents from drawing any conclusion of the comparative efficacy.

In Labbé *et al*., 2014 a cohort of 8 patients after being treated with 0.1% mercaptamine eye drops for 4 weeks received 0.5% mercaptamine (as a gel, four times daily) up to 4 years. The authors concluded that the gel was superior to 0.1% AGEPS formulation in terms of efficacy, although the exposure to 0.1% cysteamine eye drops was too short to be considered useful for comparative purposes. Gräf *et al.*, 1992 reported a paired-eye comparison between 0.1% and 0.5% formulations administered every two hours during waking hours in a two-year-old boy. In the right eye the 0.1% solution cleared the cystine crystals fully within 26 weeks. In the left eye, the 0.5% solution resulted in removal of the cystine crystals after 12 weeks.

Some of the papers cited by the applicant also suggest that higher concentrations could be preferable to 0.1% mercaptamine eye drops. Bradbury *et al.,* (1991) found a small improvement in visual function in 3 patients and minimal improvement in corneal crystal density in 2 patients receiving topical cysteamine 0.2%. The authors suggest administering 0.5% concentration at least 6 times a day to obtain the quickest improvement in visual function. Gräf (1992) indicated that efficacy depends on the concentration and the number of daily instillations, and recommended a dose of 0.5% at 5–6 times a day. Also, Kaiser-Kupfer et al (1990) pointed out the variable success in clearing corneal crystals achieved with 0.1% mercaptamine. In this study, 6 patients initially treated with 0.1%, were switched to 0.5% eye drops, due to the lack of response.

The uncertainties about the efficacy of the 0.1% formulation are even greater for older patients (age >4 years). Whereas from the results published by Gahl *et al.* 2000, it can be concluded that there is a possibility of clearing cystinotic crystals in the patients of all ages using 0.5% concentration of mercaptamine, this has not been shown with 0.1% concentration in the reported data. None of the older patients reported in the main study (Kaiser-Kupfer *et al.,* 1990) treated with the 0.1% formulation reached the end point. As the corneal crystal density increases with age, crystal packed corneas may be less sensitive to the action of mercaptamine, especially in 0.1% concentration.

The posology proposed by the Applicant is 1 drop in each eye at least 5 times a day or every waking hour for optimal efficacy. This dosing was in principle based on the published studies. The efficacy of mercaptamine eye drops is dependent on the initial crystal load in the cornea and the frequency of instillations whereby a higher frequency of instillations increases chances to clear the crystals. This is supported by the majority of presented studies. Best results are usually obtained with a very high number of instillations from 6 to even 12 times daily and compliance has been considered a critical issue in the response to mercaptamine. Given the poor adherence to the treatment repeatedly reported in the submitted studies, the high frequency of administration required for Dropcys is expected to be a disadvantage for this product and can raise difficulties for the patients, especially for the young or adolescent patients at school.

Given the limited available information, further posology recommendations based on other relevant factors (age, density of the deposits, duration of treatment and clinical variant) cannot be given. The Applicant has initially requested that Dropcys should be also indicated to prevent corneal deposits. The claim of the prevention was based on the results of ten patients (one patient reported in Kaiser-Kupfer *et al.,* 1990, and nine patients briefly described in Jain *et al.*, 1988). In all cases, patients presented with corneal deposits. In the first case, the crystals appeared a few months after the treatment was started, apparently due to poor

compliance, and were reduced when the treatment compliance was improved. In the second paper, the authors stated that cysteamine eye drops prevented new cystine crystal deposition. Whereas the corneal crystal accumulation is reversible by cysteamine eye drops therapy, the reappearance of crystals once the local treatment is suspended seems likely. In this sense, the recommendation of maintenance of treatment in order to prevent new corneal crystal deposits was considered to be reasonable. This is considered secondary prevention (or maintenance of the effect). No information was available for patients without corneal deposits (truly naïve patients), so the indication for primary prevention was not considered appropriate.

2.5.4. Conclusions on the clinical efficacy

Although the role of topical mercaptamine eye drops in the treatment of corneal crystal deposits appears sufficiently supported by the scientific literature, clinical recommendations and the routine use of hospital preparations, the evidence supporting the use of 0.1% concentration in the formulation proposed by the Applicant is very limited. The main analysis of efficacy principally relies on the results of one study (Kaiser-Kupfer et al., 1990), in which a reduction of corneal crystals density has been shown in only 5 children, all younger than 4 years old. This study however used a different formulation than the one proposed for Dropcys. Moreover, based on the information available from this publication, the effect size in comparison to placebo and the extent to which the reduction in cystine crystals achieved by 0.1% mercaptamine eye drops translates into a clinically relevant outcome, such as reduction of photophobia, is not known. Altogether, the study from Kaiser-Kupfer did not allow concluding on a robust treatment effect. The retrospective studies and case studies provided very limited evidence for efficacy of Dropcys and were considered to be only supportive.

The CHMP was of the view that the available data did not provide sufficient evidence to conclude on a clinically relevant treatment effect of 0.1% mercaptamine in the proposed eye drop formulation for the treatment and prevention of corneal cystine deposits in patients with cystinosis.

2.6. Clinical safety

The safety analysis of Dropcys was based upon data available in the published literature.

Patient exposure

Exposure to 0.1% mercaptamine eye drops

The number of patients described in literature who were exposed to 0.1% mercaptamine eye drops is presented in the Table 12 below. Some of these patients were considered as non-evaluable due to the absence of safety data in the published articles.

Table 12: Patient exposure to 0.1% mercaptamine

Reference		N pts	Duration of exposure (y)	Frequency per day	Long term exposure (pts treated ≥6 months)
NIH studies	*Kaiser-Kupfer 1987*	*2*	*0.33 and 0.42*	8-12	*0*
	Jain 1988	10	Up to 1.8		NA
	Kaiser-Kupfer 1990	16 (incl. *2* above)	0.08 to 3.25		10
AGEPS studies	*Broyer 1994*	*7*	*NA*	6	*NA*
	Broyer 1995	*23 (incl. 7 above)*			
	Dureau 2003	29 (incl. *23* above)	1.2 to 17.9		19
	Labbé 2014	8 (baseline/run-in)	0.08	4	0
Gräf 1992		1	0.5	6-8	1
Blanksma 1996		3	1	5	3
Tavares 2009		1	1	10	1
Total		**68**			**34**

Only the studies conducted in France, i.e. Broyer *et al.,* 1994, Broyer *et al.,* 1995, Dureau *et al.,* 2003, and Labbé *et al.,* 2014, have reported specifically on the AGEPS formulation containing 0.1% mercaptamine and 0.02% BAK (identical to Dropcys). These studies included a total of 37 patients as the patients in Broyer's studies have been accounted for in Dureau's study. Although the publications from Broyer do not specify the exact concentration of mercaptamine, only the AGEPS formulation was prepared and supplied in France at the time the study was conducted.

The 0.1% concentration has also been evaluated in other studies: mainly those from the NIH by Kaiser-Kupfer *et al.,* (1987, 1990) and Jain *et al.,* 1988 as well as in 3 case reports. The formulation used in these studies differed from Dropcys with regards to excipients and preservatives as well as conditions of preparation and storage.

The posology was 6 times per day in all French studies except one, Labbé *et al.,* 2014, where it was 4 times per day. The dosing administration was "every hour when awake" in the NIH studies, which is relatively imprecise. The Applicant estimated that the drops were administered 8-12 times daily. The minimum figure of 8 times/day was inferred from the details in Iwata *et al.* (1998) where the patients considered to be compliant were described as taking eye drops 8 times or more daily; the maximum figure of 12 was derived from Gahl et al. (2000) where it was noted that the 10 responders were taking eye drops 8-12 times/day.

The shortest exposure to 0.1% mercaptamine AGEPS was during the run-in phase of the latest study published (Labbé *et al.,* 2014), which lasted 1 month. The longest exposure was in Dureau *et al.,* 2003 study where 9 subjects were followed up for several years. Taking into account all 0.1% formulations, 34 patients were exposed for over 6 months

It is estimated that approximately 100 patients received AGEPS formulation in France as a hospital-only preparation over 25 years until September 2013. However, no reports of an adverse reaction were made to AGEPS or to the French Agency (ANSM) during this time.

Exposure to different concentrations of mercaptamine.

5 patients were exposed to 0.2% mercaptamine 6 times per day for 6 months (Bradbury *et al.,* 1991) and 4 to 0.3% mercaptamine 4 times/d for 7 months (MacDonald *et al.,* 1990).

157 patients were exposed to 0.5% formulation. However, as no treatment details were provided for 113 patients from Gahl *et al.* (2000), safety information is only available for 67 patients.

Table 13 Patient exposure to 0.5% mercaptamine

Reference		N pts	Duration of exposure (y)	Frequency per day	Long term exposure (pts treated ≥6 months)
Jones 1991		1	0.25	12	0
Gräf 1992		1	0.5	6-8	1
NIH studies	Kaiser-Kupfer 1990	14	0.08 to 0.75	8-12	NA
	Iwata 1998	12	0.75-2.5		12
	Gahl 2000	*113 (mini-review)*	*≥1*		*113*
	Tsilou 2003	19	1		19
Khan 2004		1	1	5	1
Bozdag 2008		*6 Healthy Volunteers*	*0.02*	*4*	*0*
Soliman 2009		11	0.25-1	6	8
Labbé 2014		8	4	4	8
Total		***67 (or 154)***			***49 (or 150)***

Adverse events

0, 1% formulation

Ten articles have been considered for the assessment of the safety profile of 0.1% mercaptamine hydrochloride eye drops (see Table 14 below). The majority of the authors reported no safety issues with mercaptamine formulations or did not report any adverse events because safety assessment was not the objective of the study. Consequently, the information available for 0.1% formulation was considered to be very limited.

Table 14: Adverse events in patients receiving 0.1% formulation

Reference		N pts	Adverse event reported
NIH studies	*Kaiser-Kupfer 1987*	*2*	No clinical toxicity from eyedrops; no conjunctival injection or soft-tissue irritation
	Jain 1988	10	No inflammatory reaction in the treated eye
	Kaiser-Kupfer 1990	16 (incl. *2* above)	No mention
AGEPS studies	*Broyer 1994*	*7*	*Unrelated to treatment (see SAE section): Amblyopia (5); Deaths (6)*
	Broyer 1995	*23 (incl. 7 above)*	
	Dureau 2003	29 (incl. *23* above)	No mention
	Labbé 2014	8 (baseline/run-in)	No significant AE related to the study drug Stinging /burning at instillation in 5 pts
Gräf 1992		1	None
Blanksma 1996		3	No mention
Tavares 2009		1	None
Total		**68**	**5 adverse drug reaction**

AEs in all formulations

All AEs reported in the literature for all mercaptamine formulations (whether or not possibly drug related) have been compiled in Table 15 below.

