CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211302Orig1s000

SUMMARY REVIEW

Deputy Division Director and Cross Discipline Team Leader Summary Review for Regulatory Action

Date	August 19, 2010
From	Wiley A. Chambers, M.D., and William . Boyd, M.D.
Subject	Deputy Division Director and Cross Discipline Team Leader Summary Review
NDA	211302
Applicant	Recordati Rare Disease Inc.
Date of Submission	February 28, 2020
PDUFA Goal Date	August 28, 2020
Proprietary Name	CYSTADROPS
Established or Proper Name	cysteamine ophthalmic solution, 0.37%
Dosage Form(s)	Topical ophthalmic solution
Recommedned Dosing Regimen	Instill one drop of CYSTADROPS in each eye, 4 times a day during waking hours
Recommended Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Lois Almoza
Medical Officer Review	Sonal Wadhwa
Statistical Review	Yan Wang
Pharmacology Toxicology Review	Maria Rivera
OPQ Review Lead DP DS Facility Reviewer Biopharm Micro	Chunchun N. Zhang Yan Nang Sharon Kelly Steve Rhieu Mei Ou Jennifer Patro
CDTL Review	William M. Boyd
OSE/DMEPA	Nasim Roosta
OPDP	Carrie Newcomer
DMPP	Maria Nguyen

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs

1. Summary

A Class 2 Resubmission of NDA 211302 was received by the Agency on February 28, 2020, in response to the Agency's Complete Response letter dated January 28, 2020. The Complete Response letter identified the following deficiencies:

- The facilities and controls used for, the manufacture, processing, packing, and holding of the drug product did not comply with the current good manufacturing practice (cGMP) regulations in 21 CFR 210 and 211.

- The methods to be used in, and the facilities and controls used for the manufacture, processing, packing and holding of the drug product were inadequate to preserve its identity, strength, quality, purity, stability or bioavailability.

CYSTADROPS is a cystine-depleting agent. It is a sterile viscous ophthalmic solution containing 5.6 mg/mL of cysteamine hydrochloride equivalent to 3.8 mg/mL of cysteamine (0.37%). Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. If not treated, cystinosis in its most severe form invariably leads to renal failure, necessitating dialysis and ultimately renal transplantation. Oral treatment with a cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease. Accumulation of cystine crystals due to cystinosis also occurs in the cornea. Due to the absence of corneal vascularization, corneal cystine crystal deposits are minimally affected by systemic treatment with cysteamine. Therefore, to treat the corneal crystal accumulation a topical treatment with a cysteamine containing eye drops is necessary to dissolve corneal cystine crystal deposits. If untreated topically, cystinosis can lead to the deterioration of visual capacity and eventually the need for a corneal graft.

The application for CYSTADROPS is submitted as a 505(b)(2) application listing Cystagon Capsules, NDA 20-392 as the listed drug product.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of CYSTADROPS (cysteamine ophthalmic solution) 0.37% dosed qid to decrease corneal cystine crystal deposits in adults and children with cystinosis. Reductions in crystal deposits (crystals) is associated with decreased ocular symptoms. Studies OCT-1 and CHOC demonstrate ability of CYSTADROPS to decrease corneal cystine crystal deposits. In Study OCT-1, the absolute mean number of crystals observed by In Vivo Confocal Microscopy (IVCM) from baseline was clinically reduced from month 6 through month 60. In Study CHOC, the absolute decrease from baseline in crystals observed by IVCM was clinically reduced at month 3. The most common ocular adverse events after treatment with CYSTADROPS (incidence approximately 10% or greater) were: eye pain, vision blurred, eye irritation, ocular hyperemia, eye pruritus, lacrimation increased, deposit eye, and instillation site discomfort. Most of these events are also associated with the disease being treated. The benefit of CYSTADROPS (cysteamine ophthalmic solution) 0.37% in decreasing corneal cystine crystal deposits outweighs the minimal risks to patients with Cystinosis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. Accumulation of cystine crystals due to cystinosis occurs also in the cornea. • Oral treatment with the cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease, but does not significantly reduce the formation of crystals in the cornea. • Direct topical treatment is necessary to dissolve corneal cystine crystal deposits and prevent serious ocular complications leading to the deterioration of visual capacity.	Without a topical cysteamine depleting medication patients with cystinosis will have a decrease in visual acuity and experience ocular pain.
Current Treatment Options	• There is currently one approved product in the United States for this indication which is Cystaran (cysteamine ophthalmic solution) 0.44%	CYSTADROPS will add another treatment option.
Benefit	• CYSTADROPS can be used less frequently (qid) than the currently approved Cystaran which is labeled to be used every 2 hours. The availability of multiple products reduces the chances of drug product shortages.	CYSTADROPS will add another treatment option.
Risk and Risk Management	• CYSTADROPS demonstrated a safety profile which was similar to Cystaran. • Labeling will identify the expected adverse reactions.	Routine monitoring and reporting of all adverse events are expected to be adequate.

