CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211302Orig1s000

PRODUCT QUALITY REVIEW(S)

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Approval

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

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.*

Labeling recommendations from the Product Quality perspective were provided to the OND PM for consideration during the original NDA review cycle.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Cystadrops® (cysteamine ophthalmic solution), 0.37% is a clear, viscous and sterile ophthalmic solution containing 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.*

Proposed Indication(s) including Intended Patient Population	For the treatment of corneal cystine crystal deposits in adults and children with cystinosis
Duration of Treatment	One drop in each eye, 4 times a day during waking hours.
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4). DMF (b) (4) was found adequate by Sharon Kelly on 11/19/2019. No further update in this review.

Drug Product: Adequate

Refer to Review #1. This review covers the update on two non-CR comments in the CR letter.

The applicant included particulate matter testing in the stability protocol, however, no stability update has been provided. The applicant will be reminded to provide stability update as a post-approval comment.

Regard to the complete analytical method transfer report from (b) (4) to (b) (4) the applicant developed and validated a new HPLC method for assay and related substances which is found acceptable.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective were provided during the original NDA review.

Manufacturing: Adequate

Refer to Review #1. This review focuses on reviewing the response on the CR comments including (b) (4) and the revised master batch record. The applicant provided adequate information to address these deficiencies.

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 which mitigated the need for PAI. All the other sites are acceptable based on the profile. Therefore, OPMA entered an overall acceptable recommendation for all the facilities in Panorama on 8/5/2020.

Biopharmaceutics: Adequate

No update, refer to review #1.

Microbiology (if applicable): Adequate

Sterilization validation (b) (4) and (b) (4) validation (b) (4) were inadequate in the original NDA

review, however, adequate studies and data have been provided in the resubmission.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Container closure • Process parameters Scale/equipment Site[3]	H	Sterilization has been validated.	L	Post-approval stability protocol will test sterility.
Assay (API), stability	Formulation Container closure Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay(preservative)	Formulation Container closure • Process parameters Scale/equipment	L	Benzalkonium chloride is used.	L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment	M	(b) (4) amber (b) (4) glass vial with 5mL fill volume.	L	
pH	Formulation Container closure • Process parameters Scale/equipment	L	(b) (4) formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	Formulation Container closure • Process parameters Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <788>.	L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

See the comments below.

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

The following comment should be included in the action letter as a post approval comment:

1. Provide the updated stability data with the particulate matter testing results when available.

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies (Specify discipline, such as Environmental)

NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph.D., 8/5/2020

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Cystadrops are for treatment of corneal cystine crystal deposits in adults and children with cystinosis.
NDA Number	211302
Assessment Cycle Number	2
Drug Product Name/ Strength	Cystadrops® 0.37% w/w
Route of Administration	Eye Drops
Applicant Name	Recordati Rare Diseases Inc
Therapeutic Classification/ OND Division	
Manufacturing Site	BACCINEX SA Rue de la Source 3 2822 Courroux, Switzerland
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: This is a sterile solution (b) (4) a glass vial with stopper. The product is a combination of (b) (4) drug substance/excipients and (b) (4) excipients. The (b) (4) is (b) (4). The dropper is (b) (4).

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0027 (28)	11/29/2019
0031 (32)	12/13/2019
0032 (33)	12/30/2019
0035 (36)	02/28/2020
0038 (39)	04/15/2020
0039 (40)	05/12/2020
0041 (42)	06/12/2020

Highlight Key Issues from Last Cycle and Their Resolution: Sterilization validation (b) (4) and (b) (4) validation (b) (4) was inadequate in the last cycle, but adequate studies and data have been provided and are reviewed here.

Remarks: A complete response was sent to the firm on January 28, 2020 and their responses to product quality microbiology deficiencies are reviewed below.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: Review of a meeting package pertaining to this NDA in n211302-20180515-mr01.doc on May 15, 2018. The first cycle review is found in N211302MR01.docx on 11/25/2019 and found inadequate.