Table 15: Incidence (per eye) of AE with various mercaptamine hydrochloride eyedrops formulations

	0.1%	0.2%	0.3%	0.5%	0.5% gel
Pts exposed (N)	65	5	4	149	8
AE possibly related to study drug					
Stinging or burning at instillation	5		1	12	6
Burning				1	
Redness				7	
Irritation				1	
Discomfort				2	
Itching				1	
Blurring					2
AE not related to study drug					
Decreased visual acuity /amblyopia	5		2	4	
Urticarial reaction		1			
Vitreous haemorrhage				1	
Deaths	6			5	

The safety data was particularly well-documented for the 0.5% formulation in the study by Tsilou *et al.* (2003). During this study, the subject or parent was asked to keep a daily calendar recording pre-listed adverse events (AE): changes in vision, blurring, redness, episodes of acute corneal pain, other pain, irritation, and itching. AE were collected after 1, 2, and 4 weeks, and every 3 months thereafter for 1 year of treatment.

Table 16 Incidence (per eye) of AE with 0,5% cysteamine hydrochloride eyedrops formulations

Formulation	NIH		Sigma-Tau		Total	
Eyes (N; %)	**35**	**100%**	**35**	**100%**	**70**	**100%**
Events persisting less than 1 hour	12	34	25	71	37	53
Events persisting in excess of 1 hour	12	34	18	51	30	43
Redness	7	20	9	26	16	23
Irritation	1	3	3	9	4	6
Discomfort	2	6	2	6	4	6
Itching	1	3	2	6	3	4
Blurring	1	3	1	3	2	3
Severe Pain	0	0	1	3	1	1
Total eyes with 1 symptom	**8**	**23**	**10**	**29**	**18**	**26**

There was no statistical difference between the 2 formulations in the number of eyes with AE persisting longer than 1 hour, which occurred in a mean 43% of the treated eyes. Stinging and burning sensations were the most common “short term” reactions (i.e. persisting less than one hour) which were twice more frequent with the Sigma-Tau formulation than with the NIH formulation. These AE occurred in a mean 53 % of the treated eyes.

In general, the most common AE associated with mercaptamine eye drops, regardless of the concentration, were related to eye disorders, especially to the eye instillation (e.g. redness, irritation, discomfort, itching, blurring, severe pain, burning sensation, loss of vision). The only AE reported with 0.1% mercaptamine were stinging and burning sensation at instillation (Labbé 2014), which occurred in 5 out of 8 patients.

Serious adverse events / deaths / discontinuations

The Table below summarizes the serious adverse events (SAE), deaths and discontinuations published in the literature and their relationship with the treatment.

Reference	N pts	Duration of exposure (y)	SAE	Discontinuations other than death	Reason
Kaiser-Kupfer 1990	14	0.08-0.75	2 deaths	2 1 child (6 y old) ; 1 adult (31 y old)	unrelated to treatment
Broyer 1995	23	NA	5 amblyopia	no	unrelated to treatment (see details above)
			6 deaths		unrelated to treatment: - encephalopathy (2) - septicemia post splenectomy (2) - multi-organ failure (2)
Iwata 1998	12	0.75-2.5	amblyopia	1 (3 y old)	unrelated to treatment
			vitreous haemorrhage	no	unrelated to treatment
Tsilou 2003	19	1	decreased visual acuity	1	unrelated to treatment: testing inconsistency
Soliman 2009	11	0.25-1	3 deaths	NA	unrelated to treatment
Total discontinuations			Deaths 11	Other 4	Total 15

In Broyer *et al*.,1995 study, six patients out of 23 died from complications secondary to the underlying disease and five patients presented severe amblyopia in at least one eye (visual acuity <5). The evolution towards a progressive loss of visual acuity is not related to mercaptamine eye drops use but to the natural evolution of the disease, as shown in Dureau et al. 2003.

In Iwata et al. 1998, a 3-year old patient was diagnosed with ameotropic amblyopia in the cystamine treated eye, not the eye receiving mercaptamine. It was also noted that one of the two 3-year old female patients was poorly compliant and discontinued treatment for this reason. It is unknown whether this was the same patient who earlier developed amblyopia. One patient with a history of diabetes mellitus for the past 3 years developed consecutive vitreous haemorrhages in each eye. These have been presumably unrelated to treatment, as it has been demonstrated that even very high concentrations of mercaptamine (50 or 100 mmol/L every half hour for 2, 6 or 8 hours) do not penetrate the aqueous humor (Hsuan *et al.,* 1996).

There was no potential relationship between discontinuations and mercaptamine topical administration.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The documentation provided in support of this application was considered very limited. Literature reports were mainly focused on efficacy data while safety data were only scarcely described. Only ten articles out of seventeen could be taken into account for the safety analysis of 0.1% mercaptamine eye drops. The total number of patients exposed to this concentration was low (68 patients) but it was still considered to be a representative group, taking into account that cystinosis is a rare disorder.

The Dropcys formulation is identical to the AGEPS formulation, used in the Broyer *et al*., 1994, Broyer *et al*., 1995, Dureau *et al*., 2003 and Labbe *et al*., 2014. Therefore, among the 68 patients exposed to 0.1% mercaptamine only 37 patients were exposed to the exact formulation for which approval is sought (0.1% mercaptamine and 0.02% BAK). The remaining patients were exposed to the proposed concentration of mercaptamine (0.1%) but with lower concentration of BAK, different storage conditions, etc. Nineteen

patients out of 37 were treated more than 6 months. Taking into account all formulations, 34 out of 68 patients (50%) received 0.1% mercaptamine concentration for more than 6 months.

The most common AE associated with mercaptamine eye drops, regardless of the concentration, are eye disorders, particularly related to the instillation (e.g. redness, irritation, discomfort, itching, blurring, severe pain, burning sensation, loss of vision). Other eye disorders such as photophobia, blepharospasm, corneal erosions and reduced visual acuity were most likely related to the underlying disease or its complications. Systemic absorption from the ocular surface is limited and no systemic adverse events are expected. Moreover, patients treated with eye drops would be also receiving mercaptamine *via* oral route which would be the main source of systemic exposure.

Underreporting of safety data was a clear limitation of the dossier. In particular, it was difficult to understand the lack of reports of adverse reactions made to AGEPS or to the ANSM concerning the use of the hospital preparation administered under compassionate use, while in the study reported by Labbe *et al.,* 2014, local adverse effects were reported in more than 50% patients treated with this formulation. The Applicant claimed that the lack of adverse reaction reports might result from "well-known under-reporting of AEs for marketed formulations". The Applicant also indicated that all AEs reported in Labbe *et al.,* 2014, were related to the underlying disease or its complications. Nevertheless, this kind of AEs should also have been observed in patients treated with the AGEPS formulation under compassionate use and reported accordingly.

Due to the low reporting rate of adverse events, long-term safety with 0.1% mercaptamine is at present unknown. This limitation can be partially solved by data available for the higher dose (0.5%). According to this information, the incidence of adverse events seems to be dose-dependent. AEs were reported with higher incidence with 0.5% mercaptamine rather than with 0.1% mercaptamine. Tsilou et al., 2003 reported the only study which addressed safety in a well-described and structured manner although only the 0.5% strength was investigated. In this study, 0.5% mercaptamine did not cause adverse events which would be unmanageable by the patients or lead to discontinuation. These data was considered to be supportive and showed that the safety profile could be acceptable with both concentrations of mercaptamine.

The frequency of administration reported in the literature varied from 4 times a day to hourly. Cases of poor compliance were mainly linked to the high frequency of administration rather than to the ocular toxicity. It was noted in the literature that there is a high variability in the treatment compliance which could negatively impact on efficacy results. In relation to safety, although stinging and burning sensation could appear in more than 50% of patients treated with 0.1% mercaptamine, the rate of discontinuations due to AEs was very low and none of them were related to treatment. Hence, topical mercaptamine seems to be well-tolerated. However, the possible increase of adverse events due to BAK content or low pH of the solution is at present uncertain.

The proposed formulation includes 0.02% of BAK which is the most commonly used preservative in ophthalmic solutions, at a concentration of 0.01-0.02%. BAK has been reported to cause eye irritation, punctate keratopathy and/or toxic ulcerative keratopathy and monitoring is necessary with the prolonged use in patients with a compromised cornea and dry eye [*Questions and Answers on Benzalkonium chloride in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for 6 human use*' (CPMP/463/00)].

Given that Dropcys has not been tested in any clinical trial and since short-term and long-term adverse events described in published literature seem to be underreported, the concentration of BAK raised safety concerns. Taking into account the intended posology (i.e. at least 5 times per day or every waking hour), the chronic nature of the disease and the expected long term use of this formulation, the total exposure to BAK

per day will be higher than the usual daily dose of BAK in other ophthalmological products. A higher incidence of adverse events due to BAK cannot be ruled out. Moreover, the inclusion of BAK as a preservative raised a concern about the use of this product in children. According to '*Guideline on pharmaceutical development of medicines for paediatric use*' *(EMA/CHMP/QWP/805880/2012 Rev. 1*), the choice of the preservative system at the lowest concentration feasible should be justified in terms of benefit-risk balance. Preservative-free paediatric formulations are generally preferable.

The Applicant proposed to reduce the level of BAK in the formulation. However, as discussed in the Quality assessment, the lowest level of preservative possible to ensure an acceptable stability has not been determined. Therefore, it is uncertain whether higher levels of BAK are being unnecessarily administered to the target population. From a safety point of view, it is important to choose the minimum concentration of BAK in order to reduce as much as possible the incidence of ocular adverse events, especially in children. At the same time, given that BAK is well recognised as a permeability enhancer, the reduction of BAK may potentially have an impact on efficacy. According to Tsilou *et al.,* 2003 study, changes in the excipients such as concentration of BAK or addition/exclusion of other excipients could lead to a different efficacy and safety profile (see also "*Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing known constituents*" *(CPMP/EWP/239/95)*).

The pH of the Dropcys solution after reconstitution ranges from 3.4 to 4.0. When the eye drops pH value gets outside the range of 4–8, the patient may feel discomfort at instillation, there may be irritation, and the drug bioavailability can decrease because of increased tearing (Baranowski *et al.,* 2014). In the *in vitro/in vivo* study by Bozdag *et al.,* (2008) the pH of the solutions was around 4.3 and was well tolerated. In the only study in which stinging/burning sensations were reported (Labbé *et al.,* 2014), these occurred in 5 out of 8 patients after use of 0.1% mercaptamine and in 6 out of 8 patients, once they had been switched to the 0.5% formulation with a higher pH 5.2. Therefore, the Applicant argued that the potential impact of the selected pH appears not to be problematic to ocular discomfort. However, as discussed earlier, the absence of reported adverse events with 0.1% mercaptamine does not provide assurance for a positive safety profile of Dropcys. Potential risks and the increased likelihood of LADRS or SAEs linked to the low pH are at present unknown due to the aforementioned limitations of the data submitted in support of this application. The pH of the product was not well justified from a pharmaceutical point of view.