3. Background

There is one approved product for this indication in the United States, Cystaran (cysteamine ophthalmic solution) 0.44% (NDA 200740). Cystaran was approved in 2012, and is approved for the treatment of corneal cystine crystal accumulation in patients with cystinosis. Its recommended dosage is one drop in each eye every 2 hours while awake.

CYSTADROPS was first approved for the treatment of corneal cystine crystal deposits by the European Commission in January 2017. CYSTADROPS is currently licensed in 31 countries worldwide (28 European Union EU member states plus Liechtenstein, Iceland and Norway).

Cystaran is stored by the patient in the freezer until use; it is then thawed and stored at room temperature for up to 7 days. Once thawed, it should not be refrozen. CYSTADROPS is stored by the patient in a refrigerator and after first opening is stored at room temperature for 7 days.

A Class 2 Resubmission of NDA 211302 was received by the Agency on February 28, 2020, in response to the Agency's Complete Response letter dated January 28, 2020. The Complete Response letter identified the following deficiencies:

1. The facilities and controls used for, the manufacture, processing, packing, and holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in 21 CFR 210 and 211. Specifically, during a recent inspection of the Baccinex SA, FEI# 3007272813, a manufacturing facility for this application, the Agency's field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required if this facility remains in the application. All submitted facilities must be in compliance with cGMP before this application may be approved.

2. The methods to be used in, and the facilities and controls used for the manufacture, processing, packing and holding of the drug product are inadequate to preserve its identity, strength, quality, purity, stability or bioavailability. Specifically,

   a. In your amendment submitted on November 5, 2019, the following deficiencies remain unresolved as adequate data are not available for evaluation. In your resubmission, please:

      i. Submit data to demonstrate that (b) (4) [redacted]. These parameters should be supported by development data and/or registration batch manufacturing data.

      ii. Clarify whether (b) (4) [redacted]

(b) (4)

iii. Revise your master batch record to reflect changes pertaining to (b) (4)

b. (b) (4)

c. We also acknowledge that you intend to complete a (b) (4) study prior to manufacture of Cystadrops commercial batches for the U.S. and that the study will simulate (b) (4) . Please provide the results of this (b) (4) simulation.

4. Product Quality

The drug product CYSTADROPS is a clear and viscous ophthalmic solution and contains 3.8 mg of cysteamine (0.37%) equivalent to 5.6 mg/mL of cysteamine hydrochloride (0.55%). The drug product is packaged in a 10 mL (b) (4) amber (b) (4) glass vial with 5 mL fill volume and closed by a bromobutyl (b) (4) stopper 20 mm and sealed with a flip off tear off aluminum vial seal. An individually packed PVC dropper applicator with HDPE closure is supplied with each vial for the patient before the first use. All the excipients are compendial. As amended, the drug product specifications (release, regulatory and in-use) include tests for appearance, minimum fill, pH, viscosity, identity, assay, impurities, osmolality, sterility, and antimicrobial effectiveness. The specifications are acceptable. All analytical methods are described in reasonable detail and have been adequately validated.

