CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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Product:	CYSTADROPS® (cysteamine ophthalmic solution) 0.37%
Indication:	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Applicant:	Recordati Rare Diseases Inc. (Recordati)
Review Division:	Transplant and Ophthalmology Products
Reviewer:	María I Rivera, PhD
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1 Executive Summary

1.1 Introduction

The Applicant is seeking approval for the marketing of CYSTADROPS® (cysteamine ophthalmic solution) 0.37% for the indication of treatment of corneal cystine crystal deposits in adults and children with cystinosis. The use of cysteamine for the treatment of cystinosis is not novel. The FDA has approved several oral and ocular applications for the treatment of cystinosis: CYSTAGON® (NDA 020392; cysteamine bitartrate), oral hard-capsules, containing 50 mg or 150 mg of cysteamine; PROCYSBI® (NDA 203389; cysteamine bitartrate), delayed release oral capsules containing 25 mg or 75 mg of cysteamine; CYSTARAN® (NDA 200740; cysteamine hydrochloride), topical ophthalmic solution 0.44%.

The European Commission has granted a marketing authorization to Orphan Europe S.A.R.L. for CYSTADROPS®, indicated for the treatment of corneal cystine crystal deposits in patients with cystinosis, as an orphan medicinal product on January 19, 2017. Orphan Europe S.A.R.L. and Recordati Rare Diseases Inc. are wholly-owned subsidiaries of the Recordati Group. CYSTADROPS® received marketing authorization in Canada on February 11, 2019, indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.

This NDA is submitted as a 505(b)(2) application with CYSTAGON® (cysteamine bitartrate) capsules as the listed drug. This NDA provides original nonclinical data in support of the ocular safety of CYSTADROPS® and relies on the FDA's previous findings of safety and effectiveness for CYSTAGON® to support the systemic safety. Published literature is also used as additional supportive information for ocular and systemic safety. The bridge for use of CYSTAGON® as the listed drug is based on dose. The daily dose of cysteamine from CYSTADROPS® (assuming 100% systemic absorption after ocular application) is no more than approximately 0.4% of the recommended daily oral CYSTAGON® dose for the treatment of cystinosis in any age group.

1.2 Brief Discussion of Nonclinical Findings

Ocular toxicity studies were conducted in rabbits with Cystadrops at daily dosing frequencies of 3X, 4X, 6X, and 9X, with treatment duration up to 3 months. The key findings include:

- Conjunctival effects (redness, congestion, swelling, discharge and chemosis), corneal effects (opacity, vascularization and staining), and iritis. The incidence/severity of these generally increased as the frequency of administration increased from 3 to 9 instillations per day.
- Cystadrops 9X/day was not tolerated and required early sacrifice of the animals (2 weeks after study initiation). During clinical examinations on the day of necropsy, corneal opacities, right eye half opened, and right eye ruined were reported.

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- Depending on the dosing frequency, microscopic findings were primarily observed in the limbus and cornea (inflammatory cells, strong dilated vessels, corneal neovascularization, thinned corneal epithelium, thinning/destruction of the limbus epithelium, keratic precipitates) and conjunctiva (extravasated lymphocytes and dilated vessels). More severe microscopic findings were observed at Cystadrops 9X/day (dilated vessels and dissociated collagen fibers in the conjunctiva, dissociated collagen fibers, neovascularization and stromal edema in the cornea).
- The NOAEL was Cystadrops 3X/day, the exposure margin is less than 1X for the intended clinical dosing regimen of Cystadrops 4X/day.
- Based on the observed adaptation with continuous treatment (i.e., findings reversed or decreased in incidence/severity with time), Cystadrops 4X/day was considered well tolerated. Therefore, the nonclinical results support the tolerability of the intended clinical dosing regimen of 4 drops daily.
- The vehicle had a significant contribution to the findings observed at a dosing frequency of 6X/day (only dosing frequency evaluated for the vehicle). Because the study did not include a 9X/day vehicle control group, the contribution of the vehicle to the findings observed in eyes treated with Cystadrops 9X/day is unknown.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

1.3.3 Labeling

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Recordati's Proposed Changes	FDA Reviewer's Recommendations
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** *Risk Summary* There are no adequate and well-controlled studies of ophthalmic cysteamine in pregnant women. CYSTADROPS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. *Data* *Animal data* Teratology studies have been performed in rats at oral doses in a range of 37.5 mg/kg/day to 150 mg/kg/day (about 240 to 960 times the recommended human ophthalmic dose on a body surface basis) and have revealed cysteamine bitartrate to be teratogenic. Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly, and exencephaly. Cysteamine was fetotoxic, resulting in intrauterine death and growth retardation in rats at oral doses of (b) (4) times the recommended human dose on a body surface basis.	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** *Risk Summary* There are no adequate and well-controlled studies of ophthalmic cysteamine in pregnant women to *inform any drug associated risks. Oral administration of cysteamine to pregnant rats throughout the period of organogenesis was teratogenic at doses 240 to 960 times the recommended human ophthalmic dose (based on body surface area) [see Data].* CYSTADROPS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Data* *Animal Data* Teratology studies have been performed in rats at oral doses in ~~a~~ *the* range of 37.5 mg/kg/day to 150 mg/kg/day (~~about~~ 240 to 960 times the recommended human ophthalmic dose *based* on ~~a~~ body surface area ~~basis~~) and have ~~revealed~~ *shown* cysteamine bitartrate to be teratogenic. Observed teratogenic findings were *intrauterine death*, cleft palate, kyphosis, heart ventricular septal defects, microcephaly, *exencephaly* and ~~exencephaly~~ *growth deficits*.
8.2 Lactation *Risk Summary* It is not known whether oral cysteamine is excreted in human milk. Because many drugs are excreted in human milk and because of the manifested potential of cysteamine for developmental toxicity in suckling rat pups when it was administered to their lactating mothers at an oral dose of 375 mg/kg/day (2,250 mg/m^2/day,	**8.2 Lactation** *Risk Summary* There is no information regarding the presence of cysteamine in human milk, the effects on the breastfed infants, or the effects on milk production. Cysteamine administered orally is present in milk of lactating rats. It is not known whether measurable levels of cysteamine would

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[(b) (4)] times the recommended human [(b) (4)] dose based on body surface area), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The incremental increase in systemic cysteamine levels derived from drug applied topically to the eye in patients treated with oral cysteamine is negligible.	be present in maternal milk following topical ocular administration of CYSTADROPS. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CYSTADROPS and any potential adverse effects on the breastfed child from CYSTADROPS or from the underlying maternal conditions.
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.	No edits recommended for the first paragraph.
Cysteamine was not mutagenic in the Ames test. It produced a negative response in an *in vitro* sister chromatid exchange assay in human lymphocytes but a positive response in a similar assay in hamster ovarian cells.	No edits recommended for the second paragraph.
Repeat breeding reproduction studies were conducted in male and female rats. Cysteamine was found to have no effect on fertility and reproductive performance at an oral dose of 75 mg/kg/day ([(b) (4)], 480 times the recommended human ophthalmic dose based on body surface area). At an oral dose of 375 mg/kg/day [(b) (4)], 2,400 times the recommended human ophthalmic dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.	Repeat breeding reproduction studies were conducted in male and female rats. Cysteamine was found to have no effect on fertility and reproductive performance at an oral dose of 75 mg/kg/day ([(b) (4)], 480 times the recommended human ophthalmic dose based on body surface area). At an oral dose of 375 mg/kg/day ([(b) (4)], 2400 times the recommended human ophthalmic dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.

Exposure margins calculations:

Human dose:

- Cystadrops 0.37%, one drop 4x/day, bilateral dosing:
  - 3.8 mg/mL X 4 drops X 2 eyes X 0.05 mL/drop = 1.52 mg/day
  - 1.52 mg/60 kg = 0.0253 mg/kg
  - 0.0253 mg/kg X 37 = 0.94 mg/m^2

Exposure margins (based on mg/m^2):

- Teratogenic effects (Rats)
  - 37.5 mg/kg/day is equivalent to 225 mg/m^2
    - Exposure Margin = 225/0.94 = 239X, rounded to 240X

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- 150 mg/kg/day is equivalent to 900 mg/m^2
  - Exposure margin = 900/0.94= 957X, rounded to 960X

- Fertility (Rats)
  - 75 mg/kg/day is equivalent to 450 mg/m^2
    - Exposure Margin = 450/0.94= 479X, rounded to 480X
  - 375 mg/kg/day is equivalent to 2250 mg/m^2
    - Exposure Margin = 2250/0.94= 2394X, rounded to 2400X

2 Drug Information

2.1 Drug

CAS Registry Number: 156-57-0

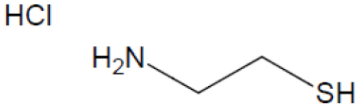
Generic Name: Cysteamine hydrochloride

Code Name

Chemical Name: β-mercaptoethylamine hydrochloride, mercaptamine hydrochloride

Molecular Formula/Molecular Weight: C_2H_7NS, HCl/113.6 g/mol

Structure:



Pharmacologic Class: Cystine-depleting agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

DMF (b) (4) Cysteamine HCl

2.3 Drug Formulation

CYSTADROPS® is a viscous eye drop solution containing 5.6 mg/mL of cysteamine hydrochloride, equivalent to 3.8 mg/mL of cysteamine, as active pharmaceutical ingredient. The qualitative and quantitative composition of CYSTADROPS® (cysteamine ophthalmic solution) 0.37% (w/w) is shown in Table 1.

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Table 1: CYSTADROPS® Composition

Components	Centesimal formula (w/v)	Centesimal formula (w/w)	Function
Cysteamine *As cysteamine hydrochloride*	3.8 mg *5.6 mg*	0.37 % 0.55 %	Drug substance
Carmellose sodium (b) (4)			
Benzalkonium chloride (b) (4)			preservative agent
Disodium edetate			
Citric acid monohydrate			
Sodium hydroxide			
Hydrochloric acid (b) (4)			
(b) (4)			
Water for injections			

2.4 Comments on Novel Excipients

There are no novel ophthalmic excipients. However, some excipients are above levels reported in in the FDA Inactive Ingredient Database: carmellose sodium (as carboxymethylcellulose sodium) is listed for ophthalmic use at 0.5%; citric acid is listed at levels up to 0.2%; hydrochloric acid is listed as used in most ophthalmic formulations to adjust pH and at concentrations up to 1.06% in a few topical formulations. Carboxymethylcellulose is listed as an excipient in systemically administered drugs with oral levels ≤241.84 mg (vs. (b) (4) mg/day at the intended ocular route and assuming 100% systemic absorption).

All excipients were present in the 3-month ocular toxicity study in rabbits performed with the formulation to be marketed (Study # O06F28312). The vehicle itself caused ocular irritation/inflammation in the rabbit at dosing frequencies above 3X/day.

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However, there is marketing experience with the intended clinical formulation. The European Commission has granted a marketing authorization to Orphan Europe S.A.R.L. for CYSTADROPS® as an orphan medicinal product on January 19, 2017. CYSTADROPS® received marketing authorization in Canada on February 11, 2019. Therefore, the excipients are considered qualified for the intended dosing regimen.