Considering that several phenotypes of cystinosis are described depending on the degree of severity and age of onset (i.e. infantile form, late-onset juvenile form and adult cystinosis) (Shams *et al.,* 2014), a comprehensive overview of safety would be helpful. However, with such low reporting rates of AEs in the cited publications, safety could not be discussed for each age group or for the various phenotypes of cystinosis.

Given the similar structure between mercaptamine and D-penicillamine, mercaptamine may interfere with the cross-linking collagen fibres leading to ocular disorders similar to those described for Ehler Danlos Syndrome (i.e. scleral fragility, rupture of ocular globe, keratoconus, retinal detachment, glaucoma, amblyopia, dry eye syndrome, strabismus and hyperextensible eyelids). The incidence of these ocular disorders as a result of ocular mercaptamine use is not very likely but cannot be ruled out.

The Applicant did not conduct a preservative efficacy study. Moreover, a concern related to the manipulation of the container by patients and the resulting risk of microbial contamination was also raised (see section 2.2.). As no eye infections were reported in the literature and detailed instructions for use were included in the proposed SmPC, the CHMP was of the opinion that this risk can be managed adequately. However, development of a more suitable container would have been preferable.

2.6.2. Conclusions on the clinical safety

Safety data reported in the published literature did not raise any major safety concerns with the use of 0.1% mercaptamine eye drops. The most commonly reported AEs were eye disorders. Stinging and burning sensation could appear in more than 50% of patients treated with 0.1% mercaptamine. However, no patient discontinued the treatment due to adverse events.

Nevertheless, several uncertainties remained as the safety profile for the proposed formulation and recommended dosing frequency was not characterised sufficiently by means of the data provided in support of this application. The number of concerns and uncertainties related to the formulation (the BAK concentration, preservative efficacy and pH) as well as the scarceness of well-documented safety data did not allow concluding that the safety profile of Dropcys is acceptable.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3)(ia) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet does not yet meet the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* The applicant was asked to address the following minor issues concerning the user consultation with target patient group population on the package leaflet.

From the data submitted, it was not entirely clear how many of the participants found and understood the information. This requires further clarification.

In addition, the package leaflet has been tested in French language. This is not *per se* a problem and should

be acceptable but an adequate justification that the text in French corresponds to the English version included in the dossier should be provided.

Lastly, it should be noted that the tested leaflet differed from the leaflet placed in the box of medicine (paper 80g/cm2), i.e. tested leaflet was twice as heavy as the final printed leaflet.

2.9.2. Labelling exemptions

A request of translation exemption of the labelling as per Article 63(1) of Directive 2001/83/EC has been submitted by the applicant and has been found partially acceptable by the QRD Group for the following reasons:

The Group agreed to propose a simplification of the 2 vials' labels as follows:

- Powder vial: to only keep the name, strength, pharmaceutical form, INN, content, and EXP and Lot. In this case, only the pharmaceutical form would need to be translated.

- Solvent vial: only the INN, the word "solvent", EXP and Lot could be kept on the label.

The words "eye drops" and "solvent" could be translated in ES, FR and DE only. All other Member States could have accepted English only labelling with the simplification agreed above.

The labelling subject to translation exemption as per the QRD Group decision above could, however, be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials could have only be translated in the language(s) as agreed by the QRD Group.

The particulars to be omitted as per the QRD Group decision described above could, however, be included in the Annexes published with the EPAR on EMA website, and translated in all languages but could have appear in grey-shaded to show that they would not be included on the printed materials.

Since the product is not recommended for authorisation, the above described exemptions are not relevant in practice.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Nephropathic cystinosis is characterized by an accumulation of cystine crystals in several tissues including ocular tissues. Progressive cystine accumulation in the eye results in photophobia and the impairment of visual function and may lead to ulcerative keratopathy and oedema of the corneal stroma and finally to blindness and related disability. Topical treatment with mercaptamine hydrochloride eye drops has been used in clinical practice for several years to remove or reduce corneal crystal density in order to alleviate the ocular symptoms. In the long term, the treatment is expected to maintain visual acuity and avoid potential

blindness. In Europe, mercaptamine eye drops are currently not licensed for marketing but are supplied as hospital formulation in several countries. The strength of the eye drops used in clinical practice differs between EU countries.

Dropsys is a mercaptamine 0.1% eye drops formulation including 0.02% BAK. The benefits of Dropcys in the treatment and prevention of corneal cystine deposits in patients with cystinosis were based on a bibliographic review of the available data in the scientific literature. According to the published literature, 68 nephropatic cystinosis patients have been treated with 0.1% mercaptamine eye drops but only 37 patients received the intended formulation (Broyer *et al.,* 1994, Broyer *et al.,* 1995, Dureau *et al.,* 2003, Labbé *et al.,* 2009 and Labbé *et al.,* 2014).

The main evidence for the efficacy of Dropcys was derived from a study by Kaiser-Kupfer *et al.* (1990), a prospective, placebo-controlled clinical trial in cystinosis patients. In this study, mercaptamine 0.1% eye drops reduced the corneal crystal density in 5 out of 7 patients but the effect size in comparison to placebo was not specified.

A retrospective study by Broyer *et al.* 1995 provided additional information from 23 patients (10-25 years) treated with mercaptamine 0.1% for an undetermined period of time. In this study, corneal deposits were graded from 0 to 3, and small differences were observed between treated patients (2.6) and untreated control group (3.0).

Uncertainty in the knowledge about the beneficial effects

As shown in the study by Tsilou *et al.* 2003, differences in the formulation (preservatives, excipients or buffers) of mercaptamine eye drops may have a significant impact on the efficacy and safety outcome in the treatment of corneal cystine deposits. Therefore, the extrapolation of the results of those studies in which formulations with a different composition has been administered is problematic.

While in principle, the effect of topical administration of mercaptamine on the reduction of corneal crystal density is accepted, the wide range of mercaptamine concentrations used in the studies suggests that the optimal concentration is higher than 0.1%. In addition, although it is acknowledged that the 0.1% strength was frequently used in France, the extent of use of this strength across EU remains unknown. Indirect data from literature suggest its use in some other EU countries.

In the prospective Kaiser-Kupfer study only seven patients were treated with 0.1% mercaptamine eye drops (NIH formulation, different from Dropcys) and 9 patients initially treated with 0.1% concentration were switched to 0.5% mercaptamine. This constitutes a very limited database to support the efficacy of the product. An *ad hoc* analysis evaluating the comparative efficacy of mercaptamine 0.1% versus 0.5% within this study showed that 71% (5/7) of patients treated with 0.1%, 75% (3/4) of those on 0.5% and 22% (2/9) of those patients who switched responded to treatment. Even if these figures appear similar, the lack of robustness of this analysis prevents from drawing any conclusion of the comparative efficacy.

Little information was available about the effect of mercaptamine 0.1% on the main complications related to the cystine crystal accumulation (such as photophobia, blepharospasm, pain, visual acuity, and visual contrast sensitivity). Only one retrospective cohort, as described in Broyer *et al.,* 1994, has shown a positive trend on photophobia.

In general, the retrospective analyses and case studies provide little support for the efficacy of Dropcys. In Dureau 2003, the authors suggest that topical cysteamine may limit more severe forms of visual disability in

cystinosis patients. However, no firm conclusions were reached regarding the potential role of the topical treatment on the evolution of the ocular manifestations of this condition. Semi quantitative assessment of the efficacy of the treatment with topical mercaptamine eye drops as described in the Broyer studies was considered to be of limited value.

There were significant concerns about the efficacy of Dropcys in patients older than 4 years. It could be assumed that young patients with fewer crystals could respond better and faster than older ones with packed corneas. In the Keiser-Kupfer *et al.,* 2000 study, the only two older patients (age 15 and 19 years) receiving 0.1% mercaptamine did not respond after 39 months of treatment and the effects observed in retrospective studies were questionable. Consequently, the efficacy of 0.1% mercaptamine in older patients has not been demonstrated.

There are some uncertainties about the beneficial effects of the different mercaptamine concentrations. It is generally acknowledged, that the initial density of cystine crystals in the cornea affects the efficacy of topical treatment with mercaptamine. The majority of the submitted publications investigated efficacy of 0.5% formulations, including in older patients but this data could not be accepted as an evidence of efficacy for 0,1% formulation. The few available indirect comparisons in the literature between 0.1% and 0.5% mercaptamine eye drops were mostly in favour of the 0.5% formulation. This includes recommendations made in an international consensus paper recently published by a number of clinical experts in the field of cystinosis (Emma *et al.,* 2014). Therefore, there are reasonable doubts that patients receiving 0.1% mercaptamine eye drops would be treated with an appropriate concentration of mercaptamine hydrochloride.

The posology recommended for Dropcys is 1 drop in each eye at least 5 times a day or every waking hour for optimal efficacy. These recommendations were in principle based on the studies available in the public domain but constitute a wide range of possible doses. It is unknown if the differences in dosing may result in significant differences in the outcome. Given the limited information, further posology recommendations based on relevant factors (age, density of the deposits, duration of treatment and clinical variant) could not be done.

Risks

Unfavourable effects

Overall, 37 patients were exposed to a formulation identical to Dropcys (0.1% mercaptamine and 0.02% BAK) including 19 for a duration longer than 6 months.

The majority of AEs reported for mercaptamine eye drops, irrespective of the concentration, were local ocular effects. Most of them were related to the eye instillation (e.g. redness, irritation, discomfort, itching, blurring, severe pain, burning sensation, loss of vision). Adverse events specifically reported with 0.1% mercaptamine were stinging and burning sensation at instillation, which occurred with an incidence higher than 50%. However, no patients discontinued the treatment due to adverse events related to treatment. No SAEs such as amblyopia and no deaths were considered related to the treatment.

Uncertainty in the knowledge about the unfavourable effects

The safety database was rather limited, in particular with regards to long-term data. Some patients were exposed to eye drops with different mercaptamine concentration or to mercaptamine 0.1% in a different formulation. Formulations containing no BAK were investigated in several publications: Gräf *et al*. 1992; Tavares *et al*. 2009 and in early NIH studies. As excipients are known to influence the safety profile of topical

formulations, the differences in the formulations studied posed additional difficulty in the evaluation of Dropcys safety profile.

AEs were generally underreported as the published articles focused on efficacy aspects. Only 10 articles could have been used for safety evaluation and only one study (Tsilou *et al.,* 2003) specifically assessed safety in a well-described and structured manner. In this study, however, only 0.5% mercaptamine was evaluated. It was also not clearly established why there were no adverse events reported for the AGEPS formulation when it was being administered in France under compassionate use program.