DRUG SUBSTANCE

The active substance must correspond to the following requirements:

Test	Specifications	Analytical procedure
Appearance	White crystalline powder, with perceptible odour of hydrogen sulphide	Visual inspection
Identification test: IR spectrum HPLC retention time (b) (4)	The IR spectrum must be equivalent to the reference standard one The HPLC RT must be equivalent to the reference standard one Positive	USP <197K> USP <621> USP <191>
Appearance of solution	Clear and colourless	USP <631>
pH	(b) (4)	USP <791>
Water content	Not more than (b) (4) %	USP <921>
Sulfated Ash	Not more than (b) (4) %	USP <281>
HPLC Related Substances	(b) (4)	In-house method USP <621>
HPLC assay (on dry basis)		In-house method USP <621>
(b) (4) residual solvents		In-house method USP <621>

Source: Module 3.2.S.4.1 Specification

DRUG PRODUCT

Qualitative and quantitative composition of CYSTADROPS

Components	Formula (mg/mL)	Centesimal formula (w/w)	Function	Reference
Cysteamine* *As cysteamine hydrochloride*	3.8 mg *5.6 mg*	0.37 % *0.55 %*	Drug substance	In house (see 3.2.S.4)
Carmellose sodium (b) (4)	(b) (4)		Viscosity agent	Current NF, Ph. Eur. 0472 current ed.
Benzalkonium chloride			Antimicrobial preservative agent	Current NF, Ph. Eur. 0371 current ed.
Disodium edetate			(b) (4)	Current USP, Ph. Eur. 0232 current ed.
Citric acid monohydrate				Current USP, Ph. Eur. 0456 current ed.
Sodium hydroxide				Current NF, Ph. Eur. 0677 current ed.
Hydrochloric acid (b) (4)				Current NF, Ph. Eur. 0002 current ed.
				(b) (4)
Water for injections				Ph. Eur. 0169 current ed.

*Note: also known as mercaptamine.

Source: Module 3.2.P.1. Description and Composition of the Drug Product

Release and Regulatory Specifications of the Drug Product

TESTS	PROCEDURES	ACCEPTANCE CRITERIA (Release)	ACCEPTANCE CRITERIA (Regulatory)
GENERAL CHARACTERISTICS			
Appearance	Visual	Viscous limpid solution	Viscous limpid solution
TESTS			
pH	EP 2.2.3	(b) (4)	
Viscosity	EP 2.2.10	(b) (4) to (b) (4) mPas at 7s-1	(b) (4) to (b) (4) mPas at 7s-1
Osmolality	EP 2.2.35	(b) (4) to (b) (4) mOsm/kg	(b) (4) to (b) (4) mOsm/kg
Particulate Matter	USP <788>	≥ 10 µm NMT (b) (4) per vial ≥ 25 µm NMT (b) (4) per vial	≥ 10 µm NMT (b) (4) per vial ≥ 25 µm NMT (b) (4) per vial
Minimum fill	USP <755>	Mean: NLT (b) (4) mL Single vial: NLT (b) (4) mL	N/A
IDENTIFICATION			
Cysteamine hydrochloride	HPLC/UV	Positive	Positive
Disodium edetate	HPLC/UV	Positive	Positive
Benzalkonium chloride	HPLC/UV	Positive	Positive
ASSAY			
Cysteamine hydrochloride	HPLC/UV	(b) (4)	Shelf-life (stored in a glass vial closed by rubber stopper) (b) (4) In-Use (stored in a glass vial equipped with a dropper applicator) (b) (4)
Disodium edetate	HPLC/UV	(b) (4)	