2.5 Comments on Impurities/Degradants of Concern

Pending CMC review

2.6 Proposed Clinical Population and Dosing Regimen

- Adults and children with cystinosis
- One drop of CYSTADROPS in each eye topically, 4 times a day during waking hours

2.7 Regulatory Background

- Pre-NDA submission dated April 11, 2018
- Pre-NDA meeting held on May 15, 2018

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

- Long-Term Evaluation of Efficacy in Reducing Cystine Crystals and of Ocular Tolerance following Multiple Daily Instillations in CTNS$^{-/-}$ Mice (Study # O06F0405)

PK/ADME

- (b) (4)% Cysteamine (b) (4) Formulations. Pharmacokinetic Evaluation in Rabbit Cornea following a Single Topical Administration. Comparison with a 0.55% Cysteamine Solution ("NIH formulation"). Orientation Study. (Study # O06F0103)
- 0.55% Cysteamine Hydrochloride (b) (4) Formulations. Comparison of Two (b) (4) Agents and Three Viscosities in Corneal Penetration following a Single Topical Administration in Albino Rabbits. Orientation Study. (Study # O06F0603)
- Cysteamine (b) (4) Formulations. Comparison of Several Cysteamine Concentrations in Corneal Penetration following a Single Topical Administration in Albino Rabbits. Orientation Study (Study # O06F0703).

General Toxicology

- Pilot Evaluation of Acute Ocular Irritation following 5 Instillations within 20 Minutes in Albino Rabbits (Study # O06F0205)

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- Evaluation of Ocular Tolerance in Albino Rabbits following Multiple Daily Ocular Administrations for 3 Months (Study # O06F0106)
- 1 and 3-Month Ocular Tolerance Study of a New Cystadrops® Formulation Four Times Daily Instilled in Albino Rabbits (Study # O06F28312)

Genetic Toxicology

- Cystagon: Reverse Mutation in Five Histidine-requiring Strains of Salmonella Typhimurium (Study # 1571/1-1052)
- Cystagon: Induction of Micronuclei in the Bone Marrow of Treated Mice (Study # 1571/2-1052)

3.2 Studies Not Reviewed

- Cysteamine. Development of an HPLC-MS Method in Rabbit Cornea. Pilot Validation. (Study # O06F0102)
- Cysteamine. Validation of an HPLC-MS Method in Albino Rabbit Cornea Using the SFSTP and FDA Guidelines (Study # O06F01042)

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Cystinosis is a rare genetic autosomal recessive disease due to a lysosomal transport defect characterized by the intracellular accumulation of cystine in many tissues. The responsible gene, *CTNS*, encodes cystinosin, a 367-amino acid integral membrane protein that transports cystine out of the lysosome. Cysteamine (mercaptamine) acts by converting cystine to cysteine and cysteine-cysteamine mixed disulfides, which are then transported out of the lysosome, thus depleting the intracellular (intra-lysosomal) accumulation of cystine. Cysteamine is a natural product of mammalian cells forming the terminal region of the acetyl-coenzyme A (acetyl-CoA) molecule. It is a degradation product of the amino acid cysteine and arises by enzymatic degradation of acetyl-CoA.

Long-Term Evaluation of Efficacy in Reducing Cystine Crystals and of Ocular Tolerance following Multiple Daily Instillations in CTNS$^{-/-}$ Mice (Study # O06F0405) – C57BL/6 strain (Ctns$^{-/-}$) knock out mice accumulate cystine in all organs tested, including cystine crystals and ocular changes similar to those observed in affected individuals. The mice were initially allocated into 2 groups: Cystadrops and one control group (untreated animals), both administered at a frequency of 3X/day. At the end of the 3rd month, the control group was divided into 2 sub-groups: one still untreated control subgroup and one subgroup of mice starting treatment 6X/day with a reference

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cysteamine solution (i.e. “NIH formulation”, containing 0.55% cysteamine hydrochloride, non-viscous). The Cystadrops dosing frequency was increased to 6X/day for the remaining 2 months of the study.

- No clear benefit with either formulation after treatment for 3 months 3X/day. In the mice receiving Cystadrops 3X/day, the number of corneal cystine crystals continued to increase but slightly less (12% at Month 3) than in the control untreated animals.

- When the frequency of installations was increased to 6X/day, Cystadrops stopped the increase in the number of crystals in the cornea, whereas a continuous increase was seen for the untreated animals. No significant difference was observed between the NIH solution and Cystadrops.

The Applicant cited a published in vitro study in human cells (Thoene et al[1]) and one published in vivo study in *Ctns*$^{-/-}$ knock-out mice (Simpson et al[2]). Application of cysteamine lead to a decrease in cystine, both *in vitro* in cystinotic human fibroblasts and *in vivo,* in the knock-out mouse model of cystinosis. After administration of cysteamine 0.55% 4X/day for 1 month in the *Ctns*$^{-/-}$ knock-out mice, the increase in crystal volume index was 15% in cysteamine treated animals *versus* 173% in untreated animals (both eyes in each animal were examined and counted).

4.2 Secondary Pharmacology

The Applicant cited additional published studies reporting other pharmacological effects of cysteamine including (a) antioxidant effect as a result of increased intracellular glutathione (GSH) levels; (b) inhibition of transglutaminase 2 (TG2); and (c) depletion of tissue somatostatin and prolactin. Cysteamine as a therapeutic antioxidant is under investigation in non-alcoholic fatty liver disease. As an inhibitor of TG2, cysteamine is also being investigated as a therapeutic agent in Huntington’s disease.

The intended daily ocular dose (1 drop up to 4 times daily in each eye or 0.94 mg/m^2) is 1383-fold lower than the recommended maintenance daily oral dose (1.30 g/m^2) of the approved CYSTAGON® hard capsules. Alternatively, as noted by the Applicant, the recommended total daily dose of cysteamine base, applied as an ophthalmic solution, is no more than approximately 0.4% of the highest recommended daily oral dose of cysteamine in any age group (see Table 13, Section 11 “Integrated Summary and Evaluation” of this review). As such, the contribution of topical ocular cysteamine to the observations of these effect is expected to be minimal.

[1] Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA. (1976) Cystinosis. Intracellular cystine depletion by aminothiols in vitro and in vivo. J Clin Invest 58(1): 180-189.

[2] Simpson JL, Nien CJ, Flynn KJ, Jester JV. (2011) Evaluation of topical cysteamine therapy in the CTNS$^{-/-}$ knockout mouse using in vivo confocal microscopy. Mol Vis 17: 2649-2654.

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4.3 Safety Pharmacology

No new safety pharmacology studies were performed. The Applicant's cited the following published studies with cysteamine administration.

- Subcutaneous (SC) doses of 50 to 250 mg/kg in rats induced CNS effects (locomotor activation, head/neck tremor, increased defecation, attenuation of passive avoidance retention test performance, reduction of cortical/ hippocampal somatostatin-like immunoreactivity, rise in somatostatin-like immunoreactivity in cerebrospinal fluid, impaired escape latencies and spatial probe behavior in the Morris water task, and/or changes in cortical levels of norepinephrine and dopamine)[3], [4].
- In experiments where spatial learning/memory and motor functioning was investigated in rats at 4 to 5 weeks following cessation of 6 weeks of daily SC doses of 150 mg/kg, increased formation of senescent glial cell changes and impaired performance in the Morris water maze were observed; there was no effect on locomotor activity[5]. The results indicated that chronic cysteamine exposure induces senescence-like changes in the dorsal hippocampus which are associated with deficits in cognitive, but not locomotor behavior and elevated levels of hippocampal and hypothalamic somatostatin.
- In a battery of learning tests, a single dose of 50 to 200 mg/kg SC in mice showed impaired acquisition of memory in the step-down test dose dependently and in the lever press test at a dose of 200 mg/kg[6]. The results suggest that the learning disorder induced by cysteamine in mice is restricted to a specific type of behavioral performance. The authors concluded that the mechanism by which cysteamine generates learning deficiency in mice may differ from that in rats.
- Slight reductions of bile secretion were observed in a study in anesthetized rats at the dose level of 340 mg/kg.

Adverse events related to the CNS have been associated with the use of oral cysteamine in humans (CYSTAGON® prescribing information, 2018). These include seizures, lethargy, somnolence, depression, and encephalopathy. The label also indicates that gastrointestinal ulceration and bleeding have been reported in patients receiving cysteamine bitartrate.

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[3] Haroutunian V, Mantin R, Campbell GA, Tsuboyama GK, Davis KL. (1987) Cysteamine-induced depletion of central somatostatin-like immunoactivity: effects on behavior, learning, memory and brain neurochemistry. Brain Res 403(2):234-242.

[4] Fitzgerald LW, Dokla CP. (1989) Morris water task impairment and hypoactivity following cysteamine-induced reductions of somatostatin-like immunoreactivity. Brain Res 505(2):246-250.

[5] Justino L, Welner SA, Tannenbaum GS, Schipper HM. (1997) Long-term effects of cysteamine on cognitive and locomotor behavior in rats: relationship to hippocampal glial pathology and somatostatin levels. Brain Res 761(1):127-134.

[6] Nakata A, Saito H, Nishiyama N. (1995) Limited impairment of learning performances in mice treated with cysteamine. Biol Pharm Bull 18(12):1773-1775.

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The proposed daily clinical ocular dose (1 drop up to 4 times daily in each eye or 0.94 mg/m^2) is 1383-fold lower than the recommended maintenance daily oral dose (1.30 g/m^2) of the approved CYSTAGON® hard capsules. Therefore, the contribution of topical ocular cysteamine to the observations of these effect is expected to be minimal.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No ocular tissue distribution studies were conducted with cysteamine, except for assessment of its uptake and elimination from the rabbit cornea. The studies were conducted in male New Zealand White albino rabbits:

- In the first study (Study # O06F0103), cysteamine hydrochloride was compared at 2 strengths (0.5% and 0.55%) and in several different formulations. One formulation contained (b) (4)% CMC ((b) (4)), an excipient used in the commercial formulation, although at (b) (4) Cysteamine content in the cornea was determined at 0.25, 0.5, and 1 hour postdose.
- In the second study (Study # O06F0603), cysteamine hydrochloride at 0.55% was tested in multiple formulations that were made viscous using a variety of agents, including CMC ((b) (4)) at (b) (4)%, (b) (4)%, and (b) (4)%. Cysteamine content in the cornea was determined at 0.25 and 1 hour postdose.
- In the third study (Study # O06F0703), cysteamine hydrochloride was tested at multiple concentrations (0.55%, 1.1%, 1.65%, and 2.2%) in a formulation that contained (b) (4)% CMC. Cysteamine content in the cornea was determined at 0.25 hour and 1 hour postdose.

Key findings include the following:

- Cysteamine 0.55% was observed to be rapidly eliminated from the rabbit cornea after topical instillation of a 100 µL solution. The T_{max} occurred at 0.25 hour postdose.
- Cysteamine was detected in the cornea up to 1 hour postdose when using formulations with a higher CMC content. The levels at 1 hour were substantially decreased compared to earlier timepoints (e.g., see Table 2 and Figure 1).
    - In comparison, cysteamine was not quantified at any timepoint (0.25 or 1 hour) after administration of the reference “NIH solution” that did not contain a viscosity agent.
- In Study # O06F0103, cysteamine was not determined in the formulation with CMC (b) (4)% (batch # EF2549) at the 1-hour postdose timepoint. This formulation showed the higher corneal AUC (10,063 ng•hr/g).
- In Study # O06F0603, higher AUC and C_{max} were obtained with the 0.55% cysteamine/CMC medium viscosity ((b) (4)%) formulation (see PK parameters in the table below).