Although it was acknowledged that safety data reported with the proposed formulation are scarce, available data for 0.5% mercaptamine were considered supportive for the safety evaluation. This represented a more conservative position and partially solved the limitation of the safety database.

Other uncertainty was related to the lack of safety analysis by age groups and by the phenotype of cystinosis. As the data were very limited, the impact of these factors on the safety profile could not be established.

The main uncertainties were related to the formulation. It is known that BAK and low pH of the solution cause eye disorders such as eye burning, severe ocular surface damage and ocular discomfort. Frequent schedule of administration and long-term use as recommended for Dropcys may lead to a high exposure of BAK and related adverse events. A reduction of the level of BAK in the formulation was proposed by the Applicant in order to minimize the incidence of adverse events. However, this reduction could not be considered until the lowest level of BAK that ensures microbiological quality of the formulation is determined. As a report of the preservative efficacy test has not been submitted, it is presently uncertain if the current BAK level (0.02%) is required or if lower BAK concentrations would be sufficient to ensure preservation. As a result, patients might be unnecessarily exposed to too high BAK concentration. This is especially concerning as Dropcys was intended to be used in children and the preservative-free formulations are generally preferred for the paediatric population.

Balance

Importance of favourable and unfavourable effects

Although the role of topical mercaptamine eye drops in the treatment of corneal crystal deposits appears sufficiently supported by reports in the scientific literature, clinical recommendations and the routine use of hospital preparations, the evidence supporting the use of a 0.1% concentration in the formulation proposed for Dropcys is limited. The main support for efficacy is derived from the results of the Kaiser-Kupfer study, in which a reduction of corneal crystals density has been shown in only 5 out of 7 patients, all younger than 4 years of age. Moreover, the extent to which reduction in cystine crystals achieved by 0.1% mercaptamine eye drops translates into a clinically relevant outcome, such as reduction of photophobia, is not known.

The safety profile of 0.1% mercaptamine appears to be acceptable, on the basis of data reported in the published literature. The most common AEs were related to eye disorders, such as stinging and burning sensation observed in more than 50% of patients treated with 0.1% mercaptamine. Incidence of LARDS seemed to increase when higher doses of mercaptamine were used. The patients seemed to be able to manage the most common adverse events.

Nevertheless, the safety data in the submitted literature were scarce and not well documented, especially with regards to long term effects and uncertainties related to the safety of the formulation remain unresolved.

The inclusion of 0.02% BAK in the proposed formulation is of particular concern, especially if posology recommendations are followed and Dropcys is administered every waking hour. Similarly, there are concerns about the high acidity of the solution (pH 3.5-5) and the resulting impact on the cornea surface following frequent and long-term exposure. It has been reported in the literature that patients apply mercaptamine eye drops less frequently than needed, in part because they cause eye burning, due to the low pH of the solution (Emma 2014). As a result, the increase of adverse events due to BAK or low pH of the solution could lead to worse treatment compliance and consequently, worse efficacy outcome.

Benefit-risk balance

Based on the available data, the CHMP is the opinion that the benefit/risk balance for Dropcys in the treatment and prevention of corneal cystine deposits in patients with cystinosis is negative.

Discussion on the benefit-risk assessment

The bibliographic references provided to support the efficacy of the 0.1% concentration in the formulation were very limited and do not allow demonstration of the efficacy of the product. These data are insufficient to demonstrate a positive benefit/risk for the product and support a marketing authorization, even considering the rare nature of the disease and the unmet medical need of the patients.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Dropcys in the prevention and treatment of corneal cystine deposits in patients with cystinosis receiving oral cysteamine therapy, the CHMP considers by majority decision that

[a] the quality, safety and efficacy of the above mentioned medicinal product are not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

Whereas

- The efficacy of Dropcys eye drops (0.1% mercaptamine) was not sufficiently demonstrated. The bibliographic references provided to support the efficacy of the 0.1% concentration for the intended formulation were very limited and did not allow demonstration of the efficacy of the product.

- Furthermore, at this stage, the development of the formulation was not appropriately justified with regard to the levels of benzalkonium chloride, ascorbic acid, the target pH and buffer capacity of the product.

The resulting impact on ocular safety has not been adequately justified taking into account that this formulation is intended to be mainly used to treat paediatric population in a very frequent schedule of administration and in long-term (chronic disease).

• No in-use stability data were provided to support the proposed posology and shelf-life after reconstitution. Moreover, the maintenance of microbiological quality of the product during the course of treatment was not established.

The CHMP is of the opinion that pursuant to Article 12(1) of Regulation (EC) No 726/2004, the quality, safety and efficacy of the above mentioned medicinal product are not properly or sufficiently demonstrated.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet and risk management plan cannot be agreed at this stage.

Divergent position to the majority recommendation is appended to this report.

5. Re-examination of the CHMP opinion of 17 December 2015

Following the CHMP conclusion that Dropcys was not approvable as the quality, safety and efficacy were not properly or sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation.

A summary of the applicant´s grounds for re-examination is presented below.

Ground 1

The efficacy of Dropcys eye drops (0.1% mercaptamine) was not sufficiently demonstrated. The bibliographic references provided to support the efficacy of the 0.1% concentration for the intended formulation were very limited and did not allow demonstration of the efficacy of the product.

Applicant's position (summarised)

The Applicant summarised the experience of treatment of ophthalmic cystinosis gathered in France with 0.1% mercaptamine hydrochloride eye drops. The proposed formulation was developed at the Enfants-Malades Hospital in Paris which was one of the most important centres of expertise in the description and management of cystinosis. (Dureau 2003). In spite of this undisputed notoriety, only few ophthalmological results have been described in published reviews (Broyer 1994, Broyer 1995).

In the retrospective comparisons, patients receiving 0.1% mercaptamine eye drops had slightly better results when compared to untreated patients (Broyer 1994, Broyer 1995). Based on these observations, most patients in France were continuously treated with 0.1% mercaptamine eye drops for 20-25 years. This represents a total of at least 50 patients x 20 years = 1000 patient-years exposure to treatment (and, at least 4 million drops administered) which per se constitutes a robust evidence base of the favourable benefit-risk of the 0.1% mercaptamine eye drops. During these decades of treatment, 0.1% mercaptamine eye drops

was produced by AGEPS and provided to all patients throughout the country with no known reports of adverse events to ANSM, AGEPS, any of the 13 regional centres of pharmacovigilance, the reference centres or local hospitals. These facts should be seen as strong evidence of the beneficial effects of the product and of its acceptable safety profile. In particular, in a patient population where poor observance to chronic systemic mercaptamine treatment is very well-established, it could not have been justified to any of these key opinion leaders, physicians or pharmacists and/or to the regulatory agencies to maintain the production, distribution and treatment of such "difficult" patients with an additional burdensome treatment such as eye drops that must be administered every waking hour and life-long.

The Applicant has also presented an overview of 0.1% mercaptamine eye drops use in other EU countries (17 patients in the UK, Germany, Switzerland, The Netherlands and Portugal).

In terms of patients' prospective exposure to 0.1 % mercaptamine eye drops, patients described in the publications have been exposed to a median (range) of nearly 4000 drops (1200-12,000) as shown in table below.

Tab 2

Reference	N° patient	Treatment duration		Eye drops frequency	Mean total eye drops exposure
			days		
Kaiser Kupfer 1990	1	24 months	732	8-12	7320
	2	14 months	427		4270
	3	4 months	122		1220
	4	5 months	152.5		1525
	5	7 months	213.5		2135
	6	34 months	1037		10,370
	7	16 months	488		4880
	17	39 months	1189.5		11,895
	18	39 months	1189.5		11,895
Gräf 1992	1	26 weeks	182	6-8	1274
Blanksma 1996	1	1 year	365	5 x 2 eyes	3650
	2				3650
	3				3650
Tavares 2009	1	1 year	365	10 x 2 eyes	7300
Median total exposure in published patients prospectively treated (range)					*3960 (1220-11,895)*
French retrospective studies (incl. Dureau 2003)	19	Median (range) 7 (4-18 years)	2555	6 x 2 eyes	582,540
French compassionate use	> 50	> 20 years	7300	6-12 x 2 eyes	Minimum 4,380,000
Labbé 2015	16 (*)	3 months	90	4 x 2 eyes	11,520

(*1 dropout)

Important note: in the study by Labbé (2015) the mean age at entry was 17 years and patients were previously treated with 0.1 % mercaptamine eye drops. This study follows one in 8 patients where the mean age at entry was 12 years for a diagnosis at a mean 7 years of age, who all were also previously treated with 0.1 % mercaptamine eye drops (Labbé 2014). Assuming both studies include relatively similar patients (same country, similar inclusion criteria, same coordinating center), then patients in Labbé 2015 would have received approximately 10 years of treatment with 0.1 % mercaptamine eye drops before inclusion. At a median regimen of 4 drops per day, this leads to an exposure of approximately 905,000 drops before inclusion (10 years x 365 days x 4 drops/eye x 2 eyes x 31 patients). The representativeness of the exposure of 3 months in 16 patients following "inclusion" is then 11,520/905,200 x 100 = 1.3%.

The use … the 0.3% concent … ry 1991), and 4 t… lrops has been de…

The key … tion from 1990. T…)u 2003), and to … few hard data in … outcome were actually similar with the 0.1% and with the 0.5% concentration. The results per treatment group can be summarized as follows:

Tab 3

Formulation schedule	0.1%	0.5%	0.1%→0.5%	Total
Endpoint reached	5	3	2	10
Endpoint not reached	2	1	7	10
Total	7	4	9	20
Percent endpoint reached	71%	75%	22%	-

This shows that 5 out of 7 patients receiving 0.1% did reach the endpoint and that the results were not improved in the other groups. These results are robust, based on an eye-randomized study vs. placebo, very strict evaluation criteria for the outcome assessed by 6 different observers, and this is why these results have served as a reference for many other teams throughout the world.

The other key information that this study demonstrated was that responders were almost all good compliers with a frequent administration every waking hour. In the 10 patients who were fully compliant, only 1 failed to reach the endpoint and in only 2 out of 10 patients who reached the endpoint compliance was poor. Therefore compliance matched efficacy in 17 out of 20 cases and was the major determinant of the success irrespective of mercaptamine concentration.

In summary, a representative group of patients were prospectively treated with 0.1% concentration and reported in the literature as recapitulated in the following Table:

Tab 4

Reference	N pts	Results in	Positive outcome
Kaiser-Kupfer 1990	16	7	5
Gräf 1992	1	1	1
Blanksma 1996	3	3	3
Tavares 2009	1	1	1
Total	**21**	**12**	**10**

Consequently, in the initial Application, 12 patients prospectively treated with 0.1% mercaptamine eye drops with results available were reported. The results were positive in 10 patients. Including all retrospective data (Jain 1988 (n=10), Broyer 1994-Broyer 1995-Dureau 2003 (n=29), and Labbé 2014 (n=8)) as well as recent poster from Labbe 2015, 85 patients reported in the literature have received a 0.1% mercaptamine eye drops.