TESTS	PROCEDURES	ACCEPTANCE CRITERIA (Release)	ACCEPTANCE CRITERIA (Regulatory)
Benzalkonium chloride	HPLC/UV	(b) (4)	
IMPURITIES			
(b) (4)	HPLC/UV	(b) (4)	
(b) (4)	HPLC/UV		
Any other impurity (each)	HPLC/UV		
Total degradation products			
MICROBIOLOGICAL CONTROL			
Sterility	EP 2.6.1	Sterile	Sterile
ANTIMICROBIAL ACTIVITY			
Antimicrobial effectiveness testing	USP <51>	N/A	Comply

Source: Module 3.2.P.5.1. Specifications

Per the Office of Product Quality Review (IQA #2) dated 8/5/20 for this application:

Drug substance, drug product, and biopharmaceutics reviewers have recommended approval of NDA 211302 as documented in IQA #1 dated 12/4/2019.

INSPECTIONS

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Recordati Industria Chimica e Farmaceutica SpA via Mediana Cisterna 4 , Aprilia, Campoverde, Italy, 4011	3002807989	Drug substance manufacturing and testing (release and stability) || 356h Status: Pending CSN	Approve - Based on Previous History
Baccinex SA Rue de la Source 3 , Courroux, n/a, Switzerland, 2822	3007272813	Manufacture and filling of drug product; sterility testing of drug product; || 356h Status: Pending SLQ	Other – 704(a)(4) responses are found acceptable, mitigating the need for PAI
(b) (4)		-All quality control tests of the drug product, except the test for sterility (registration batches only) LCP	No Evaluation Necessary
		Manufacturer responsible for batch release of finished drug product || 356h Status: Pending SLQ	No Evaluation Necessary
		All quality control tests of the drug product, except the test for sterility; Storage of stability samples LCP, NEC	Approve - Based on Previous History
		Packaging of Drug Product SLQ	Other – 704(a)(4) responses are found acceptable, mitigating the need for PAI

704(a)(4) responses for the drug product manufacturing facility Baccinex SA (FEI# 3007272813) and secondary packaging site for the drug product (b) (4) are found acceptable.

The Office of Pharmaceutical Manufacturing Assessment has issued an overall acceptable recommendation for all the facilities on Aug 5, 2020. Therefore, NDA 211302 is recommended for APPROVAL from the Product Quality perspective.

5. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review dated 12/5/19:

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.

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.
- 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.

Pharmacology/Toxicology recommends approval of the application.

6. Clinical Pharmacology

A Clinical Pharmacology review was not required for this application. All patients receiving CYSTADROPS are already on oral Cystagon Capsules for cystinosis.

The CYSTADROPS application relies on the systemic safety of the listed drug Cystagon (cysteamine bitartrate) Capsules per 21 CFR 320.24(b)(6). The in vitro bridging between the clinical and commercial formulations has been established based on comparable pH, osmolality and viscosity values.

See the OPQ Integrated review dated 12/4/19, Chapter VI Biopharmaceutics.

7. Clinical Microbiology

This product is not an anti-infective.

8. Clinical/Statistical- Efficacy

From the original Clinical Review dated 1/22/20:

The two studies which provide the main support for safety and efficacy were: Study OCT-1 which enrolled 8 patients and Study CHOC which enrolled 32 patients. Both studies were conducted in France.

Study OCT-1: "Adaptive dose regimen of CYSTADROPS for cOrneal Crystal deposiTs and ocular manifestations in nephropathic cystinosis: An open-label, dose-response pilot study"

Primary Efficacy Endpoint

- Change in In Vivo Confocal Microscopy (IVCM) total score from baseline

The IVCM total score was a composite of the IVCM score for each of the 7 corneal layers; the presence of crystal deposits in each individual layer was graded on a scale from 0 to 4, so that the IVCM total score could range from 0 to 28. Higher scores designate larger amounts of crystal deposits; a decrease in IVCM total score indicates a reduction in corneal crystals in at least one layer of the cornea.