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Table 2: Corneal PK Parameters of Cysteamine after a Single Topical Administration (100 µL) of 0.55% Cysteamine with CMC (b) (4)%, (b) (4)% or (b) (4)% in Both Eyes of Albino Rabbits

Treatment	*Time after the instillation (h)*	Cysteamine concentration (ng/g of cornea)	
		Mean	*SD*
0.55% Cysteamine with CMC low viscosity	*0.25*	45 659.6	23 525.5
	1	4 193.1	8 060.2
	T_{max} *(h)*	*0.25*	
	C_{max} *(ng/g)*	45 659.6	
	$AUC_{(0.25\text{-}1h)}$*[(ng/g) x h]*	18 695	
0.55% Cysteamine with CMC medium viscosity	*0.25*	83 857.3	41 566.7
	1	4 238.8	8 610.2
	T_{max} *(h)*	*0.25*	
	C_{max} *(ng/g)*	83 857.3	
	$AUC_{(0.25\text{-}1h)}$*[(ng/g) x h]*	33 036	
0.55% Cysteamine with CMC high viscosity	*0.25*	69 167.7	30 754.6
	1	5 952.0	6 680.6
	T_{max} *(h)*	*0.25*	
	C_{max} *(ng/g)*	69 167.7	
	$AUC_{(0.25\text{-}1h)}$*[(ng/g) x h]*	28 170	

- In formulations with the same (b) (4)% CMC content (Study # O06F0703), no clear relationship was observed between corneal concentration and concentration of cysteamine in the eye drop formulation (Figure 1).
  - Formulations ranked from the highest C_{max} or $AUC_{0.25\text{-}1hr}$ to the lowest were: 1.65% > 0.55% > 1.1% > 2.2%.
  - Overall, the highest C_{max} and $AUC_{0.25\text{-}1hr}$ values were obtained with the 1.65% (C_{max} of 89.9 µg/g and $AUC_{0.25\text{-}1hr}$ of 34.0 µg/g•hr) and 0.55% cysteamine hydrochloride concentrations (C_{max} of 83.9 µg/g and $AUC_{0.25\text{-}1hr}$ of 33.0 µg/g•hr).

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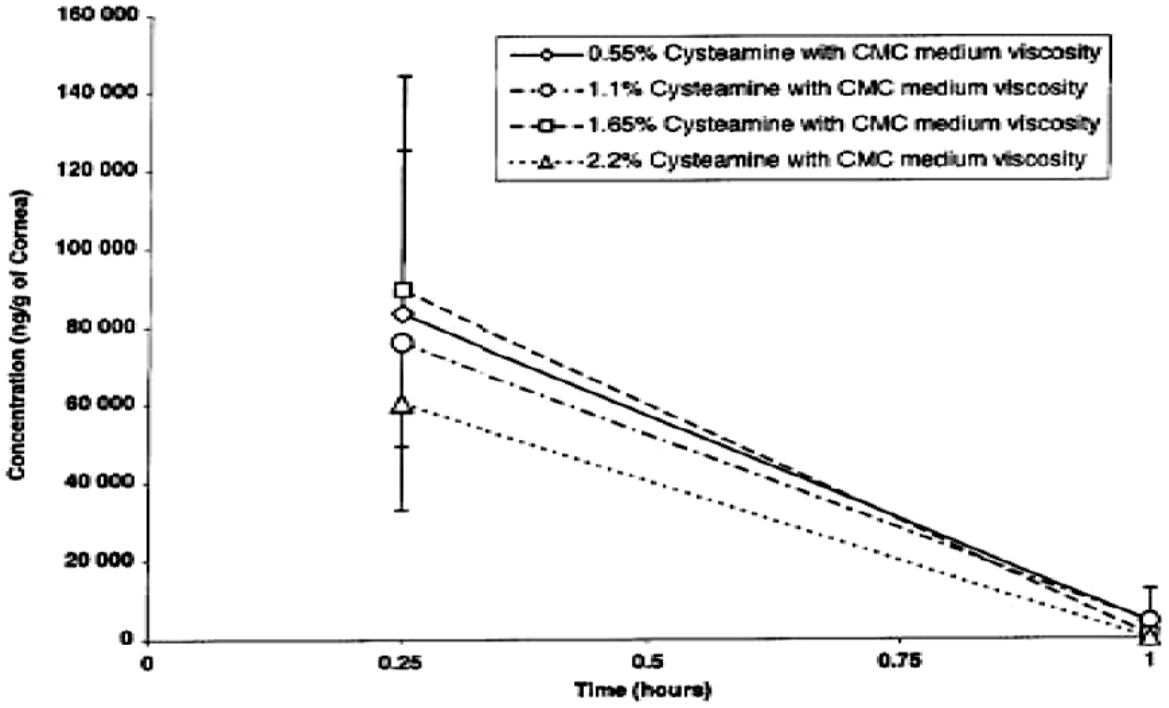
Figure 1: Mean Concentrations ± Standard Deviation (SD) (n=4) of Cysteamine in Rabbit Cornea after Application of Different Doses in a Formulation with the Same CMC Content ((b) (4)%) (Study # O06F0703)



Given the lack of a dose response for both cysteamine concentration or CMC content, it is hard to predict the residence time of cysteamine in the eye of the intended marketing formulation. The extent of cysteamine distribution outside the cornea following topical administration has not been determined.

The Applicant summarized several studies from the published literature related to the pharmacokinetics of cysteamine after systemic administration. In summary,

- Oral cysteamine hydrochloride in rats (250 mg/kg, 3 doses at 4-hour intervals) distributed to red blood cells, plasma and the two brain tissues studied, with a clear reduction of concentrations at the 24-hour timepoint, *i.e.,* 16 hours after the last dose (given at 8 hours after the first dose).
- Fasted male rats given an intraduodenal administration of 20 mg/kg cysteamine bitartrate showed that cysteamine is rapidly absorbed from the small intestine, undergoes significant hepatic first-pass metabolism (40% oral bioavailability), crosses the blood brain barrier, and is almost undetectable in plasma, CSF, and body tissues 2 hours after dosing.
- At an SC dose of 50 mg/kg cysteamine hydrochloride in mice, a dose shown to affect learning and memory in animal studies (see 4.3 Safety Pharmacology), plasma C_{max} (80 µM; 9.1 µg/mL) was observed rapidly after injection and the

Reference ID: 4622356

plasma elimination was also rapid with essentially undetectable levels at 2 hours postdose.

- Since cysteamine is an endogenous compound, the Applicant stated that it could be expected that its clearance/metabolism following systemic administration is similar if not identical to that which occurs endogenously.

The extent of systemic absorption of cysteamine after topical ocular administration of CTATADROPS® is unknown. The proposed daily clinical ocular dose (1 drop up to 4 times daily in each eye or 0.94 mg/m^2) is 1383-fold lower than the recommended maintenance daily oral dose (1.30 g/m^2) of the approved CYSTAGON hard capsules. Therefore, the contribution from topical cysteamine, if any, is negligible compared to the systemic levels at the approved oral dose.

The genetic toxicity studies submitted by the Applicant as well as nonclinical studies relied upon from the listed drug (CYSTAGON®) were conducted with cysteamine bitartrate. The Applicant stated that data from the bitartrate salt of cysteamine are expected to be relevant to cysteamine hydrochloride (CYSTADROPS®) as both salts are expected to dissociate rapidly into active cysteamine and the salt constituent following contact with moisture (*i.e*., in the eye or in the gastrointestinal tract). A published single oral dose bioequivalence study in healthy volunteers has shown no significant difference between cysteamine bitartrate, cysteamine hydrochloride, and phosphocysteamine with respect to PK and tolerability[7].

6 General Toxicology

6.1 Single-Dose Toxicity

Pilot Evaluation of Acute Ocular Irritation following 5 Instillations within 20 Minutes in Albino Rabbits (Study # O06F0205; non-GLP) – The study evaluated the ocular irritation potential of two 0.55% cysteamine hydrochloride formulations. One formulation contained carboxymethylcellulose (CMC) sodium with (b) (4); the other formulation contained CMC sodium without (b) (4). Both formulations were compared to the vehicle that included (b) (4). The concentration of CMC was not specified.

The irritation potential was evaluated after five 50 µL instillations within 20 minutes in the right eye of New Zealand White male rabbits (3/group). Ocular observations with an ophthalmoscope using the Draize scale were performed for both treated and untreated eyes of all animals before treatment (baseline), then 1 minute after the first instillation, then 5 minutes, 30 minutes, 1 hour, 4 hours, and 24 hours after the last instillation.

Key Findings:

[7] Tennezé L, Daurat V, Tibi A, Chaumet-Riffaud P, Funck-Brentano C. (1999) A study of the relative bioavailability of cysteamine hydrochloride, cysteamine bitartrate and phosphocysteamine in healthy adult male volunteers. Br J Clin Pharmacol 47(1):49-52.

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- Slight conjunctival redness and all chemosis was noted in all groups (Table 3).
- Corneal opacity was observed in the vehicle control group (with (b) (4)
- For the three groups, the effects were reversible; not observed 24 hours after the last instillation.
- Both cysteamine formulations and the vehicle were classified as very slightly irritants.
    - The mean ocular irritation index (MOI) calculated at each time was between 0 and 5.3 (T_{max} = 1 hour), 0 and 2.6 (T_{max} = 1 to 4 hours), and 0 and 3.3 (T_{max} = 4 hours) for 0.55% cysteamine/CMC with (b) (4) 0.55% cysteamine/CMC without (b) (4) and CMC with (b) (4) vehicle, respectively.

Table 3: Ocular Evaluation (Draize scale) after 5 Instillations of Cysteamine/CMC (b) (4) and the CMC/ (b) (4) Vehicle

Treatment	Time-point after the last instillation	Score mean (n=3)											
		CONJUNCTIVA						CORNEA				IRIS	
		Redness (0-3)		Chemosis (0-4)		Discharge (0-3)		Degree of opacity (0-4)		Area of opacity (0-4)		Iritis (0-2)	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
(b) (4) (0.55% cysteamine hydrochloride with (b) (4) (b) (4))	Baseline	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	5min	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	30min	1.7	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1H	2.0	0.0	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	4H	1.3	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	24H	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
(b) (4) (0.55% cysteamine hydrochloride without (b) (4))	Baseline	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	5min	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	30min	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1H	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	4H	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	24H	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
vehicle (b) (4) with (b) (4)	Baseline	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
	1min	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
	5min	0.7	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
	30min	1.3	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
	1H	1.0	0.0	0.3	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
	4H	1.3	0.0	0.3	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
	24H	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0

6.2 Repeat-Dose Toxicity

Study title: Evaluation of Ocular Tolerance in Albino Rabbits following Multiple Daily Ocular Administrations for 3 Months

Study no.:	O06F0106
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 23, 2007
GLP compliance:	No **Note:** This study did not claim GLP compliance due to lack of extended (18-month) stability data for the test item its vehicle and certificates of identity and analysis for the vehicle from the Applicant. The study was audited by the test facility Quality Assurance group on several occasions and the Applicant believes it provides high-quality data.
QA statement:	Yes
Drug, lot #, and % purity:	Cystadrops (0.55% cysteamine hydrochloride topical ocular formulation), batch # F6105, (b) (4)% to (b) (4)% pure (per product specifications report in French on page 276 of the Study Report) Note: The content of CMC in this formulation was (b) (4)% (whereas the commercial formulation contains (b) (4)% CMC).