Contrary to the situation in France, in the USA the NIH carried on with the development of a 0.5% concentration formulation. It is interesting to speculate on the motivation of the team at the NIH Eye Institute. For them, a higher concentration (than 0.1%) or a higher frequency of administration (of the 0.1%) would be necessary in some cases (Kaiser-Kupfer 1990). We believe that the initial rationale as expressed by Dr Kaiser-Kupfer (1988, 1990) and Prof Gahl (2000) was to clear more rapidly heavily packed corneal crystals which occurs as untreated patients get older, particularly as the compliance, which is key to treatment success, is notoriously low in cystinosis patients and the administration should be repeated every waking hour.

As shown by Gräf (1992) a concentration of 0.5% administered 6-8 times per day could indeed achieve corneal clearing within 12 weeks vs. 26 weeks with a concentration of 0.1%. However, this more rapid action should be put in perspective with a life-long treatment. This faster action is not disputed but this does not

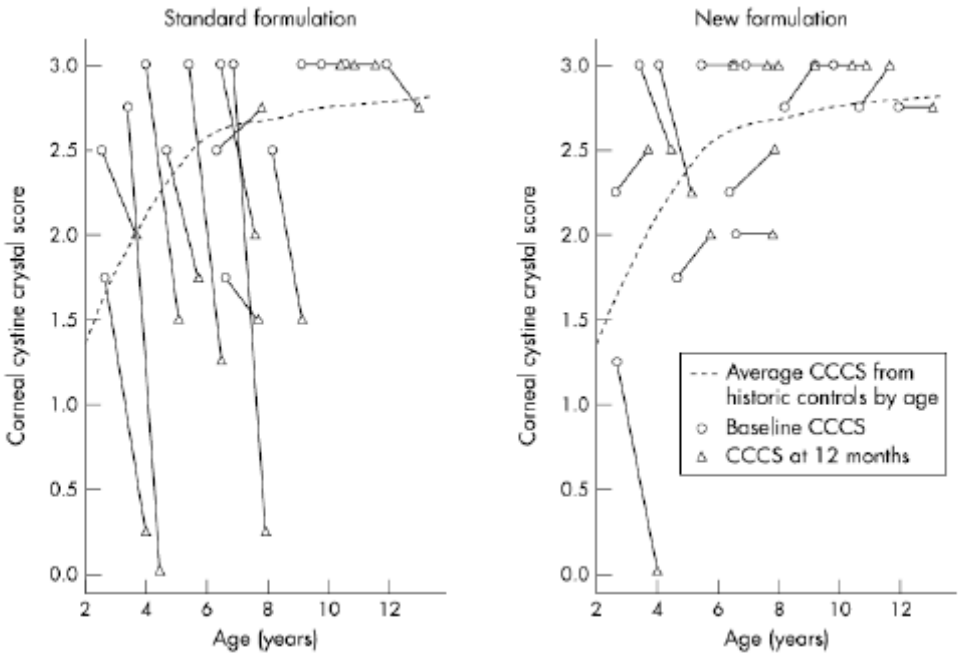
imply that the 0.1% concentration given at the appropriate frequency (every waking hour) is not effective. Gräf (1992) did report that the 0.1% concentration administered 6-8 times per day was effective in a 2-year old patient. Blanksma (1996) also showed positive findings on corneal punctate erosions with a 0.1% formulation given 5 times a day in 3 patients of 15, 17 and 32 years, respectively, as did Tavares (2009) using IVCM in a severely affected 20 year old patient receiving a 0.1% formulation 10 times a day.

A great deal of discussion in CHMP's grounds for refusal centred around the fact that different formulations of the same concentration may achieve very different efficacy results and therefore that the efficacy data which was obtained with other 0.1% mercaptamine formulations than that from AGEPS cannot be used in support of the present Application.

For various reasons this should be revised. First of all, there is reasonable evidence from the literature that the various concentrations of mercaptamine eye drops when directly or indirectly compared do not necessarily refer to a single formulation. For example, the fact that recent reviews (Emma 2014) recommend the use of the 0.5% mercaptamine rather than any other concentration does not take into account potential or existing differences in the formulations. Secondly, the Application for the AGEPS 0.1% formulation is based on the well-established use of the product in the absence of any other pharmacological treatment currently approved. Hence the Application is not based on prospectively generated data.

Furthermore, at the origin of this discussion was a study where two different 0.5% mercaptamine eye drops formulations were compared (Tsilou 2003). This study showed extremely different efficacy results, against the new formulation, as can be seen on the evolution of corneal crystal scores on the Figure below.

Fig 2



The CHMP did not appear to consider the explanation put forward by the authors themselves that, due to immediate discomfort associated with the administration of the new formulation, it was possible that the eye drops were washed out of the eyes due to tearing (and therefore associated with almost no efficacy). The

other hypothesis, that the new formulation did not penetrate the corneal stroma as effectively as the standard formulation, was not supported by a valid biological basis according the authors (Tsilou 2003).

During the evaluation, some discussion centred on the fact that the 0.1% formulation may not be as effective in older subjects, based on the observations from Kaiser-Kupfer (1990). In compliant patients however, it has been shown that even heavily packed corneal crystals can be cleared after several years of treatment (Gahl 2000). The age itself is not a negative cofactor of efficacy; rather it is correlated with the baseline density of crystals in the cornea.

The literature showed that amongst patients treated with 0.1% mercaptamine eye drops 14 were less than 5 years old and 19 were more than 5 years old. This compares with the figures of 20 and 29, respectively in patients treated with a 0.5% mercaptamine eye drops as shown in Table below.

Tab 5

Age	<5 y	>5 y
0.1%	Kaiser-Kupfer 1990 (7) Gräf 1992 (1) Dureau 2003 (6)	Kaiser-Kupfer 1990 (2) Blanksma 1996 (3) Dureau 2003 (13) Tavarès 2009 (1)
Total 0.1%	**14**	**19**
0.5%	Kaiser-Kupfer 1990 (2) Jones 1991 (1) Gräf 1992 (1) Iwata 1998 (3) Tsilou 2003 (4) Soliman 2009 (9)	Kaiser-Kupfer 1990 (2) Iwata 1998 (11) Tsilou 2003 (11) Soliman 2009 (7) Labbé 2014 (8)
Total 0.5%	**20**	**39**

The data already presented above (Kaiser-Kupfer 1990, Gräf 1992, Blanksma 1996, Tavares 2009) highlight that the 0.1% concentration was effective in young and in older patients. The retrospective data are also supporting this (Broyer 1994, Broyer 1995).

In the 1990's when the original formulations were developed, subjects with high levels of crystal deposits at baseline were probably more frequently encountered than today. Since the discovery of the CTNS gene, diagnosis and initiation of mercaptamine treatment occur earlier in the course of the disease than in the 1990s. Even for Kaiser-Kupfer (1990) the best ophthalmic therapy of all was prophylaxis. Several physical determinants, namely the saturable lysosomal uptake above 10 mmol/L (Pisoni 1995), the counterproductive extreme viscosity (Mishima 1981, Bozdag 2008, Buchan 2010), the significant corneal cell toxicity of concentrations above 10 mmol/L (Shin 2011), are all in favour of a solution with low concentration of mercaptamine eye drops (10 mmol/L or 0.1%).

Today there are even less reasons than at the beginning of the development of these formulations (Kaiser-Kupfer 1990) to administer a high concentration of mercaptamine to pre- or mildly-symptomatic patients. The 0.1% mercaptamine eye drops have been shown to be effective and safe in both prospective and retrospective studies and in extensive clinical experience over 2 decades, and should, therefore, be granted marketing approval.

Ground 2

Furthermore, at this stage, the development of the formulation was not appropriately justified with regard to the levels of benzalkonium chloride, ascorbic acid, the target pH and buffer capacity of the product. The resulting impact on ocular safety has not been adequately justified taking into account that this formulation is intended to be mainly used to treat paediatric population in a very frequent schedule of administration and in long-term (chronic disease).

Applicant's position (summarised)

Preservative efficacy

The Benzalkonium chloride (BAK) content (0.02%) of the AGEPS 0.1% mercaptamine formulation was maintained at this concentration following instructions the from French Medicines Agency (24-Nov 2010) where it was indicated that the drug's intended formulation should remain exactly the same in quality and quantity, including the excipients, as that of the drug used compassionately in France for over 25 years.

Moreover, BAK is a well-known excipient and its efficacy as a preservative in multi-dose eye drops is widely accepted. Despite the potential toxic effect reported, it is still used in several eye drops for human use at different concentrations, including the concentration proposed in Dropcys eye drops (i.e. 0.02%).

The efficacy of antimicrobial preservation according to the requirements of the European Pharmacopoeia chapter 5.1.3 has been performed at release and at the end of shelf-life on the industrial batches presented in the Dossier (11F015; 11F084 and 11F086). All the results are compliant with the specifications.

The preservative efficacy has been demonstrated, therefore, on non-opened bottles at the preservative concentration of 0.02% BAK as proposed in the current formulation.

Microbiological contamination

1) *Contamination study:*

to simulate the use of the product in practice, a preliminary test was made with *Staphylococcus aureus*, *Candida albicans* and *Aspergillus brasiliensis*. Several vials were contaminated once a day with a concentration of 10^5 - 10^6 CFU/ml for 8 days and stored at room temperature. The results at T= 0, 3 and 8 days at room temperature showed that there was no growth of microorganisms, and no other contamination was detected. These experimental conditions were stricter than those specified in the recommended storage conditions after reconstitution which are "to be stored in a refrigerator (2°C – 8°C)".

2) *In-use stability study:*

This study has been criticized as the sampling frequency did not reflect the use of the reconstituted Dropcys according to the proposed posology.

However, as the shelf-life was not determined before the in-use stability study, the study design intentionally covered a period 3 times longer than that of the shelf-life after reconstitution (7 x 3= 21 day period) and included interim tests at D0, D3, D8, D15 and D21. Bottles were stored in refrigerated conditions and kept for 5 minutes at room temperature 4 times/working day over the period. The efficacy

of antimicrobial preservation was compliant to the Eur. Ph. 5.1.3 at each time point tested, including after the 21 day period.

In a study following the CHMP protocol, the bottles would be stored in the fridge for 7 days and taken out of the fridge at least 5 times a day, i.e. for a total of 35 times. In the study performed, the bottles were kept stored in the fridge for 21days and taken out of the fridge 4 times/working day i.e. for a total of 60 times. Therefore the efficacy of antimicrobial preservation tested during this in-use stability study was demonstrated under more extreme conditions than those specified in the proposed conditions of use.