Study OCT-1: Primary Efficacy Endpoint (IVCM Score)

	Day 1	Day 30	Day 180	Month 12	Month 24	Month 36	Month 48	Month 60
IVCM total Score								
N	16	16	16	16	16	16	16	16
Mean (sd)	11.38	9.88	8.63	8.13	7.88	7.50	8.19	7.94
Min, Max	7, 18	5,16	5, 18	5, 12	3, 15	3, 14	5, 15	3, 15
Change From Baseline								
Mean (sd)	0	-1.50 (2.45)	-2.75 (2.29)	-3.25 (2.08)	-3.50 (2.07)	-3.88 (2.31)	-3.19 (3.04)	-3.44 (2.78)
P Value		0.0381	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Change From Baseline (%)								
Mean (sd)	0	-11.73% (25.09%)	-25.76% (18.63%)	-30.16% (16.87%)	-33.12% (20.83%)	-35.78% (21.57%)	-29.58% (25.37%)	-32.71 (25.40%)

The absolute mean change in IVCM total score from baseline was statistically significant at all time points.

Study CHOC: "Cysteamine Hydrochloride for nephrOpathic Cystinosis, open-label Phase 3 pivotal study"

Primary Efficacy Endpoint

- Total score of the corneal cystine crystal density measured by In-Vivo Confocal Microscopy (IVCM) in the 7 corneal layers. Scores were assessed by an independent masked reader

Study CHOC: Primary Efficacy Endpoint at Month 3 (IVCM Score)

	CYSTADROPS N=22	**CH 0.10% N=20**	**P value**
IVCM Score at Baseline			
Mean	10.6 (4.2)	10.8 (3.5)	
Absolute Change From Baseline in IVCM Score			
Mean	-4.60 (3.1)	-0.455 (3.4)	<0.0001
Min, Max	-11.0, -0.600	-7.60, 6.50	
Percent Change From Baseline			
Mean	-40.4% (16.0)	-0.679% (33.0)	

The absolute change from baseline in IVCM score compared between test drug and control was statistically significant at 3 months.

Cysteamine hydrochloride (CH) 0.10% eye drops is labeled to be given q2h while awake. In this trial it was only given qid; however, this was a superiority comparison not a noninferiority comparison, and it is acceptable that the product was not given as labeled.

The data contained in this submission establishes the efficacy of CYSTADROPS ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

9. Safety

From the original Clinical Review dated 1/22/20:

The main support for safety is from 2 clinical studies (Studies OCT-1 and CHOC) and the reference to Agency's finding of safety for NDA 20-392 Cystagon Capsules. Study OCT-1 enrolled 8 patients and had a duration of 5 years. Study CHOC enrolled 32 patients and had a duration of 3 months.

Demographics: Study OCT-1

Gender	CYSTADROPS N=8
Male	2
Female	6
Age (years) At Time of Inclusion	
Mean (sd)	12.1 (4.6)
Min, Max	7, 21

Demographics: Study CHOC

Gender	CYSTADROPS N=15	CH 0.10% N=16
Male	7	8
Female	8	8
Age (years) At Time of Inclusion		
Mean (sd)	19.2 (15.5)	15.1 (10.3)
Min, Max	2.8, 62.6	3.5, 36.0

Treatment Compliance/Exposure

Study OCT-1: Compliance (N=8)

	Instillations Prescribed-Mean	Instillations Administered-Mean
Day 1-30	4.0 (0.53)	4.0 (0.53)
Day 30-90	3.9 (0.83)	3.9 (0.83)
Day 90-180	2.9 (0.83)	3.0 (0.93)
Month 9-12	2.9 (0.83)	3.0 (0.93)
Month 12-18	2.9 (0.83)	3.0 (0.93)
Month 18-24	2.9 (0.83)	3.0 (0.93)
Month 24-30	2.8 (0.71)	2.9 (0.83)
Month 30-36	2.9 (0.83)	2.9 (0.83)
Month 36-42	2.9 (0.83)	2.9 (0.83)
Month 42-48	3.0 (1.07)	3.0 (1.07)
Month 48-60	3.0 (1.07)	3.0 (1.07)