Key Study Findings

- Cystadrops (0.55% cysteamine hydrochloride topical ocular formulation) or its vehicle caused conjunctival effects (redness, congestion, swelling, discharge and chemosis), corneal effects (opacity, vascularization and staining), and iritis. The incidence/severity of these generally increased as the frequency of administration increased from 3 to 9 instillations per day. It appears that the vehicle has a significant contribution to the findings observed at a dosing frequency of 6X/day. Because the study did not include a 9X/day vehicle control group, the contribution of the vehicle to the findings observed in eyes treated with Cystadrops 9X/day is not clear.

- Cystadrops 9X/day was not tolerated and required early sacrifice of the animals (2 weeks after study initiation). During clinical gross examinations on the day of

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necropsy, corneal opacities, right eye half opened, and right eye ruined were observed.

- Microscopic findings were comparable in the Cystadrops 6X/day and vehicle 6X/day dose groups, indicating a significant contribution by the vehicle. These included effects in the cornea (thinned epithelium) and conjunctiva (extravasated lymphocytes and dilated vessels). More severe microscopic findings were observed at Cystadrops 9X/day (e.g., dilated vessels and dissociated collagen fibers in the conjunctiva; dissociated collagen fibers, neovascularization and stromal edema in the cornea). Because there was not a vehicle control group administered 9X/day, the contribution of the vehicle to these more severe findings is unknown.

- Cystadrops 3X/day or 6X/day or its vehicle 6X/day did not induce cornea anesthesia or damage of the cornea (thickness, endothelium cells density) after 3 months dosing.

- Because the findings observed in the Cystadrops 3X/day group were similar to those observed in the 0.9% NaCl control group and/or generally of slight severity, the NOAEL was considered to be Cystadrops 3X/day.

Methods

Doses:	0 (0.9% NaCl) 6X/day, 0 (vehicle) 6X/day, Cystadrops 3X/day, Cystadrops 6X/day, Cystadrops 9X/day
Frequency of dosing:	• Three times: every 5 hours • Six times: every 2 hours • Nine times: every 1.15 hours
Route of administration:	Topically (right eye only)
Dose volume:	50 µL
Formulation/Vehicle:	Cystadrops vehicle
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	5
Age:	~8 to 9 weeks
Weight:	1.6 – 2.2 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None considered to have an impact in the integrity of the data

Observations and Results

Mortality (Daily)

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One vehicle control female (R # 14) showed breathing difficulties and decreased body weight, and was euthanized on Day 72. For this animal, no ocular examinations, corneal sensitivity or confocal microscopy evaluations were performed before sacrifice.

Due to ocular effects (see below), rabbits in the Cystadrops 9X/day group were sacrificed for ethical reasons 2 weeks after the start of treatment.

Clinical Signs (Daily)

In high-dose animals (Cystadrops 9X/day), findings described as corneal opacities, right eye half opened, and right eye ruined were observed (Table 4). As noted above, these animals were euthanized early due to the severity of the findings observed.

Table 4: Adverse Clinical Ocular Signs in High-Dose Animals

		Males					Females				
		7	35	23	46	42	10	20	2	11	31
Clinical examinations	Body Skin and fur Urinary and genital zones Nose Mouth	**No clinical findings**	No clinical findings	No clinical findings	No clinical findings	No clinical findings	No clinical findings	**No clinical findings**	**No clinical findings**	No clinical findings	No clinical findings
	Eyes	**Corneal opacity on the right eye**	Corneal opacity on the right eye	Right eye ruined	**Right eye half openned**	Right eye ruined	Right eye closed	**Right eye half openned**	**Right eye closed**	**Right eye ruined and partial corneal opacity on the right eye**	Right eye half openned
	Lymphoid nodes	**No clinical findings**	No clinical findings	Severe inflammation with many white hard spheres at the neck	No clinical findings	No clinical findings	No clinical findings	**No clinical findings**	**No clinical findings**	No clinical findings	No clinical findings
	Ears Legs Rigor mortis			No clinical findings	Haemorrhage on the posterior legs						
	Other				No clinical findings						

Note: These findings were reported as part of the clinical examinations conducted on the day of necropsy.

Body Weights (Prestudy and weekly during study)

At Day 15, a slight decrease in body weight (4.9% in males, 3.3% in females) and body weight gain (39% in males, 29% in females) was observed in animals administered Cystadrops 9X/day, compared to vehicle control. No significant difference was observed between vehicle control and saline control animals.

Feed Consumption (Weekly)

At Day 15, food consumption was decreased (46% in males, 43% in females) in animals administered Cystadrops 9X/day, compared to vehicle control. No significant difference was observed between vehicle control and saline control animals.

Ophthalmoscopy

Reference ID: 4622736

Ocular Examinations with an Ophthalmoscope (Draize's scale) (Twice a day for the first 28 days [before the first and after the last daily administration], then once a day during the remaining 56 days [after the last daily administration)

Findings observed included slight to severe conjunctival redness, slight to moderate conjunctival chemosis, slight conjunctival discharge, slight to moderate corneal opacity and slight iritis. The corneal opacity and iritis were transient in Cystadrops 3X/day- or 6X/day- and vehicle 6X/day-treated eyes. The ocular effects occurred with higher incidence in the vehicle and Cystadrops-treated eyes, compared to the saline control. The data from the vehicle control compared to the Cystadrops group, treated at a similar dosing frequency (i.e., 6X/day), shows that the vehicle had a significant contribution to the findings. Because the study did not include a vehicle 9X/day control group, the contribution of the vehicle to the findings observed in eyes treated with Cystadrops 9X/day is not clear. The findings are summarized in Table 5.

Table 5: Summary of Ocular Observations – Draize Score

Cystadrops (0.55% cysteamine HCl)									Vehicle			0.9% NaCl		
3 x/day			6 x/day			9 x/day			6 x/day			6 x/day		
Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score
Slight to moderate conjunctival redness *(scores 1; 2)*	10/10	262/ 3330	Moderate conjunctival redness *(scores 1; 2)*	10/10	584/ 3330	Moderate to severe conjunctival redness *(scores 2; 3)*	10/10	282/ 750	Moderate conjunctival redness *(scores 1; 2; 3)*	10/10	429/ 3291	Slight conjunctival redness *(scores 1; 2)*	10/10	44/ 3330
Slight conjunctival chemosis *(scores 0; 1; 2)*	7/10	55/ 4440	Slight to moderate conjunctival chemosis *(scores 1; 2; 3)*	10/10	278/ 4440	Slight to moderate conjunctival chemosis *(scores 1; 2)*	10/10	70/ 1000	Slight conjunctival chemosis *(scores 1; 2)*	10/10	202/ 4388	Slight conjunctival chemosis *(scores 0; 1)*	2/10	2/ 4440
Slight conjunctival discharge *(scores 0; 1)*	1/10	1/ 3330	Slight conjunctival discharge *(scores 0; 1)*	9/10	31/ 3330	Slight conjunctival discharge *(scores 0; 1)*	4/10	4/ 750	Slight conjunctival discharge *(scores 0; 1; 2)*	7/10	19/ 3291	No other effect *(score 0)*	10/10	NA
Slight corneal opacity *(scores 0; 1)*	1/10	1/ 4440	Slight cornea opacity *(scores 0; 1; 2)*	7/10	129/ 4440	Slight to moderate cornea opacity *(scores 0; 1; 2; 3)*	8/10	56/ 1000	Slight cornea opacity *(scores 0; 1; 2)*	4/10	51/ 4388			
Iritis *(scores 0; 1)*	1/10	1/ 2220	Iritis *(scores 0; 1)*	3/10	9/ 2220	Iritis *(scores 0; 1; 2)*	7/10	29/ 500	Iritis *(scores 0; 1)*	1/10	1/ 2194			

RE: Right Eye

Notes: The maximum sum of the scores (i.e. number of animals x number of ocular observations x maximum value of the score). Animals administered Cystadrops 9X/day were euthanized on Day 15 or 16.

Ocular Examination with a Slit-Lamp (McDonald-Shadduck's scale) (Before the treatment period, once a week for the first 4 weeks [before the first daily administration] then every two weeks during the 8 following weeks)

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The administration 0.9% NaCl 6X/day induced very slight conjunctival redness or chemosis. The administration of vehicle 6X/day induced moderate conjunctival redness and other effects in the conjunctiva, cornea and iris. Findings were similar in the vehicle and Cystadrops-treated eyes. However, the incidence and/or severity increased with increasing frequency of administration. As similar findings were observed in the Cystadrops 6X/day and vehicle 6X/day control groups, it appears that the vehicle has a significant contribution. Because the study did not include a vehicle 9X/day control group, the contribution of the vehicle to the findings observed in eyes treated with Cystadrops 9X/day is not clear. The findings are summarized in Table 6.

Table 6: Summary of Slit Lamp Observations

Cystadrops (0.55% cysteamine HCl)									Vehicle			0.9% NaCl		
3 x/day			6 x/day			9 x/day			6 x/day			6 x/day		
Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence	Sum score
Slight conjunctival congestion *(scores 0; 1)*	6/10	6/ 240	Slight conjunctival congestion *(scores 0; 1)*	9/10	21/ 240	Slight to severe conjunctival congestion *(scores 0; 1; 2; 3)*	9/10	17/ 60	Slight conjunctival congestion *(scores 0; 1)*	8/10	17/ 237	Slight conjunctival congestion *(scores 0; 1)*	4/10	5/ 240
Slight conjunctival swelling *(scores 0; 1)*	3/10	4/ 320	Slight conjunctival swelling *(scores 0; 1)*	9/10	22/ 320	Slight to mid-moderate conjunctival swelling *(scores 0; 1; 2)*	6/10	8/ 80	Slight conjunctival swelling *(scores 0; 1)*	6/10	14/ 316	No other effect *(score 0)*	10/10	NA
Slight conjunctival discharge *(scores 0; 1)*	1/10	1/ 240	Slight conjunctival discharge *(scores 0; 1)*	7/10	8/ 240	Slight conjunctival discharge *(scores 0; 1)*	4/10	4/ 60	Slight conjunctival discharge *(scores 0; 1)*	3/10	3/ 237			
Cornea vascularization *(scores 0; 1)*	1/10	2/ 160	Slight cornea opacity *(scores 0; 1; 2)*	6/10	11/ 320	Slight to moderate cornea opacity *(scores 0; 1; 2; 3)*	8/10	15/ 80	Slight cornea opacity *(scores 0; 1)*	2/10	4/ 316			
			Cornea vascularization *(scores 0; 1)*	5/10	14/ 160	Cornea vascularization *(scores 0; 1)*	4/10	4/ 40	Cornea vascularization *(scores 0; 1)*	6/10	13/ 158			
						Slight hyperemia *(scores 0; 1)*	5/10	5/ 80						

RE: Right Eye

Corneal Sensitivity (Before the treatment period, 5 and 30 min after the first daily instillation on Day 1, Day 28 and Day 84)

Cystadrops and its vehicle did not induce anesthesia of the cornea.