	Performed	Recommended
Testing temperature	Storage in 2-8°C conditions Room temperature 5 minutes / 4 times per day	Storage in 2-8°C conditions Room temperature 5 minutes / 5 times per day
Testing period	21 days	7 days
Testing frequency *	D0, D3, D8, D15 and D21	D0, D1, D2, D3, D4, D5, D6, D7
Testing beyond the recommended period *	3	0
Study design	Bottles opened 4 / day Expulsion of one drop / day	Bottles opened 5 / day Expulsion of one drop, 5 / day
Total bottle openings	15 working days x 4 times/day= 60	7 days x 5 times/day= 35
Test parameter	Efficacy of antimicrobial preservation	Efficacy of antimicrobial preservation

* according to CPMP/QWP/2934/99 "Note for guidance on in-use stability testing of human medicinal products", the testing should be performed over the period i.e. at the end of the proposed in-use shelf life and if possible at intermediate time points

3) *Sterility study:*

as discussed during the CHMP Oral Explanation on November 18th 2015, a sterility study has been performed on approximately 100 expired bottles of Dropcys immediately after reconstitution and after 7 days in conditions of use. The bottles were stored at refrigerated temperature for 7 days and taken out of the fridge at least 5 times a day with a sample of one drop taken out from each bottle once a day. At the end of the 7 days, the remaining part of the solution from all bottles was pooled and the sterility test performed according to Eur. Ph. 2.6.1. The pooled solution remained sterile after 7 days under conditions of use.

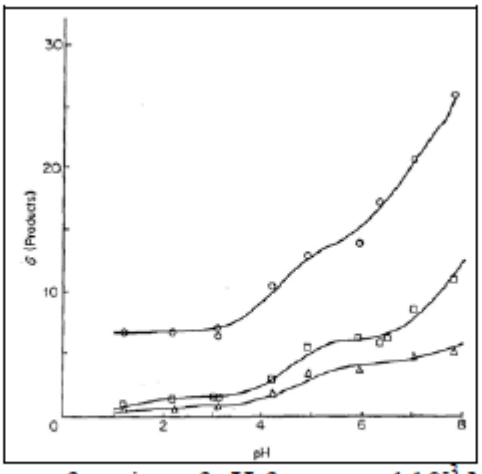
Based on the results of the 3 studies above, it can be concluded that the microbiological quality of the eye drops solution is maintained after the attachment of the applicator by the patient and during the treatment at home, justifying the BAK level in the proposed formulation to guarantee safe use of the product in practice.

Moreover, as all the available batches have expired, it was not appropriate to perform another contamination study as requested by the CHMP during the procedure, this study can be easily and rapidly performed on a fresh batch prior to commercialization of the product.

pH target and ascorbic acid

The original development was carried out 30 years ago by AGEPS, the Central Pharmacy in Paris, a public institution and it was based on the knowledge of the chemical properties of the active substance with the aim of producing an ophthalmic preparation with an acceptable stability profile.

Molecules carrying a thiol group (i.e. cysteine, mercaptoethanol and cysteamine) are known to be sensitive to oxidation in aqueous solutions. Thiol groups have been studied in oxygenated aqueous solutions and the effect of pH on the rate of thiol oxidation determined (Patai 19741). A representative illustration of these studies is presented in the Figure below. In conclusion, higher pH values (more basic) were found to increase the oxidation of thiols and the formation of disulphide compounds. On the contrary, little disulphide and hydrogen peroxide were formed at lower pH from 1 to 3 (more acidic):



G (Products) as a function of pH for aerated 10^{-3} M cysteamine
○= G(-RSH), □ = G(RSSR), Δ = G(H_2O_2)

A few experiments have been initiated during the procedure to answer requests from the CHMP in order to clarify the ascorbic acid content and the target pH. In these experiments the assays of mercaptamine hydrochloride and cystamine have been performed at D0, D3, D5, D7 and D10 for various finished product formulations.

These data show that the degradation of mercaptamine hydrochloride into cystamine is pH dependant. At the highest pH value, about one half of the mercaptamine is already degraded at baseline, suggesting a degradation during the preparation of the formulation itself. At the intermediate pH value, the degradation, although slower, is apparent within only 3 days. At the proposed pH value, both mercaptamine and cystamine contents remain within their respective specifications for at least 10 days. The applicant concluded that the optimal pH value is the one proposed in the Dropcys formulation.

The concentration of ascorbic acid also affects the degradation of mercaptamine, even if the results are less demonstrative than with increasing pH. At the concentration used in the final formulation, the level of cystamine is compliant with specifications after 10 days, whereas at lower concentrations of ascorbic acid the content of cystamine is not compliant after 7 days. The results obtained with the ascorbic acid free formulation are comparable to results with the intermediate pH value above. For technical reasons, and as previously described, the protocol used in this experiment is different to that for the patient's use. The container was not the commercial bottle, with a larger volume of solution, and it was kept at room temperature for a shorter duration. The samples tested were consequently less exposed to temperature variations and, consequently, the degradation should be even more significant than under the proposed conditions of use. The applicant concluded that the optimal ascorbic acid concentration is the one proposed in the Dropcys formulation.

Furthermore, the results presented for the validation batches and during the stability studies show that the proposed pH and ascorbic acid concentration ensure optimal stabilization of mercaptamine hydrochloride in solution during the manufacturing process and at the end of shelf-life by preventing the degradation of the active substance.

Safety impact

AGEPS has been continuously preparing a sterile formulation of 0.1% mercaptamine hydrochloride eye drops for 25 years in France. This formulation was identical to the one proposed in this Application. During this period of extensive use, none of the 13 regional pharmacovigilance centres, neither AGEPS, nor ANSM, received any adverse event report. Additionally, in the US, where a 0.1% formulation of mercaptamine hydrochloride was also used, no adverse events were observed (Jain 1988, Kaiser-Kupfer 1990). These facts should be seen as strong evidence that the 0.1% mercaptamine eye drops have an acceptable safety profile.

The "Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing known constituents" (CPMP/EWP/239/95) states that in locally applied products a change in formulation or in dosage form may influence the efficacy and/or safety of the product. It has been shown that - although empirically developed - the formulation of Dropcys and particularly its pH and ascorbic acid content can both be justified by the absence of the degradation product, cystamine, which is formed when the very unstable active ingredient is placed in solution. Clinical evidence comparing mercaptamine and cystamine eye drops has also demonstrated the lack of efficacy of the latter (Iwata 1998), therefore the formulation is justified on the grounds that the level of cystamine remains within the lowest specifications possible with the current formulation.

When the pH value is outside the range of 4–8 which is tolerated by the eye, the patient may feel discomfort (Baranowski 2014). In the only study in which stinging/burning sensations were reported after the 0.1% mercaptamine eyedrops (Labbé 2014), these occurred in 5 out of 8 patients, whereas they occurred in 6 out of 8 patients, once they had been switched to the comparator in spite of its much higher pH (5.2). Therefore the potential impact of the pH appears not to be problematic for ocular safety.

The supporting clinical literature contains studies with various concentrations and formulations of mercaptamine containing more or less BAK. In the original US studies no BAK was added, whereas later the NIH pharmacy added 0.01% BAK to the formulation (Gahl 2000). The local preparations of 0.1% mercaptamine used in the case reports from Gräf (1992) and Tavares (2009) did not include BAK. Another study of 0.1% mercaptamine used 0.01% BAK and does not mention adverse events (Blanksma 1996). A higher incidence of AE due to BAK has not been reported in the only population-based long-term study (Dureau 2003) or in the extensive use over 25 years in France (1000 patient-years and more than 4 million drops of 0.1 % mercaptamine hydrochloride AGEPS used).

The Applicant asserted that BAK is a well-known excipient and its efficacy as a preservative in multi-dose eye drops is widely accepted. Despite the potential toxic effect reported, it is still used in several eye drops at different concentrations, including the concentration proposed in Dropcys eye drops (i.e. 0.02%).

The products listed in the table below include benzalkonium chloride at 0.02%:

Invented name	DCI	Use
Acular®	ketorolac tromethamine	post-op use
Lumigan®	Bimatroprost	chronic use
Xalatan®	Latanoprost	chronic + paediatric use

The BAK concentration proposed for Dropcys is the same as used in currently authorised ophthalmic preparations indicated for long-term treatment (including at least one indicated for paediatric use.)

Long-term exposure to BAK has been shown to cause punctate kerathopathy and/or toxic ulcerative kerathopathy (Baudouin 20102). However, the effects of BAK are difficult to distinguish from the effects of the active constituents of topical preparations and also from the complications of the diseases they are prescribed to treat. According to the current best practices for ophthalmic solutions, special warnings concerning the potential side effects of BAK should be communicated to patients using Dropcys.

Ground 3

No in-use stability data were provided to support the proposed posology and shelf-life after reconstitution. Moreover, the maintenance of microbiological quality of the product during the course of treatment was not established.

Applicant's position (summarised)

This last issue on maintenance of microbiological quality has been discussed above (Ground 2: Microbiological contamination).

Study performed and presented in the initial Dossier

The study design applied covered a period 3 times longer than the proposed shelf-life after reconstitution and did not include results at D7. However as the shelf-life was not determined beforehand, the design intentionally covered a period 3 times longer than that of the shelf-life after reconstitution (7 x 3= 21 day period) and included interim tests (notably one at D8) . Bottles were stored in refrigerated conditions and kept 5 minutes at room temperature 4 times/working day over the period. These conditions were close to the conditions of use.

The proposed shelf-life after reconstitution (7 days) has been proposed according to the results at D8.

All the results are compliant with the in-use specification, except for the mercaptamine content.
The CHMP has requested a stability study with a testing frequency of reconstituted mercaptamine corresponding to every day during 7 consecutive days in line with the proposed posology of the medicinal product. This request should be revised as according to CPMP/QWP/2934/99 "Note for guidance on in-use stability testing of human medicinal products", the testing should be performed over the period i.e. at the end of the proposed in-use shelf life and if possible at intermediate time points.

Study to be performed prior to commercialisation

A new in-use stability study has been designed in line with the proposed posology of the medicinal product and the guideline CPMP/QWP/2934/99, to establish a period of time during which the multi-dose product can be used whilst retaining quality within an accepted specification once the product is reconstituted. This test was designed to simulate the use of the product in practice with sampling taking place under normal environmental conditions of use. Unfortunately, as the available batches have expired and are therefore potentially already out of specifications, it was not appropriate to perform a full in-use stability study during the procedure. This in-use stability study will be performed on a fresh batch and the results sent to EMA prior to commercialization of the product to confirm the shelf-life after reconstitution.