Study CHOC: Treatment Exposure

	CYSTADROPS N=15	CH 0.10% N=16
Duration of Treatment (Days)		
Mean	86.3 (19.9)	92.7 (5.46)
Total Number of Instillations*		
Mean	316 (83.9)	370 (89.5)

*The theoretical duration of treatment was between 86 and 94 days, with a dose regimen of 4 drops per day for a theoretical total of 344 to 376 instillations.

Deaths

There were no deaths reported in either study.

Treatment Emergent Adverse Events

Study OCT-1: Treatment Emergent Adverse Events

System Organ Class	Number of Events
Eye disorders	5
Infections and infections	8
Surgical and medical procedures	12
Musculoskeletal disorders	7
Nervous system disorders	8
Renal and urinary disorders	2
GI disorders	3
Immune system disorders	4
Injury, poisoning, and procedural complications	4
Investigations	5
Metabolism disorders	7
Ear disorders	1
Reproductive disorders	1
Skin disorders	1
Social circumstances	1
Blood disorders	2

Study OCT-1: Ocular Treatment Emergent Adverse Events

	Number of Events
Chalazion	1
Corneal neovascularization	0
Dry eye	0
Hordeolum	1
Papilledema	1

Study CHOC: Treatment Emergent Adverse Events

System Organ Class	Number of Events CYSTADROPS N=15	Number of Events CH 0.10% N=16
Eye disorders	31	57
Infections and infections	7	6
Respiratory disorders	1	2
Nervous system disorders	3	0
General disorders	2	0
Injury, poisoning, and procedural complications	1	1
Metabolism disorders	1	1
Musculoskeletal disorders	2	0
Investigations	2	0
Ear disorders	1	0
GI disorders	1	0
Immune system disorders	1	0
Renal disorders	1	0
Skin disorders	0	1
Social circumstances	1	
Vascular disorders	0	1

Serious Adverse Events

Study OCT-1
Six patients experienced a total of 48 SAEs; of these, 46 were hospitalizations related to the underlying cystinosis disease and not to the topical administration of CYSTADROPS. Of the 2 remaining SAEs, 1 (corneal neovascularization) was reported as medically significant and 1 (knee deformity) was reported as persistent or significant disability/incapacity.

Study CHOC
Four patients reported 4 SAEs, two cases of gastroenteritis, one case of tiredness and one case of a corneal graft rejection.

Periodic Safety Update Report (PSUR)

Per the Periodic Safety Update Report (PSUR) covering 19 July 2018 to 18 January 2019:

No safety signals were newly identified, ongoing or closed during the reporting period. A summary of the safety concerns for CYSTADROPS at the beginning of the reporting period for this PSUR is presented in Table 8.

Table 8: Summary of safety concerns

Important identified risks	• Severe eye irritation
Important potential risks	• Punctate keratopathy and/or toxic ulcerative keratopathy (due to BAK) • Corneal neovascularisation • Ocular manifestations of Ehlers-Danlos like syndrome (EDLS) • Increased risk of infection and medication error due to device assembly failure
Missing information	• Patients with other ocular co-morbidities • Patients receiving concomitant treatment with ophthalmic products containing BAK • Long-term safety

BAK=Benzalkonium chloride; EDLS=Ehlers-Danlos like syndrome.
Source: Cystadrops Risk Management Plan (RMP) Version 1.3 (dated 30 September 2015), Module SVIII, Table 14.

On March 27, 2020, an updated Safety Report was provided with data for the reporting period from 01 November 2019 to 18 January 2020. Cystadrops is currently licensed in 34 countries worldwide (28 European Union member states plus Canada, Columbia, Iceland, Liechtenstein, Mexico and Norway).