Confocal Microscopy (Pretreatment and prior to sacrifice [Days 15/15 for Cystadrops 9X/day; Day 85 for all other groups])

Cystadrops and its vehicle had no effect in the thickness of the cornea and the corneal endothelium cell density.

Reference ID: 4602256

Gross Pathology (Days 15 or 16 for the animals administered 9X/day, Day 72 for animal R # 14, and Day 85 for all the other animals)

The vehicle control female euthanized on Day 72 (R # 14) had some anomalies in the thoracic cage and on the lungs (thoracic cage full of pus, atrophy of the left lung which was covered with pus; the right lung was full of pus).

In the high-dose group (Cystadrops 9X/day), 5 animals (4 males and 1 female) had some anomalies in their liver (1 small pus sac, 1 or 2 microcysts, and/or beginning of necrosis on one lobe).

Assuming 100% systemic absorption, the intended cysteamine human ophthalmic dose is more than 1000-fold lower than the approved oral maintenance dose; the intended CMC dose is 11.6X lower than levels reported in the inactive ingredient data base for systemic administration. These findings are not considered toxicologically relevant.

Histopathology (Both eyes, conjunctivae, eyelids [except from the left eye of the animal R # 35, technical error], nictitating membrane, Harderian gland and lachrymal gland)

Adequate Battery – Yes. Cysteamine is approved for oral use. The intended human ophthalmic dose is more than 1000-fold lower than the approved oral maintenance dose. Evaluation of systemic tissues was not needed.

Peer Review - No

Histological Findings

Some signs of irritation (extravasated lymphocytes, lymphatic follicles) were observed across treatment in the conjunctiva, eyelids and nictitating membrane in both the treated and untreated eyes. As the findings were also noted in untreated left eyes, these were considered partly due to mechanical effects of animal frequent manipulations or ocular instillations. In left untreated eyes (and some treated eyes), there was some area of de-epithelialization considered likely due to scratching.

In animals administered Cystadrops 6X/day or vehicle 6X/day, microscopic damage in the cornea were observed as areas of thinned epithelium (small, large, or central); extravasated lymphocytes (with higher incidence in treated eyes compared to untreated left eyes) and dilated vessels (one Cystadrops 6X/day-treated eye) were observed in the conjunctiva. There was not a marked difference between eyes treated with the vehicle 6X/day and Cystadrops 6X/day, indicating the findings were primarily vehicle-related.

In animals administered Cystadrops 9X/day (euthanized after 2 weeks of treatment), microscopic signs of acute inflammation were observed in the treated right eye and included:

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- Conjunctiva: Dilated vessels and dissociated collagen fibers, numerous subepithelial and intrastromal extravasated lymphocytes
- Cornea: Dissociated collagen fibers, neovascularized and edematous stroma, beginning of neovascularization, thinned epithelium, dissociated and edematous stroma with numerous cells (activated fibroblasts, polymorphonuclear cells, plasmocytes)
- Eyelids: areas of dissociated stromal collagen fibers and extravasated lymphocytes, dilated vessels

Cystadrops 9X/day was not tolerated. The extend and severity of the findings was increased in eyes treated with Cystadrops 9X/day. Because there was not a vehicle control group administered 9X/day, the contribution of the vehicle to the findings in not clear.

The ocular tissues affected on each group are shown in Table 7. The findings considered vehicle or test article related and their severity are shown in Table 8. The data support the vehicle causes eye irritation.

Table 7: Microscopic Findings in Rabbits after Administration for 3 Months

Evaluation of the treated eye (Right eye)	Cystadrops (0.55% cysteamine HCl)						Vehicle		0.9% NaCl	
	3 x/day		6 x/day		9 x/day		6 x/day		6 x/day	
	Effect	Incidence	Effect	Incidence	Effect	Incidence	Effect	Incidence	Effect	Incidence
Histology	Pathological findings on: • conjunctivae • nictating membrane • eyelids	5/10 2/10 7/10	Pathological findings on: • conjunctivae • cornea epithelium • nictating membrane • eyelids	6/10 8/10 5/10 7/10	Pathological findings on: • conjunctivae • cornea epithelium • cornea stroma • ciliary processes • anterior chamber • posterior chamber • nictating membrane • eyelids	10/10 4/10 6/10 1/10 1/10 1/10 1/10 5/10	Pathological findings on: • conjunctivae • cornea epithelium • nictating membrane • eyelids	5/10 5/10 3/10 5/10	Pathological findings on: • conjunctivae • nictating membrane • eyelids	3/10 5/10 7/10

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Table 8: Incidence and Severity of Microscopic Findings

Treatment	0.9% NaCl (Saline Control)		(b) (4) (Vehicle Control)		0.55% Cysteamine Hydrochloride					
Dosing Frequency[b]	6x/Day		6x/Day		3x/Day		6x/Day		9x/Day	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Histopathology [Right Eye (Treated)]										
Cornea - Epithelium: Thinning										
Slight	0	0	1	4	0	0	3	3	2	1
Moderate	0	0	0	0	0	0	1	1	0	1
Cornea - Stroma: Neovascularized, dissociated and/or edematous stroma; extravasated lymphocytes in limbal stroma; and/or dissociated collagen fibers										
Slight	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	3	1
Severe	0	0	0	0	0	0	0	0	1	1
Conjunctivae: Extravasated lymphocytes; lymphatic follicles; dilated vessels; and/or dissociated collagen fibers										
Slight	2	1	1	4	3	2	2	3	1	0
Moderate	0	0	0	0	0	0	1	0	3	5
Severe	0	0	0	0	0	0	0	0	1	0
Postdose Evaluation: None.										

- No Noteworthy findings; (b) (4) F = female; GLP = Good Laboratory Practice; M = male; NA = not applicable; NaCl = sodium chloride

[b] Each dose of control or test item consisted of 50 µL instillation into the right eye.

Special Evaluation

At sacrifice, lenses of all animals were weighed. The lens weight of the right and left eyes (treated and untreated) was comparable in all groups. The lens weight in the animals treated with Cystadrops 9X/day was lower compared to all other animals. This was attributed to the age of sacrifice (2.5 months before all the other animals).

Dosing Solution Analysis – The dosing solution was used as provided. Stability data was reported for Cysteamine Hydrochloride 0.55% for up to 9 months (95.1% label claim at -20ºC or 89.4% at 5ºC) and up to 6 months (91.5% at 25ºC/60% RH).

Reference ID: 4622756

Study title: 1 and 3-Month Ocular Tolerance Study of a New Cystadrops® Formulation Four Times Daily Instilled in Albino Rabbits

Study no.:	O06F28312
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 21, 2013
GLP compliance:	Yes
QA statement:	Exception: No certificates of analysis or stability was provided by the Applicant for Cystadrops formulated (b) (4)% CMC Yes
Drug, lot #, and % purity:	Cystadrops (0.55% cysteamine hydrochloride topical ocular formulation with (b) (4)% CMC), batch # CYT1107-01. Cystadrops (0.55% cysteamine hydrochloride topical ocular formulation with (b) (4)% CMC), batch # F13119, 101.8% pure

Key Study Findings

- After administration of Cystadrops 4X/day in either (b) (4)% CMC formulation (same as clinical) or (b) (4)% CMC formulation for up to 3 months, an inflammatory/irritation reaction was observed. Findings included conjunctival effects (redness, congestion, swelling, discharge, and chemosis), cornea effects (opacity, vascularization and staining), and iritis. In general, the effects were slight (score of 1) but there were some instances of higher severity. Conjunctival redness/congestion (both formulations) and slight corneal opacity and vascularization (one animal on each formulation) were still present at 3 months. However, all findings decreased in incidence/severity or resolved with time despite continued dosing.

- After one month of treatment, microscopic findings in both formulations included signs of severe inflammation primarily in the cornea and limbus (inflammatory cells, dilated vessels and corneal neovascularization). Animals treated with Cystadrops/(b) (4)% CMC, showed slight to moderate thinning/destruction of the limbus epithelium and powder-like material in the anterior chamber. Moderate conjunctival inflammation was observed in animals administered Cystadrops/(b) (4)% CMC. The microscopic ocular findings decreased in incidence and/or severity during the second and third months of treatment, showing an adaptation to the treatment.

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- The Applicant concluded that both Cystadrops/ (b) (4) % CMC and Cystadrops/ (b) (4) % CMC formulations were well tolerated when administered 4X/day. Based on the presence of conjunctival congestion/redness and microscopic findings of acute inflammation still present at 3 months, this reviewer believes there was no NOAEL.

Methods

Doses:	Cystadrops (b) (4) % CMC (called “Former Formulation” in the Study Report) Cystadrops (b) (4) % CMC (called “New Formulation” in the Study Report)
Frequency of dosing:	4X/day (3-hours apart) for 1 or 3 months
Route of administration:	Topically (right eye only; left eye used as control)
Dose volume:	50 µL
Formulation/Vehicle:	Cystadrops vehicle with (b) (4) % or (b) (4) % CMC
Species/Strain:	Rabbits/New Zealand White
Number/Sex/Group:	5
Age:	Approximately 2-3 months
Weight:	2.462 to 2.844 kg for males; 2.455 to 2.708 kg for females
Satellite groups:	None
Unique study design:	The ocular tolerance of Cystadrops (0.55% cysteamine hydrochloride) was assessed in 2 formulations which differed in the content of CMC.
Deviation from study protocol:	None considered to have an impact in the integrity of the data

Observations and Results

Evaluations performed are shown it the following table:

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	1-month groups	3-month groups
Body weights	Pre-test, Day 0, then weekly and one day before sacrifice	Pre-test, Day 0, then weekly and one day before sacrifice
Clinical signs	Daily	Daily
Ophthalmoscopy (Draize's scale)	Pre-test and twice daily (before the first and after the last administration per day)	Pre-test, twice daily during the first 28 days (before the first and after the last administration per day), then once daily (after the last administration) for the remaining 2 months
Slit-lamp (McDonald-Shadduck's scale)	Pre-test and weekly (prior to first administration of the day)	Pre-test, weekly during the first 28 days then twice a month for the remaining 2 months (each occasion: prior to first administration of the day)
Corneal sensitivity	Pre-test, Day 1 and Day 28 (each occasion: 5 and 30 minutes after the first daily instillation)	Pre-test, Day 1, Day 28 and Day 84 (each occasion: 5 and 30 minutes after the first daily instillation)
Necropsy and Macroscopic Organ/Tissue Evaluations	Day 29	Day 85
Histopathology	Both eyeballs and Lacrimal/Harderian glands	Both eyeballs and Lacrimal/Harderian glands

Gross Pathology – Conducted in selected organs: adrenal (2), brain, heart, kidney (2), liver, lungs with mainstem bronchi, spleen, ovary (2), testis (2) with epididymis

Mortality

One male (# 31) allocated to the 3-month Cystadrops/(b) (4)% CMC formulation group was sacrificed on Day 12 due to a broken paw.