(b) (4)

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Jennifer Patro

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Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 6/16/2020 11:24:43AM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

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/s/

CHUNCHUN N ZHANG
08/05/2020 01:25:25 PM

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete Response

Satisfactory information and responses have been submitted to support the quality of drug substance, biopharmaceutics and drug product aspects. The outcome of the most recent inspection of drug product manufacturing facility (Baccinex SA, FEI# 3007272813) has resulted in Office of Process and Facilities recommending Withhold. Additionally, quality micro and manufacturing process have found inadequate with remaining outstanding deficiencies. Therefore, NDA 211302 is recommended for Complete Response from Product Quality perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Cystadrops® (cysteamine ophthalmic solution), 0.37% is a clear, viscous and sterile ophthalmic solution containing 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.

Proposed Indication(s) including Intended Patient Population	For the treatment of corneal cystine crystal deposits in adults and children with cystinosis
Duration of Treatment	One drop in each eye, 4 times a day during waking hours.
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4). DMF (b) (4) was found adequate by Sharon Kelly on 11/19/2019.

Drug Product: Adequate

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. No novel excipient is used. No overage is used in the formulation. 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. The applicant plans to transfer all the analytical methods except sterility to (b) (4) as the commercial drug product testing facility. However, the complete method transfer report hasn't been provided at the time of the review on 11.26.2019. It will be included as one non-CR comment in the Section D below.

The applicant provided stability data for 24 months for three batches with the same to-be-marketed composition and 9 months for one primary stability batch (F18188) at -20°C. The applicant provided 6 months drug product long term stability data for two primary batches and 3 months for one primary stability batch stored at 5°C. Additionally, the applicant has submitted the in-use stability data to support the proposed 7 days at (b) (4) 25°C when the vial is opened and attached a dropper applicator. Based on the submitted stability data, the proposed storage plan is found acceptable pending stability update with the particulate matter testing:

- (b) (4),
- (b) (4) store the (b) (4) drug product in the secondary packaging at 5°C for 6 months;
- Once opened, a dropper applicator is attached and the drug product is stored at (b) (4) 25°C for up to 7 days.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

Manufacturing: Inadequate

The proposed drug product manufacturing process consists of (b) (4) . During the NDA review several

information requests regarding to (b) (4), hold time, and executive batch records etc were conveyed to the applicant. However, there are some remaining outstanding issues as listed in the Section D below.

Biopharmaceutics: Adequate

Biopharmaceutical reviewer Dr. Mei Ou has found acceptable without in vivo bioavailability studies for the proposed drug product. It is scientifically justified that the current application relies on the systemic safety of the list 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.

Microbiology (if applicable): Inadequate

The product is a combination of (b) (4) drug substance/excipients and (b) (4) excipients. The (b) (4) is (b) (4). The dropper is (b) (4). Two remaining outstanding issues are listed in the Section D below.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Container closure • Process parameters Scale/equipment Site[3]	H	Sterilization has been validated.	L	Post-approval stability protocol will test sterility.
Assay (API), stability	Formulation Container closure Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay(preservative)	Formulation Container closure • Process parameters Scale/equipment	L	Benzalkonium chloride is used.	L	

Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment	M	(b) (4) amber (b) (4) glass vial with 5mL fill volume.	L	
pH	Formulation Container closure • Process parameters Scale/equipment	L	(b) (4) formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	Formulation Container closure • Process parameters Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <788>.	L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

See the comments below.

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

The following comments should be included in the action letter as non-CR comments:

1. We acknowledge your revised drug product specifications including a test for particulate matter. As you committed in the response dated on 11/22/2019, the Agency reminds you to provide the stability update with the particulate matter testing in the NDA resubmission.

2. The complete analytical method transfer report from (b) (4) to (b) (4) should be provided in the NDA resubmission.

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

The following are CR statements and should be included in the action letter:

Please note any quality amendment submitted after Nov 23, 2019 are not reviewed as it is submitted late in the review cycle.