Severe eye irritation remains an important identified risk for Cystadrops. The important potential risks include punctate keratopathy and/or toxic ulcerative keratopathy (due to benzalkonium chloride), corneal

neovascularization, ocular manifestations of Ehlers-Danlos like Syndrome, and increased risk of infection and medication error due to device assembly failure.

Review of the data collected during the reporting period and cumulative data does not reveal any new safety concerns that are not reflected in the current Risk Management Plan and prescribing information for Cystadrops; therefore, no changes to these documents are currently proposed. The overall benefit-risk profile of Cystadrops remains favorable when the drug is used in its approved indication and duration of treatment.

The data contained in this submission establishes the safety of CYSTADROPS ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no issues that were thought to benefit from a discussion at an advisory committee meeting.

11. Pediatrics

This product triggers PREA due to its new dosing regimen. There is an agreed Pediatric Study Plan (PSP) under IND 140943 which includes a deferral of a pediatric study. However, European postmarketing data was noted to include pediatric patients under 2 years of age. This data was supportive of safety in children from birth to 2 years of age. Efficacy of the drug product can be extrapolated to pediatric patients less than 2 years of age from adults and pediatric patients above 2 years old. Additional safety and efficacy information is not needed to label the drug product in all pediatric patients.

12. Other Relevant Regulatory Issues

BIOSTATISTICS
From the original Biostatistics Review dated 11/18/19:

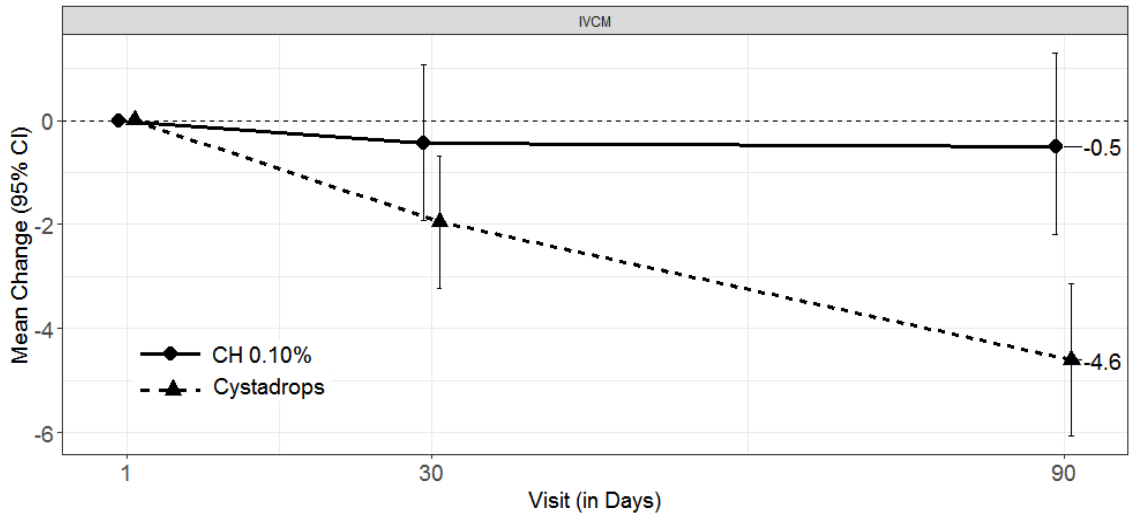
The OCT-1 study was an open-label adaptive, dose-response Phase 1/2a study. This study enrolled 8 subjects (16 eyes) aged from 7 to 21 years to receive CYSTADROPS up to five years. CYSTADROPS was instilled 3-5 times per day for the initial month (average 4 instillations). The dose regimen was then adapted to efficacy results at study visits (Months 1, 3, 6, 9, 12, and subsequently every 6 months until Month 48). On average, CYSTADROPS was instilled 3 times per day from Month 1 onward.