One male (# 21) in the Cystadrops/(b) (4)% CMC formulation was found dead on Day 40. This rabbit showed clinical signs of inappetence and distended abdomen the day prior to being found dead. Microscopic findings of severe inflammation of the abdominal and intestinal areas were observed. The Applicant stated that although no cause of death could be established, it seems unlikely that this was a treatment related effect since there were no other rabbits observed with a poor condition in the same formulation group. The GI tract is a target organ for cysteamine, which may suggest a potential relationship to the test article. However, as the approved oral formulation for cysteamine is over 1000X higher than the intended topical ocular dose, this finding is not considered toxicologically relevant.

Clinical Signs

Per summary information (data not shown), half or totally closed treated eyes were noted for a few seconds after administration of both formulations.

Body Weights/Body Weight Gains

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No test article-related effects

Ophthalmoscopy

Ocular Examinations with an Ophthalmoscope (Draize's scale):

Similar findings were observed for both formulations. These included slight conjunctiva redness, slight conjunctival chemosis and/or discharge (generally, scores of 1 with some scores of 2), cornea opacity (generally, scores of 1 with some scores of 2, 3 or 4) and/or iritis reaction (generally, scores of 1 with some scores of 2). Overall, the severity and incidence were comparable between the 2 groups. Except for the observation of slight conjunctival redness, the incidence/severity of the findings decreased with continuous dosing, which was more notable for the Cystadrops/(b) (4)% CMC formulation.

No relevant ocular findings were noted in the left (untreated) eyes.

Ocular Examination with a Slit-Lamp:

Findings included conjunctival redness (all animals), chemosis and/or discharge, corneal opacity, corneal vascularization (severe for one female administered Cystadrops/(b) (4)% CMC [F # 6]), corneal staining (marked or extreme in some animals), aqueous flare, and/or iris hyperemia (Tables 9 and 10). The findings were classified as slight in the Study Report, and the severity scores were generally 1; however, there were some incidences of scores of 2 or 3. The slit-lamp findings correlated well with results obtained with ophthalmoscopy. The severity of the findings in the right (treated) eye was similar between the two treatment groups. No ocular effects were observed in the untreated left eyes.

Cornea opacity, cornea vascularization, cornea staining, aqueous flare, and iris hyperemia decreased in incidence/severity or disappeared from both treatment groups over the second and third months of treatment compared to the observations during the first month.

Reference ID: 4622736

Table 9: Slit-Lamp Ophthalmoscopy Findings during the First Month: Cystadrops/ (b) (4) % CMC (Former Formulation) vs Cystadrops/ (b) (4) % CMC (New Formulation)

Cystadrops (former formulation)			Cystadrops (new formulation)		
Effect (RE)	Incidence	Sum score	Effect (RE)	Incidence*	Sum score*
Slight conjunctival congestion *(scores 0; 1; 2)*	15/20	25/240	Slight conjunctival congestion *(scores 0; 1)*	14/20	25/231
Slight conjunctival swelling *(scores 0; 1; 2)*	6/20	11/320	Slight conjunctival swelling *(scores 0; 1; 2)*	7/20	10/308
Slight conjunctival discharge *(scores 0; 1)*	3/20	2/240	Slight conjunctival discharge *(scores 0; 1)*	1/20	1/231
Slight cornea opacity *(scores 0; 1; 2)*	8/20	12/320	Slight cornea opacity *(scores 0; 1; 2; 3)*	7/20	13/308
Cornea vascularization *(scores 0; 1; 2)*	8/20	12/160	Cornea vascularization *(scores 0; 1; 2)*	7/20	12/154
Cornea staining *(scores 0; 1; 2; 3; 4)*	17/20	50/320	Cornea staining *(scores 0; 1; 2; 3; 4)*	16/20	44/308
Aqueous flare *(scores 0; 1; 2)*	5/20	6/240	Aqueous flare *(scores 0; 1)*	9/20	9/231
Iris hyperhemia *(scores 0; 1)*	2/20	3/320	Iris hyperhemia *(scores 0; 1; 2)*	4/20	8/308

Table 10: Slit-Lamp Ophthalmoscopy Findings during the Second and Third Months: Cystadrops/ (b) (4) % CMC (Former Formulation) vs Cystadrops/ (b) (4) % CMC (New Formulation)

Cystadrops (former formulation)			Cystadrops (new formulation)		
Effect (RE)	Incidence*	Sum score*	Effect (RE)	Incidence**	Sum score**
Slight conjunctival congestion *(scores 0; 1)*	5/9	8/108	Slight conjunctival congestion *(scores 0; 1)*	6/9	15/108
Slight conjunctival swelling *(scores 0; 1)*	1/9	1/144	Slight conjunctival swelling *(scores 0; 1)*	1/9	1/144
Slight conjunctival discharge *(scores 0; 1)*	1/9	1/108	Slight conjunctival discharge *(score 0)*	0/9	0/108
Slight cornea opacity *(score 0)*	0/9	0/144	Slight cornea opacity *(scores 0; 1; 2; 3)*	4/9	13/144
Cornea vascularization *(scores 0; 1)*	1/9	4/72	Cornea vascularization *(scores 0; 1; 2)*	2/9	9/72
Cornea staining *(scores 0; 1; 2)*	1/9	3/144	Cornea staining *(scores 0; 1; 2)*	1/9	3/144
Aqueous flare *(scores 0; 1)*	2/9	2/108	Aqueous flare *(scores 0; 1)*	1/9	1/108
Iris hyperhemia *(score 0)*	0/9	0/144	Iris hyperhemia *(score 0)*	0/9	0/144

RE: Right Eye *Animal R#21 sacrificed on Day 40 - **Animal R#31 sacrificed on Day 12.

Corneal Sensitivity

There was no significant difference in mean values; the Applicant concluded Cystadrops did not induce anesthesia. Individual animal listings showed increased

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number of mechanical stimuli required to induce blinking in one animal administered Cystadrops/ (b) (4) % CMC (F # 29: 10 stimuli at 5 min and 8 stimuli at 30 minutes postdose on Day 28; baseline or left eyes values ranged from 1 to 3 stimuli). The effect was not observed on Day 84; it was then considered of no toxicological relevance.

Note: *From the values observed in the saline control group in Study # O06F0106, individual animal values up to 4 stimuli appears to be within normal range.*

Gross Pathology

Findings in the kidneys were observed in 2 animals in the Cystadrops/ (b) (4) % CMC formulation group (M # 3 and F # 6) in the one-month sacrifice. The kidney changes were: multiple infarct areas (seen as white depressed areas) in the male, and a cystic mass in the female. Given the different nature of the findings in both animals and the findings were not present at the 3-month sacrifice, they were considered unrelated to the test-article.

Histopathology

Adequate Battery – Yes (see comments under Study # O06F0106 above).

Peer Review - No

Histological Findings

At one month (Table 11), microscopic signs of severe inflammation were observed primarily in the limbus area and corneal stroma (inflammatory cells, strong dilated vessels and corneal neovascularization) with both formulations. Slight to moderate thinning/destruction of the limbus epithelium was observed in animals administered Cystadrops/ (b) (4) % CMC. All animals administered Cystadrops/ (b) (4) % CMC presented powder-like material in the anterior chamber; probably corresponding to keratic precipitates (per study report). Moderate conjunctival inflammation was observed in animals administered Cystadrops/ (b) (4) % CMC.

Reference ID: 4622756

Table 11: Microscopic Findings at One Month: Cystadrops/ (b) (4) % CMC (Former Formulation) vs Cystadrops/ (b) (4) % CMC (New Formulation)

Formulation	(b) (4) % CMC		(b) (4) % CMC	
Total Number of Animals (1-month group / 3-month group)	M: 10 (5 / 5)	F: 10 (5 / 5)	M: 10 (5 / 5)	F: 10 (5 / 5)
Histopathology (Right Eye)[i]				
1-Month Sacrifice				
No. of animals evaluated	5	5	5	5
Conjunctivae: Inflammatory cells or extravasated lymphocytes				
Moderate	0	0	2	2
Cornea - Stroma: neovascularization with or without slight edema				
Slight	0	2	1	1
Moderate	3	0	0	1
Limbus - Stroma: inflammatory cells with or without dilated vessels				
Slight	0	2	3	1
Moderate	0	1	0	2
Severe	5	2	2	2
Limbus - Epithelium: thinned or destroyed epithelium				
Slight	3	1	0	0
Moderate	2	2	0	0
Anterior chamber: Powder like material				
Slight	5	5	0	1

[i] Only noteworthy findings are presented. No consistent histopathological findings were noted in other ocular tissues examined (*e.g.*, iris, ciliary body, lens, vitreous, retina, choroid, sclera, optic nerve, extraocular muscles, Harderian gland, and lachrymal gland).

At three months (Table 12), signs of acute inflammation were continued to be observed, primarily in the limbus stroma (extravasated lymphocytes, dilated vessels and lymphatic follicles). No powder-like material in the anterior chamber was observed in animals treated with Cystadrops/ (b) (4) % CMC formulation.

Reference ID: 4622236

Table 12: Microscopic Findings at Three Months: Cystadrops/ (b) (4) % CMC (Former Formulation) vs Cystadrops/ (b) (4) % CMC (New Formulation)

Formulation	(b) (4) % CMC		(b) (4) % CMC	
Total Number of Animals (1-month group / 3-month group)	M: 10 (5 / 5)	F: 10 (5 / 5)	M: 10 (5 / 5)	F: 10 (5 / 5)
Histopathology (Right Eye)[i] - continued				
3-Month Sacrifice (Day 84)				
No. of animals evaluated	4	5	4	5
Conjunctivae: extravasated lymphocytes				
Moderate	1	1	0	0
Limbus - Stroma: extravasated lymphocytes with or without dilated vessels or lymphatic follicles				
Slight	1	3	3	1
Moderate	0	1	1	2
Severe	1	1	0	2
Postdose Evaluation: None.				

- = No Noteworthy findings; CMC = carboxy methyl cellulose; F = female; GLP = Good Laboratory Practice; M = male; No. = number.
[i] Only noteworthy findings are presented. No consistent histopathological findings were noted in other ocular tissues examined (*e.g.*, iris, ciliary body, lens, vitreous, retina, choroid, sclera, optic nerve, extraocular muscles, Harderian gland, and lachrymal gland).

In addition, an area of damaged retina nearby pars plana (disorganization of the 2 nuclear layers) was observed in one male (# 24) administered Cystadrops/ (b) (4) % CMC formulation at 3 months. For both formulations, fewer ocular findings and/or lower severity were observed after 3 months of treatment showing adaptation to the treatment.

Dosing Solution Analysis

The dosing solutions were used as provided by the Applicant. A statement of stability for Cysteamine Hydrochloride 0.55% (b) (4) % CMC was submitted stating that the product is considered stable for (b) (4) months at (b) (4) °C or (b) (4) °C; after opening, the product is considered stable for 1 week at (b) (4) °C.