1. During a recent inspection of the Baccinex SA, FEI# 3007272813, manufacturing facility for this application, our field investigators conveyed deficiencies to the representatives of this facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. Regarding your response submitted on November 5, 2019, the following deficiencies remain unresolved as adequate data is not available for evaluation. Address the following:
   a) Submit data required to demonstrate (b) (4) These parameters should be supported by development data and/or registration batch manufacturing data.
   b) Clarify whether (b) (4)
   c) Revise your master batch record to reflect changes pertaining to (b) (4)

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

The following are CR statements and should be included in the action letter:

(b) (4)

(b) (4)

2. It is acknowledged 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) . Provide successful results of this (b) (4) simulation.

8. Other Deficiencies (Specify discipline, such as Environmental)

NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph.D., 12/4/2019

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	211302
Assessment Cycle Number	1
Drug Product Name/ Strength	Cystadrops® 0.37% w/w
Route of Administration	Eye Drops
Applicant Name	Recordati Rare Diseases Inc
Therapeutic Classification/ OND Division	
Manufacturing Site	BACCINEX SA Rue de la Source 3 2822 Courroux, Switzerland
Method of Sterilization	(b) (4)

Assessment Recommendation: **Inadequate**

Assessment Summary: This is a sterile solution (b) (4) a glass vial with stopper. The product is a combination of (b) (4) drug substance/excipients and (b) (4) excipients. The (b) (4) is (b) (4). The dropper is (b) (4).

List Submissions being assessed (table):

Document(s) Assessed	Date Received
001 (1)	03/28/2019
0012 (13)	06/28/2019
0014 (15)	09/13/2019
0017 (18)	10/17/2019
0018 (19)	10/21/2019
0020 (21)	10/30/2019
0024 (25)	11/18/2019
0026 (27)	11/22/2019

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is the applicant's first NDA submission to the Agency. Large portions of data were missing from the 03/28/2019 submission.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): See "List of Deficiencies" at the end of the document.

Supporting Documents: Review of a meeting package pertaining to this NDA in n211302-20180515-mr01.doc on May 15, 2018. The sterilization of the (b) (4) was previously reviewed in D (b) (4) M06R01.docx on June 25, 2019 and found adequate.

Substantial sections of the routine production and validation documentation are lacking from the submission dated 3/28/2019. The following comment is issued as an IR:

Deficiency (May 15, 2019): Please note that the subject NDA is lacking substantial documentation of sterilization validation information. Please refer to the Agency's 1994 Guidance document "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" for documentation recommendations when you are preparing your responses to microbiology information requests. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-documentation-sterilization-process-validation-applications-human-and-veterinary-drug

Response from the Applicant (June 28, 2019): The applicant acknowledges the comment and states they have supplied the requested additional information.

S DRUG SUBSTANCE

The drug substance is supplied non-sterile (b) (4) .

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(3.2.P.1 Description and Composition of the Drug Product.pdf)

- **Description of drug product –** Cystadrops or cysteamine hydrochloride is a viscous solution with pH (b) (4). This is a sterile, preserved, multi-use product (b) (4) 10 mL amber glass vials with a (b) (4) mL fill.
- **Drug product composition –**

Ingredient	Function	Quantity mg/mL
Cysteamine	API	3.8
Carmellose sodium	Viscosity Agent	(b) (4)
Benzalkonium chloride	Anti-microbial preservative	(b) (4)
Disodium edetate	(b) (4)	(b) (4)

Citric acid monohydrate	(b) (4) (b) (4)
Sodium hydroxide	
Hydrochloric acid (b) (4) (b) (4)	
Water for injection	

Description of container closure system –

- (b) (4) amber (b) (4) glass 10 mL vials from (b) (4)
- 20 mm bromobutyl (b) (4) stoppers from (b) (4)
- 20 mm tear off aluminum seal, green plastic cap from (b) (4)
- PVC dropper with HDPE closure from (b) (4) (pictured below from Draft Labeling Text.pdf, pg 8 of 9)

Assessment: *Adequate*
The description of the drug product and container closure system are adequate.