The CHOC study was a 3-month, open-label, randomized, multi-center, active-controlled Phase 3 study designed to demonstrate superiority of CYSTADROPS to the standard of care in France (Cysteamine hydrochloride eye drops solution 0.10% [CH 0.10%]) in reducing corneal cystine crystal deposits. In this study, a total of 32 subjects (64 eyes) at least 2 years of age with corneal cystine crystal deposits were randomized to either CYSTADROPS or CH 0.10%. Subjects were to receive one instillation of topical eye drops four times per day for 90 days in both eyes. During the treatment period, subjects had scheduled visits at Days 1, 30, 60 (Phone call), and 90.

In both studies, key efficacy evaluations were assessed based on: (i) corneal cystine crystal density as measured by In Vivo Confocal Microscopy (IVCM), (ii) using corneal cystine crystal score (CCCS) during slit lamp examination, (iii) photophobia (assessed by the investigator during slit-lamp examination), and (iv) crystal thickness (CT) in both eyes. The IVCM score provided a quantitative evaluation of the cystine crystals in seven layers of the cornea through multiple images where each layer was scored in 0-4 scale. The total IVCM score was a composite score of the scores attributed to each layer (range 0-28). CCCS was scored in a 0-3 scale in 0.25 increments and Photophobia was assessed on a 0-5 scale based on an objective assessment by the investigator.

In the pivotal Phase 3 study (CHOC), CYSTADROPS treated eyes demonstrated substantial reduction in the primary efficacy variable of corneal cystine crystal density (as measured by IVCM) from baseline throughout the study compared to CH 0.10% treated eyes. In this study, CYSTADROPS treated eyes yielded an average reduction of 4.6-unit in the total IVCM from baseline at Day 90 compared to a mean reduction of 0.5-unit in the CH 0.10% treated eyes (Figure 1). The treatment difference (*CYSTADROPS minus CH 0.10%*) in the mean reduction in the total IVCM score at Day 90 was 3.84 (95% CI: (2.11, 5.58); p-value < 0.001).
Also, CYSTADROPS treated eyes demonstrated significant reduction in the secondary efficacy variables of CCCS, CT, and photophobia compared to CH 0.10% treated eyes. For example, 30% and 47% of CYSTADROPS treated eyes demonstrated at least 1-unit improvement in CCCS and in photophobia from baseline at Day 90, respectively, compared to 0% and 6% of CH 0.10% treated eyes.

Figure 1: Mean change in total IVCM score from baseline over time
(Full Analysis Set)



Source: Appendix Table 8

The single arm study OCT-1 provided supporting evidence for the primary and secondary efficacy findings in the CHOC study. Also, most of the published literatures provided supportive evidence regarding the treatment benefit of topical application of cysteamine in improving corneal crystals density and photophobia.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

No OSI consult was requested and no audit completed. Both studies were performed in France, and it was determined that the foreign data submitted could be relied upon without the need for an inspection.

FINANCIAL DISCLOSURE

Covered Clinical Study (Name and/or Number): OCT-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor: Not applicable		

Covered Clinical Study (Name and/or Number): CHOC

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor: Not applicable		

OPDP

The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete labeling on 7/14/20.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, CYSTADROPS, and granted conditional acceptance on 4/22/20.

DMEPA completed a labeling review of the submitted USPI and carton/container labeling on 4/24/20.

DMPP

The Division of Medical Policy Programs (DMPP), in conjunction with OPDP, completed a review of the substantially complete patient Instructions for Use (IFU) on 7/9/20.

13. Patient Experience Data

Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	

		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

14. Regulatory Action

NDA 211302 CYSTADROPS (cysteamine ophthalmic solution) 0.37% will be approved for the treatment of corneal cystine crystal deposits in adults and children with cystinosis. There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

15. Labeling

The agreed-upon labeling for NDA 211302 CYSTADROPS (cysteamine ophthalmic solution) 0.37% is included below.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
08/19/2020 06:42:47 AM

WILEY A CHAMBERS
08/19/2020 09:01:07 AM