7 Genetic Toxicology

No studies have been conducted with cysteamine hydrochloride. The information provided by the Applicant includes original studies conducted using cysteamine bitartrate (CYSTAGON®) and supporting information from the published literature. The language proposed by the Applicant for labeling in this section is the same as that in (CYSTAGON® (6-6-2007) and Cystaran® (10-2-2012) FDA approved labels.

Reference ID: 4622256

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Cystagon: Reverse Mutation in Five Histidine-Requiring Strains of Salmonella Typhimurium (Final Report)

Study no.:	1571/1-1052
Study report location:	EDR Module 4.2.3.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 28, 1997
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Cystagon, batch # 09-0303, 99.1% pure

Key Study Findings

Cysteamine bitartrate was negative for mutagenicity both in the presence or absence of S9 mix, under the conditions of the assay.

Methods

Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA102
Concentrations in definitive study:	1000, 2000, 3000, 4000, and 5000 µg/plate
Basis of concentration selection:	Initial toxicity-mutagenicity assay in all 5 *S. typhimurium* strains at concentrations of 8 to 5000 µg/plate. A small reduction in revertant numbers was observed at the high dose in TA100 and TA102, both in the presence and absence of S9 mix, suggestive of toxicity.
Negative control:	Purified water
Positive control:	

Chemical	Source	Stock* concentration (µg/mL)	Final concentration (µg/plate)	Use Strain(s)	Use S-9
2-nitrofluorene (2NF)	(b) (4)	50	5.0	TA98	-
Sodium azide (NaN_3)		20	2.0	TA100 TA1535	- -
9-aminoacridine (AAC)		500	50.0	TA1537	-
Glutaraldehyde (GLU)		250	25.0	TA102	-
2-aminoanthracene (AAN)		50	5.0	All strains	+

With the exception of NaN_3 and GLU, which were prepared in water, all stock solutions were prepared in sterile anhydrous analytical grade dimethyl sulphoxide (DMSO). NaN_3, 2NF, AAC, GLU and AAN were stored in aliquots at 1-10°C in the dark.

Reference ID: 4622256

Formulation/Vehicle:	Purified water
Incubation & sampling time:	Pre-incubation method; after pouring in the agar plates, the plates were inverted and incubated at 37°C in the dark for 3 days.

Study Validity

The study is considered valid per regulatory standards. The negative and positive control values were within expected range. Samples of dosing solution analysis were stored (until 1998) but not evaluated. However, slight toxicity was observed at 5000 µg/plate, indicating adequate concentrations were evaluated.

Results

Cystagon did not cause an increase in the number of revertants colonies in any bacterial strain ± S9 mix. In strain TA102, there was a diminution of the background bacterial lawn at 500 µg/plate ± S9 mix, which was considered as clear evidence of toxicity in this strain.

Information from the Published Literature:

Stich *et al*.[8]: Cysteamine was tested at concentrations of 0 (control), 10^{-4}, 10^{-3}, or 10^{-2} M (7.72 µg/mL to 772 µg/mL) ± S9 mix in an Ames assay conducted in *S. typhimurium* strains TA98 and TA100. No increases in revertant colony counts were noted at any concentration. No increases were also noted in the presence of Cu^{2+}, which accelerates cysteamine oxidation and liberation of H_2O_2.

7.2 *In Vitro* Assays in Mammalian Cells

No studies were conducted with cysteamine hydrochloride or cysteamine bitartrate.

Information from the Published Literature:

MacRae and Stich[9] - Cysteamine was positive for genotoxicity in the sister chromatid exchanges (SCEs) assay in Chinese hamster ovary (CHO) cells. The SCE frequency increased over spontaneous level in the concentration ranges of $1.6X10^{-4}$ to $3.1X10^{-4}$ M (12.3 to 23.9 µg/mL) and 10^{-2} to $2X10^{-2}$ M (772 to 1543 µg/mL) and felt to the spontaneous range between these (i.e., $1.3X10^{-3}$ to $5X10^{-3}$ M; 1003 to 3858 µg/mL). Addition of Cu^{2+}enhanced this effect.

[8] Stich HF, Wei L, Lam P. (1978) The need for a mammalian test system for mutagens: Action of some reducing agents. Cancer Lett 5(4):199-204.

[9] MacRae WD, Stich HF. (1979) Induction of sister-chromatid exchanges in Chinese hamster ovary cells by thiol and hydrazine compounds. Mutat Res 68(4):351-365.

Reference ID: 4622376

Speit and Vogel- Cysteamine did not produce a positive genotoxic response in the in vitro SCE assay following incubation with human lymphocytes at concentrations of 0 (control), 10^{-5}, $5X10^{-5,}$ 10^{-4}, $5X10^{-4}$, or 10^{-3} M (0.77 to 77.2 µg/mL). In cultured Chinese hamster V79 cells, catalase inhibited SCE induction by cysteamine and by hydrogen peroxide. It was considered that the difference in genotoxic activity in the different cell types was likely related to the inability of the Chinese hamster cells to degrade the H_2O_2 formed from cysteamine.

Inoue et al.[10] - Cysteamine hydrochloride was not genotoxic in the in vitro SCE assay following incubation with human lymphocytes at concentrations of 0 (control) or 10^{-3} M (114 µg/mL).

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Cystagon: Induction of Micronuclei in the Bone Marrow of Treated Mice (Final Report)

Study no.:	1571/2-1052
Study report location:	EDR Module 4.2.3.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 24, 1997
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Cystagon, batch # 09-0303, 99.1% pure

Key Study Findings

Cystagon (cysteamine bitartrate) was negative for genotoxicity, under the conditions of this assay.

[10] Inoue K, Shibata T, Kosaka H, Uozumi M, Tsuda S, Abe T. (1985) Induction of sister chromatid exchanges by N-nitrosocimetidine in cultured human lymphocytes and its inhibition by chemical compounds. Mutat Res 156(1-2):117-121.

Reference ID: 4622378

Methods

Doses in definitive study:	0 (saline) and 300 mg/kg
Frequency of dosing:	Two administrations 24-hours apart
Route of administration:	IV
Dose volume:	20 mL/kg
Formulation/Vehicle:	Saline
Species/Strain:	CD-1 mice
Number/Sex/Group:	5
Satellite groups:	An additional 5 males and 5 females were administered the test article and used as spares.
Basis of dose selection:	Initial toxicity range-finding study - the test article was administered once daily on two consecutive days at doses of 300 and 350 mg/kg/day (n=3/sex/dose). Observations were made for 4 days following the second administration. Clinical signs were observed at both doses; mortalities occurred at 350 mg/kg.
Negative control:	Saline
Positive control:	Cyclophosphamide (CPA), single dose at 40 mg/kg IV

Study Validity

The study is considered valid per regulatory standards. The incidence of micronucleated PCE in vehicle control groups was within historical vehicle control range; the positive control, CPA, induced a statistically significant increase in the frequency of micronucleated PCE. Dosing solution analysis data was not submitted. However, clinical signs and mortalities were observed, indicating adequate concentrations were evaluated.

Results

The following clinical signs were observed: prostration, unsteady gait, tremors, irregular breathing and convulsions. Two animals (one/sex) died immediately following the first dose and 6 males died immediately following administration of the second dose.

There were no statistically significant increases in the incidence of micronucleated PCEs in groups treated with cysteamine bitartrate at 24 or 48 hours postdose, compared to controls.

PCE/NCE ratios in Cystagon-treated animals were similar to vehicle controls at both sampling times.

8 Carcinogenicity

No studies were conducted. The language proposed by the Applicant for labeling in this section (i.e., Section 13.1 “Carcinogenesis, Mutagenesis, Impairment of Fertility”)

Reference ID: 4622358

is the same as that in CYSTAGON® (6-6-2007) and CYSTARAN® (10-2-2012) FDA approved labels. See label recommendations under Section 1.3.3 of this review.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted. Relevant studies with oral administration of cysteamine were identified in the literature. The total daily ocular dose of cysteamine is no more than approximately 0.4% of the highest recommended oral dose of cysteamine in any age group. As noted by the Applicant, it is not likely that any systemic exposure resulting from ocular dosing will provide any additional contribution to the assessment of reproductive risk conducted with oral cysteamine.

9.1 Fertility and Early Embryonic Development

The Applicant cited the information in the current label for CYSTAGON® and also referred to information in the Hazardous Substance Data Bank[11]. The language proposed by the Applicant in this section (i.e., Section 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility") is the same as that in the FDA approved labels for CYSTAGON® (6-6-2007) and/or CYSTARAN® (10-2-2012). See label recommendations under Section 1.3.3 of this review.

9.2 Embryonic Fetal Development

The Applicant cited the study by Beckman et al., 1998[12]. In this study, pregnant Wistar rats were given cysteamine (as phosphocysteamine) by oral gavage from Gestation Day (GD) 6.5 to 18.5 at doses of 0 (control; water), 37.5, 75, 100, or 150 mg/kg/day and fetuses were assessed for survival, growth, and structural abnormalities on GD 20.5. Per information in the publication, hydrolysis of phosphocysteamine in the gastrointestinal tract rapidly produces equimolar quantities of cysteamine (oral administration of phosphocysteamine is equivalent to giving cysteamine).

This study has been previously reviewed by the FDA under Cystagon's NDA (see nonclinical review dated November 27, 2000; Mercado Search 360). Treatment-related findings consisted of significant decreases in maternal body weights at 150 mg/kg/day and significant increases in adverse fetal effects (intrauterine death, intrauterine growth retardation, abnormalities of external and visceral structures, and abnormalities of skeletal development) at 100 and 150 mg/kg/day. The most common morphological abnormalities consisted of cleft palate (without cleft lip) and kyphosis. The authors concluded 75 mg/kg/day was the apparent NOAEL. However, the data showed an increased incidence of cleft palate, kyphosis and heart ventricular septal defects also at

[11] HSDB. (2006) Cysteamine. In: Hazardous Substances Data Bank. Accessed at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+60-23-1 [Last Revision Date: 20060227; Last accessed: November 29, 2018].

[12] Beckman DA, Mullin JJ, Assadi FK. (1998) Developmental toxicity of cysteamine in the rat: effects on embryo-fetal development. Teratology 58(3-4):96-102.

Reference ID: 4622736

this dose. The previously agreed label language for FDA approved marketing applications indicates cysteamine was teratogenic in teratology studies conducted at doses in the range of 37.5 to 150 mg/kg/day.

The language proposed by the Applicant in this section (specifically, Section 13.1 "Data" and Section 8.2 "Risk Summary") is the same as that in the FDA approved labels for CYSTAGON® (6-6-2007) and/or CYSTARAN® (10-2-2012). See label recommendations under Section 1.3.3 of this review.

9.3 Prenatal and Postnatal Development

The Applicant identified 2 studies from the published literature.

Fawcett et al.[13] – This citation is for an abstract (#26). As such, only summary information is provided (no data was shown) – The long-term effects of cysteamine were assessed by evaluation of physiologic and neurobehavioral endpoints in offspring exposed to cysteamine from day 6.5 postconception until postnatal day 21 (*the dose range administered was not specified*). Fetal brain somatostatin was significantly decreased for up to 8 hours post administration but had recovered after 24 hours. Postnatal evaluations indicated delayed auditory startle reflex only in offspring receiving 75 mg/kg/day. There were no changes in other neurobehavioral or physiologic parameters.