The protocol previously applied and the one to be applied on the next fresh batch are summarized in the table below:

	Performed	To be performed
Testing temperature	Storage in 2-8°C conditions Room temperature 5 minutes / 4 times per day	Storage in 2-8°C conditions Room temperature 5 minutes / 5 times per day
Testing period	8 days	7 days
Testing Samples	Batch 11F086	Fresh batch to be produced
Study design	Bottles opened 4 / day Expulsion of one drop / day	Bottles opened 5 / day Expulsion of one drop, 5 / day
Test parameters*	Appearance Assay of mercaptamine Assay of cystamine Unspecified impurity Total impurity Efficacy of antimicrobial preservation	Appearance Assay of mercaptamine Assay of cystamine Unspecified impurity Total impurity Efficacy of antimicrobial preservation

* The physical, chemical and microbial properties of the product being susceptible to change during its storage after reconstitution these properties have to be tested and determined over the period of the proposed in-use shelf life.

Study a minima *to support the in-use shelf-life*

As the available batches have expired, the proposed protocol has not yet been performed. Nevertheless, in order to answer the issue raised by CHMP, it has been decided to perform a study *a minima* as presented at D181 and discussed during the Oral Explanation on 18th November 2015.

This study is summarized hereafter:

	Performed
Testing temperature	Storage in 2-8°C conditions Room temperature 5 minutes / 4 times per day
Testing period	7 days
Testing Samples	Batch 13F014 Expired on March 2015
Study design	Bottles opened 5 / day Expulsion of one drop, 5 / day
Test parameters	Assay of mercaptamine Assay of cystamine Sterility*

* The sterility test has been performed instead of the efficacy of antimicrobial preservation as the time was too short.

The in-use stability study performed on the expired batch was carried out on approximately 100 bottles as the quantity needed for the sterility test is important. The remaining solution of all the bottles was pooled in one sample for analysis.

Mercaptamine and cystamine assays
According to the mercaptamine and cystamine assay results obtained at D0 and D7, the drug product is stable for at least 7 days after reconstitution with 0.9% sodium chloride, stored at 5°C ± 3°C and tested under in-use conditions. These results are similar to the above results (after 8 days).

- Sterility

At D0, the sterility was verified, despite the long storage period of the batch used. At D7, the sterility was also verified according to European Pharmacopoeia on the remaining pooled volume.

The applicant concludes that proposed shelf-life of 7 days after reconstitution appears to be acceptable and will be confirmed by the Applicant prior to commercialization of the product based on a full in-use stability study with a fresh batch.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant.

Ground 1

The CHMP acknowledges the origins of the proposed formulation, its extensive use in a referral centre for treatment of cystinosis and the duration of use (25 years)of mercaptamine 0.1% eye drops France . In addition to the use in France, literature reports from 5 EU countries reporting the treatment of 17 patients with ocular mercaptamine over a period of 1991-2014 were provided by the applicant. Based on the

estimated total number of drops administered to patients, the CHMP acknowledged that there was documented clinical use of 0.1% mercaptamine eye drops.

The applicant tried to address the lack of adequate data to support efficacy by discussing the extent of use and duration of use and calculating a large total number of drops of 0.1% mercaptamine eye drops used by eminent practitioners in the treatment of cystinosis. The CHMP did not accept this as an appropriate or acceptable evidence of efficacy as evidence of use cannot as such be equated to evidence of efficacy, as elaborated further below. Similarly, evidence of use based on a clinical decision for an individual benefit-risk analysis cannot be equated to a conclusion of favourable benefit-risk analysis for the treatment of the target population. The submitted literature did not provide sufficient evidence of beneficial effects of Dropcys.

Although the CHMP acknowledged that there is a strong mechanical plausibility for the benefit of mercaptamine in ocular cystinosis, the available data do not support an inference of adequate efficacy for Dropcys.

Based on the data presented by the applicant, the CHMP agreed that the clinical experience with 0.2% and 0.3% mercaptamine eye drops was quite small and anecdotal. It was also agreed that the concentrations 0.1% and 0.5% were the two concentrations which were more often described in the available literature for the treatment of ocular cystinosis.

In order to justify the efficacy of the 0.1% mercaptamine eye drops, the Applicant relied predominantly on Kaiser-Kupfer 1990 study. The CHMP agreed that this study is the most robust of the available data but did not agree with the interpretation and conclusions drawn by the applicant.

Kaiser-Kupfer 1990 was a study in 29 patients who were treated with mercaptamine eye drops in one eye whilst the other eye was treated with normal saline. As there were 4 drop-outs, results from 25 patients are available; 16 patients were less than 4 years and 9 were over 4 years old.

In this study, only 7 patients received 0.1% alone, 9 patients received 0.1% initially but were switched to 0.5% and 9 patients received 0.5% only. The results showed that:

- Of the 7 patients who received 0.1% alone, 5 patients responded.

- Of the 9 patients who initially received 0.1% and then switched to 0.5%, 2 patients responded. For the remaining 7 patients who did not respond, although the total duration of treatment is provided, the time on treatment with 0.1% and the time on treatment with 0.5% were not provided. With regards to the two responding patients, one was on 0.1% for 34 months before switching to 0.5% and the other was on 0.1% for 16 months before switching to 0.5%.

- Of the 9 patients who received 0.5% alone, 6 patients did not have adequate duration of treatment according to the study authors, and the remaining 3 patients responded.

Taking the above into consideration, the argument presented by the applicant that there is 71% response with 0.1% formulation (5 out of 7 responding) cannot be accepted. Based on the study dataset, the intent to treat population with 0.1% was 20 patients (7 treated with 0.1%, 9 started on 0.1% and switched to 0.5% and 4 drop-outs). Therefore, it could be argued that the response with 0.1% was 5 patients out of 20 (= 25%).

Analysis of the data shows that there were 15 non-responders. Of these, 2 patients received 0.1% for 39 months and did not respond. There were also 6 patients who were assigned to receive 0.5% and did not show a response; however all these patients had inadequate duration of treatment as expressed by the investigators (4 patients had 0 months of treatment, 1 patient had 1 month of treatment and 1 patient had 4

months of treatment). The remaining 8 non-responders had initially received 0.1% and then changed to 0.5% and the duration on each dose is not available in these patients. Therefore the effect or lack of effect of each dose cannot be analysed in this group.

In conclusion, the Kaiser-Kupfer study was not designed to compare the 0.1% and 0.5% dose strength, but the 0.5% was introduced as the response in the patients treated initially with 0.1% did not meet the expectations of the investigators. The adequate efficacy of 0.1% formulation could not be concluded. The remaining prospective data mentioned by the applicant was relatively too small or uncontrolled and as such inadequate to change the above conclusions drawn from the Kaiser-Kupfer 1990 study.

In addition, the study by Kaiser-Kupfer 1990 was conducted with a different formulation of 0.1% mercaptamine (NIH formulation) as compared to the proposed formulation. A direct extrapolation of the results from other formulations is not appropriate for ocular formulations as the permeability and ocular distribution can potentially be different due to the differences in the excipients. This is indeed supported by Tsilou 2003 study, where different formulations had different efficacy results. Regardless of the reason (difference in permeability, difference in tolerability or any others) the formulations were not equivalent despite the equal quantities of the active substance in both the formulations.

With regards to the concern on the efficacy in older patients (> 4 years), the applicant could not present any prospective, randomized, masked, comparator data from literature to refute this concern. The applicant only presented limited evidence of use in literature, which is not conclusive evidence of efficacy. Moreover, the dataset of older patients presented by the applicant included two patients from Kaiser-Kupfer 1990 study who did not demonstrate adequate response even after 39 months of treatment with 0.1% mercaptamine.

Overall, the applicant did not present any robust arguments to consider that the submitted data is adequate to support the efficacy of Dropcys in the claimed indication.

Ground 2

In summary, at this stage, the development of the formulation is not appropriately justified with regard to the levels of benzalkonium chloride and the target pH of the product. The resulting impact on ocular safety has not been adequately justified taking into account that this formulation is intended to be mainly used to treat paediatric population in a very frequent schedule of administration and in long-term (chronic disease).

The presence of ascorbic acid may be acceptable. However, information on the buffer capacity of the proposed formulation should have been provided.

Comparability of the proposed formulation with formulations studied in the literature

As this is a bibliographical application, it is important to demonstrate that the formulation proposed by the applicant is similar to that used in the bibliographical literatures quoted by the applicant to support 0.1% mercaptamine eye drops application. Insufficient information is provided on the formulation tested in the bibliographic literatures. The available data are extracted in Table below. In majority cases, the formulations had lower level of benzalkonium chloride, higher pH (or unclear) and did not contain ascorbic acid.

Table 17. 0.1% Formulation information from provided bibliographic literature

Studies/Product	API concentration	Benzalkonium chloride concentration	pH	Ascorbic acid
Kaiser-Kupfer 1987a	0.11% (10mM) mercaptamine in normal saline	None	Unclear, likely to be neutral	None
Kaiser-Kupfer 1990	0.1% (10mM) or 0.5% (50mM) mercaptamine in normal saline	None	Unclear, likely to be neutral	None
Gräf 1992 (German)	0.1% or 0.5%	None	5.3	unclear
Dureau 2003	Unclear, retrospective study	unclear	Unclear	unclear
Blanksma 1996	Unclear: stated as 0.5% and 5mM (which equals to 0.05%)	0.01%	Unclear	unclear
Tavarès 2009	0.11%	Unclear concentration	Unclear	None
Dropcys	0.1%	0.02%	3.4-4.0low	0.02%

Regarding the proposed formulation, appropriate development pharmaceutics to optimise the product formulation in terms of quality with respect to safety have not been undertaken.

Levels of benzalkonium chloride

The applicant chose 0.02% benzalkonium chloride because it was used at the AGEPS. In addition, 0.02% or even higher concentration of benzalkonium chloride is used in commercial eye drops, such as Acular, Lumigan or Xalatan. However, it is to be noted that the posology for the commercial products mentioned is either not as frequent as that proposed for this formulation or for short-term treatment only.

It is noted that the applicant was advised by the French Agency AFSSAPS (now ANSM) in 2010 that the benzalkonium chloride concentration used must be discussed and supported since:
"Recent debates on the issue have led the health authorities to conclude that while it would be impossible to remove this preservative from all eye drops, manufacturers are nonetheless asked to limit its use in so far as this is possible."

The applicant has not followed the advice to minimise the level of benzalkonium chloride.

Benzalkonium chloride is well-known for its ocular toxicity and irritancy. The presence of benzalkonium chloride is however essential to ensure the microbiological quality of the product during use. Therefore its concentration should be the minimal effective concentration. This is supported by the following guidelines:
The draft Questions and Answers on Benzalkonium chloride in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00) stats that "*When present in medicinal products, the concentration of benzalkonium chloride is optimised so that the minimum sufficient amount is present to achieve compliance with the Ph. Eur. test for efficacy of antimicrobial preservation*."