A separate group of pregnant Wistar rats were given an oral dose of cysteamine (100 mg/kg) on day 18.5 postconception. Peak maternal cysteamine levels occurred 2 hours postdose with a concomitant increase in plasma glycine and decrease in duodenal somatostatin. Peak fetal plasma concentrations greatly exceeded the maternal levels. The results suggest that fetal cysteamine is eliminated by transfer back to the maternal circulation resulting in persistently elevated maternal levels and cysteamine may accumulate to potentially harmful levels in the fetus and/or mother. The authors concluded that the observed fetal and postnatal effects may result from elevated glycine levels, somatostatin depletion, or other undetermined mechanisms.

Assadi et al.[14] – The study was conducted to assess the renal effects of cysteamine. In the first study (part of Beckman et al study above), cysteamine was given to pregnant rats on days 6.5–18.5 postconception at oral doses of 0, 37.5, 75, 100, and 150 mg/kg per day. The dams were sacrificed on day 20.5, and the fetal kidneys were removed and prepared for histological examination. In the second study, cysteamine was given to the dams on days 6.5–19.5 postconception in oral doses of 0, 37.5, 50, and 75 mg/kg per day, as well as postnatally between Days 4 and 21, and renal function was assessed on

[13] Fawcett LB, Beckman DA, Sherrell LK, Pugarelli JE, Assadi FK. (2000) Pregnancy alters the pharmacokinetics of cysteamine in the pregnant rat and effects postnatal development [Presented at: Teratology 40th Annual Meeting]. Teratology 61(6):445 [abstract 26]. Available at: http://onlinelibrary.wiley.com/doi/10.1002/1096-9926(200006)61:6%3C435::AID-TERA2%3E3.0.CO;2-B/full.

[14] Assadi FK, McCue P, Jefferis S, Shi M, Beckman DA. (1999) Effects of pre- and postnatal cysteamine exposure on renal function in the rat. Pediatr Nephrol 13(9):812-815.

Reference ID: 4622736

Day 35. There were no histological adverse effects in the fetuses even at doses shown to cause growth retardation and malformations (see Beckman et al study above) or functional effects in the offspring.

11 Integrated Summary and Safety Evaluation

This NDA was submitted under section 505(b)(2). The listed drug is CYSTAGON® (cysteamine bitartrate) Capsules (NDA 20392). The Applicant conducted one acute and two 3-month ocular toxicity studies to support the ocular safety of CYSTADROPS. The systemic safety of cysteamine is supported by the previous findings of safety and efficacy of the listed drug. If complete systemic absorption is assumed at the intended ocular dose for CYSTADROPS, the approved oral maintenance dose for CYSTAGON® is over 1000-fold higher (or ≤0.4% of the recommended daily oral dose of cysteamine for the treatment of cystinosis in any age group, Table 13). Therefore, dose comparison provides an adequate bridge for the listed drug and topical ocular nonclinical data.

Table 13: Comparison of Cysteamine Ocular Dose to Oral Dose

Patient Group	Ocular Dose (mg cysteamine free base/day)[a]	Recommended Oral Dose (cysteamine free base)[b]	Oral Dose (mg cysteamine free base/day)	Ocular Dose c.f. Oral Dose (% of Oral Dose)
Adult	1.52	1950 mg/m^2/day (maximum dose)	3315 [c]	0.04 %
	1.52	1300 mg/m^2/day (maintenance dose)	2210 [c]	0.07 %
Pediatric	1.52	150 mg every 6 hours (for child body weight of 5–9 kg)	600	0.25 %
	1.52	100 mg every 6 hours (for child body weight of 0–4.5 kg)	400	0.38 %

[a] Calculation of total ocular dose per day based on 4 drops per eye per day, where the volume of 1 drop is 50 µL and the concentration of cysteamine free base is 3.8 mg/mL (*i.e.*, 0.19 mg cysteamine/drop X 8 drops/patient/day = 1.52 mg cysteamine free base/day).

[b] Source: Product Label for CYSTAGON (CYSTAGON® [prescribing information], 2018)

[c] Calculation of total oral dose per day based on an adult body surface area of 1.7 m^2 (U.S. FDA Guidelines, 2005).

In male New Zealand White rabbits, 5 instillations within 20 minutes of 50 µL of 0.55% cysteamine hydrochloride (with or without (b) (4)) or vehicle (with (b) (4) resulted in slight to moderate conjunctiva redness and slight conjunctiva chemosis. The vehicle as well as the cysteamine solutions were considered as very slightly irritant. These findings were reversible.

In both 3-month ocular toxicity studies conducted with CYSTADROPS in rabbits, the concentration of cysteamine hydrochloride in the formulation was 0.55%, representing the amount in the intended commercial formulation. In the first study, an early pilot clinical formulation was used to identify an optimal daily dosing regimen. The CMC content was

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(b) (4)% (whereas the commercial formulation contains (b) (4)% CMC). In the second study, formulations containing (b) (4)% or (b) (4)% CMC (carmellose sodium) were compared.

In the first 3-month rabbit study, the dose groups evaluated include 0.9% NaCl 6X/day control, vehicle 6X/day control, Cystadrops 3X/day, Cystadrops 6X/day, and Cystadrops 9X/day. The right eye was treated; the left eye was left untreated. Cystadrops or its vehicle caused conjunctival effects (redness, congestion, swelling, discharge and chemosis), corneal effects (opacity, vascularization and staining), and iritis. The incidence/severity of these findings generally increased as the frequency of administration increased from 3 to 9 instillations per day. Cystadrops 9X/day was not tolerated and required early sacrifice of the animals (2 weeks after study initiation). Corneal opacities, right eye half opened, and right eye ruined were reported as findings during clinical examinations on the day of necropsy. The vehicle has a significant contribution to the findings observed at a dosing frequency of 6X/day. Because the study did not include a 9X/day vehicle control group, the contribution of the vehicle to the findings observed in eyes treated with Cystadrops 9X/day is unknown.

Microscopic findings were comparable in the Cystadrops 6X/day and vehicle 6X/day dose groups, indicating a significant contribution by the vehicle. These included effects in the cornea (thinned epithelium) and conjunctiva (extravasated lymphocytes and dilated vessels). More severe microscopic findings were observed at Cystadrops 9X/day (dilated vessels and dissociated collagen fibers in the conjunctiva, dissociated collagen fibers, neovascularization and stromal edema in the cornea). Because there was not a vehicle control group administered 9X/day, the contribution of the vehicle to these more severe findings is unknown.

Overall, the ophthalmoscopy findings in the Cystadrops 3X/day group were generally similar to those observed in the 0.9% NaCl control group or of slight severity for those findings not present in the 0.9% NaCl control group. Microscopic findings (limited to the conjunctiva) where similar between both groups. The NOAEL was Cystadrops 3X/day.

In the second 3-month rabbit study, groups evaluated included Cystadrops/CMC (b) (4)% formulation and Cystadrops/CMC (b) (4)% formulation. Both formulations were administered at a frequency of 4X/day. The right eye was treated; the left eye was left untreated. Animals were terminated after 1 month or 3 months of treatment. The ophthalmoscopy findings after 1 or 3 months of treatment were similar to those observed in the first 3-month study described above. Conjunctival findings (primarily congestion) were still present at 3 months; however, all findings decreased in incidence/severity or disappeared from both treatment groups over the 2nd and 3rd month of treatment. At the 1-month termination, microscopic findings of severe inflammation were observed primarily in the limbus area and corneal stroma (inflammatory cells, strong dilated vessels and corneal neovascularization) with both formulations. Slight to moderate thinning/destruction of the limbus epithelium was observed in animals administered Cystadrops/(b) (4)% CMC. All animals administered Cystadrops/(b) (4)% CMC presented powder-like material in the anterior chamber; probably corresponding to keratic

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precipitates (per study report). Moderate conjunctival inflammation was observed in animals administered Cystadrops/ (b) (4) % CMC. At the 3-month termination, signs of acute inflammation were continued to be observed, primarily in the limbus stroma (extravasated lymphocytes, dilated vessels and lymphatic follicles). However, fewer ocular findings and/or lower incidence/severity were observed after 3 months of treatment. Although there was no NOAEL in this study, the data indicates adaptation to treatment with both formulations despite continuous dosing.

The following table shows a summary of the key ocular findings. At the NOAEL of Cystadrops 3X/day, the exposure margin is below 1 for the proposed dosing regimen of Cystadrops 4X/day. Based on the adaptation with continuous treatment, Cystadrops 4X/day was considered well tolerated. Therefore, the nonclinical results support the tolerability of the intended clinical dosing regimen of 4 drops daily. However, the rabbit studies do not support dosing frequencies of 6X or 9X, suggesting a steep dose response curve for the current Cystadrops formulation. No clear difference in ocular findings was seen between Cystadrops itself and the vehicle (only evaluated at a dosing frequency of 6X/day). The existing marketing experience with CYSTADROPS® in Europe and Canada provides further support for the proposed dosing regimen.

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Table 14: Exposure Margins

Dosing frequency	Comments	Exposure Margin (0.37% 4X/day; 0.76 mg/eye)
3X	NOAEL – findings similar to those observed in 0.9% NaCl or of slight severity (a vehicle control group at 3X/day was not evaluated)	0.75
4X	LOAEL - After 1 month: conjunctival redness, chemosis and/or discharge, corneal opacity, corneal vascularization, corneal staining, aqueous flare, and/or iris hyperemia; microscopic findings of severe inflammation primarily in the limbus area and corneal stroma (inflammatory cells, strong dilated vessels and corneal neovascularization), thinning/destruction of the limbus epithelium, keratic precipitates At 3 months: Fewer ocular findings suggesting adaptation to treatment despite continuous dosing; conjunctiva redness/congestion and extravasated lymphocytes, dilated vessels and lymphatic follicles in the limbus stroma	1
6X	Conjunctival effects (redness, congestion, swelling, discharge and chemosis), corneal effects (opacity, vascularization and staining), and iritis Microscopic findings in the cornea (thinned epithelium) and conjunctiva (extravasated lymphocytes and dilated vessels) The vehicle had a significant contribution to the findings observed at a dosing frequency of 6X/day (i.e., findings were similar among both groups).	1.5
9X	Not tolerated Early sacrifice (2 weeks after study initiation) due to severe irritation; gross observations of corneal opacities, right eye half opened, and right eye ruined Microscopic findings of dilated vessels and dissociated collagen fibers in the conjunctiva, dissociated collagen fibers, neovascularization and stromal edema in the cornea A vehicle control group at 9X/day was not evaluated. The contribution of the vehicle to these more severe findings is unknown.	2.25

Note: The cysteamine concentration (0.55% cysteamine hydrochloride; 0.37% cysteamine) and dosing volume (50 µL) is the same for both rabbits and humans. Therefore, dosing frequency was used to calculate exposure margins.

The maximal nonclinical study duration of 3 months is below the 6-month study duration generally recommended to support chronic ocular dosing in humans. However, based on the existent marketing experience with CYSTADROPS® in Europe and Canada, it was determined that longer-term ocular toxicology studies were not considered necessary to support this 505(b)(2) application.

There is no objection from the nonclinical perspective to recommend approval of this NDA.

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/s/

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