Similarly, the EMA public statement on antimicrobial preservatives in ophthalmic preparations for human use (EMEA/622721/2009) states that "*When preservatives are required, the concentration should be at the*

minimum level consistent with satisfactory antimicrobial function in each individual preparation and a thorough justification for the choice of the preservative should be provided."

The fact that the proposed formulation has a higher benzalkonium chloride concentration than other reported formulations in the provided bibliographic literature (Table 1) is of a concern. Moreover, the impact of this higher benzalkonium chloride concentration has not been demonstrated by the applicant.

The applicant should therefore have carried out the in-use stability studies with various concentration of benzalkonium chloride to identify the minimal effective concentration required.

Regarding the microbiological contamination risk, the applicant had carried out three different studies to support the microbiological quality of the eye drops solutions. However, the products used for testing are not characterised. Benzalkonium chloride level is not quantified at release or in the stability data. Although limit for benzalkonium chloride is included in the release and shelf-life specifications, it cannot be concluded that the proposed product complies with these limits throughout the studies. Although benzalkonium chloride is likely to be stable in aqueous solution, the applicant should have characterised their product fully to justify the benzalkonium chloride level in the preparation. Without justified limits and appropriate routine controls, it cannot be assured that the microbiological contamination risk of the product is adequately maintained and whether the minimal effective concentration was chosen.

Ascorbic acid and buffer capacity

The applicant has provided experimental data to confirm the efficacy of ascorbic acid. The presence of ascorbic acid at 50%, 75% and 100% of the proposed concentration has improved the stability of the active substance when compared to formulation without ascorbic acid. No significant differences were observed between different concentrations of ascorbic acid. The effect of ascorbic acid is likely due to its ability to act as an antioxidant and/or a buffering agent. There appears to be little evidence to cause concern at the proposed level of ascorbic acid in the drops, even with life-long use. 10% ascorbic acid ophthalmic solutions are approved for multiple daily uses in other markets. Hence, the level of ascorbic acid present should not be an issue as such. However, no further information has been provided on the buffer capacity of the proposed formulation. This needs to be discussed as a low buffer capacity or no buffer may mean that the solution does not remain acidic when in contact with the eye, whereas a high buffer capacity are likely to affect the pH in the eye over longer duration after application. Therefore, due to the low pH of the proposed formulation, minimal concentration of ascorbic acid (if it acts as a buffering agent) should be used. Information on the buffer capacity of the proposed formulation should have been provided.

Target pH

The active substance contains several molecules with thiol group (i.e. cysteine, mercapto ethanol and mercaptamine) which are known to be sensitive to oxidation in aqueous solutions. It is acknowledged that the selected pH as proposed in the current formulation results in a preparation with acceptable stability.

Nevertheless, the main concern is that the low buffered pH of the eye drops could be contributing to reported eye disorders, and this concern cannot be considered solved only in view of the fact that a similar product has been used for 25 years in a public institution, since the requirements for Marketing Authorisation are for the applicant to duly demonstrate with data the quality, safety and efficacy of the product.

It was highlighted by the applicant that the burning sensations were also reported in a comparator product with a pH of 5.2. It is however evident from the literature and the US product, that similar products have a higher pH. The justification for the proposed pH of 3.4-4.0 is not considered sufficient and not accepted.

The applicant also claims that a certain pH range has been investigated. However this is not correct. Data for all the pH ranges comprised in the claims have not been submitted and therefore uses of lower pHs have not been fully justified from the quality perspective. Further investigations in optimal pH ranges are required and at present there is no clear evidence base to toxicologically justify the proposed pH 3.4 for an ophthalmic solution taking into account life time use of at least 5 times a day.

Impact on ocular safety

In defence of the ocular safety of the proposed formulation, the applicant referred to the extent of clinical use of the 0.1% mercaptamine eye drops (for 25 years; over 4 million drops in France and in US) and the lack of significant safety concerns in the published literature. However, this cannot be accepted as conclusive evidence of safety, especially considering that the potential risks under discussion are significant safety concerns of long-term use. The CHMP did not find the Applicant's argumentation reassuring given the significant under-reporting anticipated with safety events occurring in clinical use, especially with the pharmacy preparations. More importantly, safety arguments do not preclude the need for a scientific approach to formulation development in accordance with the fundamental principles of pharmaceutical sciences.

With regard to the clinical acceptability of the proposed BAK concentration in Dropcys, the applicant referred to other ocular products containing similar BAK concentrations but failed to take into consideration that Dropcys would be used much more frequently - up to once every waking hour. In addition, the applicant referred to safety of other mercaptamine eye drops that contained 0.01% BAK, which is 50% lower than what is proposed for Dropcys. Finally, the data for the proposed formulation was found to be too limited to provide adequate reassurance. Regardless of the above considerations, none of these data could preclude the need for good pharmaceutical development whereby the minimum needed concentration of BAK for the antimicrobial function is used.

With regard to the acceptability of low pH of the proposed formulation (3.4 -4), which is outside the known range for good ocular tolerability, the applicant referred to one publication (Labbé 2014), where stinging/burning sensation was reported in 5 out of 8 patients treated with 0,1% mercaptamine eye drops and in 6 out of 8 patients once they were switched to a comparator which had a higher pH of 5.2. This dataset was too small and there were too many confounding factors to make any robust interpretation of the kind suggested by the applicant.

The finished product is intended to be used every hour or at least 5 times a day for chronic use. A formulation containing a higher level of preservatives and such low pH could potentially have an irreversible adverse effect on ocular surface epithelium. It cannot therefore be confirmed that the proposed formulation is safe over long term usage.

Ground 3

In summary, at this stage, no in-use stability data is provided to support the proposed posology and shelf-life after reconstitution. Moreover, the maintenance of microbiological quality of the product during the course of treatment is not established.

Physical-chemical stability during in-use shelf life

The applicant considers that the proposed shelf-life of 7 days after reconstitution is acceptable based on the in-use stability data. According the SmPC, the recommended dose is “1 drop in each eye every hour that you are awake for optimal efficacy or at least 5 times a day”. In order to prove that the microbiological quality of the eye drop solution is maintained after the applicator attachment by the patient and during the treatment in patient´s home, the use of the product should be simulated in practice.

An in-use stability data were provided in the initial dossier, however, the sampling frequency did not reflect the use of the reconstituted Dropcys according to the proposed posology in the SmPC. It is acknowledged that the finished product was sampled over 21 days and these data were provided. The physical-chemical stability of the active substance was acceptable up to Day 3. The efficacy of antimicrobial preservation was confirmed at the end of 21 days. The content of benzalkonium chloride was however not quantified throughout the in-use stability studies and this is not accepted.

An additional in-use stability study was provided on expired samples. The product sample was opened 5 times a day (the minimum requirement listed in the SmPC). Due to the time constraint, the Applicant only studied assay of mercaptamine and cystamine and sterility at Day 0 and 7. All data comply with the proposed specification.

Based on the above data, considering the undesirable high level of benzalkonium chloride is present in the finished product, the proposed in-use stability of 7 days may be acceptable for this formulation to support physical-chemical and microbiological quality. However, data had not been provided as per approved specifications nor in-line with the posology (every awaken hour or at least 5 times per day for 7 days). The applicant had committed to carry out in-use stability studies post-authorisation. This is however not acceptable by the CHMP.

In addition, the applicant was requested to re-formulate the finished product. Any changes in the formulation would have an impact on the in-use stability of the finished product. The applicant should have therefore conducted new in-use stability studies on the optimised formulation in line with the shelf-life specification (including the levels of benzalkonium chloride). The in-use stability studies should have had a sampling frequency of more than 5 times a day according to the proposed posology in the SmPC.

Microbiological quality of the product

The proposed product is to be reconstituted prior to use. The reconstitution process is complex and requires 14 steps (7 for the preparation of the product and 7 for the administration of the eye drops). Due to the complexity, there is potential risk of microbiological and particulate contamination during reconstitution. The sterility of the proposed product may not be maintained even when the patients are sufficiently trained to handle the assembly of the container and the administration of the eye drops if it is to be used in patient’s home.

Therefore, even if the planned in-use stability testing protocol involves adding more microorganisms in the contamination procedure than normally seen in these types of studies it is argued it is difficult to establish good microbiological quality in a prospective testing.

Moreover, the maintenance of microbiological quality of the product during the course of treatment was not established as contaminations would occur as accidences rather than that observed in the routine in-use stability studies. The container closure system is not considered fit for purpose in relation to patient usability and potential risk of contamination of the product during assembly of the container by patients.

The CHMP therefore strongly recommend that the Applicant re-develop the container closure system to improve usability and mitigate the risk of potential microbiological and particulate contamination during reconstitution.

In comparison, the similar product (Cystaran) licensed in the US is a sterile ophthalmic solution packed in a 15ml LDPE bottle. It is stored in freezer during long-term storage and thawed for ~24 hours before use. The thawed bottle is stored at 2°C to 25°C (36°F to 77°F) for up to 1 week during use.

The use of freezer to resolve the issue of active substance stability is preferred when compared to reconstitution, as it minimise the risk of microbiological contamination or possible misuse of the product during reconstitution.

In conclusion, inadequate in-use stability data were provided to support the proposed posology and shelf-life after reconstitution. The applicant was requested to re-formulate the finished product. To this end, the applicant should conduct appropriately designed in-use stability studies using the optimised formulation in line with the posology in the SmPC. The in-use stability studies should include full characterisation of the finished product throughout the in-use shelf life.

Overall conclusion

Based on the review of the data and justifications submitted by the applicant, the CHMP is of the opinion that the applicant has not been able to demonstrate a favourable risk-benefit for Dropcys.

The previous benefit/risk evaluation remains unchanged.

6. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that

[a] the quality, safety and efficacy of the above mentioned medicinal product are not sufficiently demonstrated pursuant to Article 12(1) of Regulation (EC) No 726/2004,

and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above

mentioned medicinal product.

Whereas

- The efficacy of Dropcys eye drops (0.1% mercaptamine) was not sufficiently demonstrated. The bibliographic references provided to support the efficacy of the 0.1% concentration for the intended formulation were very limited and did not allow demonstration of the efficacy of the product.

- Furthermore, at this stage, the development of the formulation was not appropriately justified with regard to the levels of benzalkonium chloride, the target pH and buffer capacity of the product. The resulting impact on ocular safety has not been adequately justified taking into account that this formulation is intended to be mainly used to treat paediatric population in a very frequent schedule of administration and in long-term (chronic disease).

- No in-use stability data were provided to support the proposed posology and shelf-life after reconstitution. Moreover, the maintenance of microbiological quality of the product during the course of treatment was not established.

The CHMP is of the opinion that pursuant to Article 12(1) of Regulation (EC) No 726/2004, the quality, safety and efficacy of the above mentioned medicinal product are not properly or sufficiently demonstrated.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet and risk management plan cannot be agreed at this stage.