P.2 PHARMACEUTICAL DEVELOPMENT

Jennifer Patro

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Date: 11/25/2019 10:24:32AM
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Elizabeth Bearr

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Date: 11/25/2019 10:25:50AM
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CHAPTER VI: BIOPHARMACEUTICS

NDA: 211302 [505(b)(2)]
Drug Product Name/Strength: Cystadrops® (cysteamine hydrochloride ophthalmic solution) 0.37%
Route of Administration: Ophthalmic
Proposed Indication: For the treatment of corneal cystine crystal deposits in adults and children with cystinosis
Applicant Name: Recordati Rare Diseases Inc.
Submission Date: 03/28/2019, 10/17/2019
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

EXECUTIVE SUMMARY

The Applicant is seeking approval for the proposed drug product, Cystadrops® (cysteamine hydrochloride) solution, 0.37%. The proposed drug product is a clear, viscous and sterile ophthalmic solution containing 5.6 mg/mL of cysteamine hydrochloride (0.55%), equivalent to 3.8 mg of cysteamine (0.37%). The proposed dose is one drop in each eye, 4 times a day during waking hours.

The listed drug (LD) product for this 505(b)(2) application is Cystagon® (cysteamine bitartrate) Capsules, 50 mg and 150 mg (approved under NDA 020392 on 08/15/1994). The oral capsule reduces intracellular cystine accumulation, thus delaying organ and tissue damage. However, due to the lack of vascularization of the cornea, systemic administration of cysteamine has no effect on corneal cystine deposits. Therefore, only topical eye drops solutions containing cysteamine can dissolve cystine crystal deposits in the cornea. A commercial ophthalmic solution for the treatment of corneal cystine crystal accumulation in patients with cystinosis is currently available in the U.S., which is Cystaran®, a topical non-viscous cysteamine ophthalmic solution containing cysteamine hydrochloride 0.65% (equivalent to cysteamine 0.44%) (approved under NDA 200740 on 10/02/2012). The recommended dosage of Cystaran® is one drop every waking hour. The proposed drug product requires a much lower number of daily instillations compared to Cystaran®, which would lead to better compliance.

The current NDA relies on the Agency's previous findings of systemic safety of the LD product. Per the Applicant, systemic toxicity upon ocular application of the proposed drug product is not expected since the recommended total daily ocular dose of cysteamine is no more than approximately 0.4% of the highest recommended oral dose of cysteamine in LD product in any age group. The Applicant conducted their own local (cornea) safety and efficacy studies for the proposed drug product, by evaluating the total score of the corneal cystine crystal density measured by in vivo confocal microscopy (IVCM) (efficacy), evaluating adverse events, as well as local adverse drug reactions (LADRs) in patients (safety). These clinical trials were conducted in cystinosis patients in France (OCT-1, a Phase 1/2a efficacy study; CHOC, a Phase 3 safety study). Supportive

clinical information was obtained from patients who were given the proposed drug product as part of the worldwide Named Patient Use (NPU) programs in the European Union (including France) and in other countries including Iceland, Switzerland, Russia, Brazil, India, Argentina, Columbia, Norway and Hong Kong, as well as 8 countries in the Middle-East and North Africa region.

The application has no new systemic non-clinical pharmacology and toxicology data provided in the current NDA due to the limited systemic exposure for the ocular product. However, the Applicant conducted their own local tolerance and toxicity study in rabbits (study O06F0106 and study O06F28312) using the to-be-marketed formulation.

Biopharmaceutics review for the current NDA focuses on the evaluation of: (1) the submitted biowaiver request, and (2) the need of in vitro bridging for the clinical formulation (used in clinical OCT-1 and CHOC studies) and the commercial formulation. Since the proposed drug product is a clear and sterile eye drops solution, in vitro dissolution is not a proposed nor required drug product specification.

Biowaiver:
The Applicant submitted a waiver request for in vivo bioavailability studies of the proposed drug product. Considering that the recommended daily dose of cysteamine applied as an eye drop solution (the proposed drug product) is no more than approximately 0.4% of the highest recommended daily oral dose of cysteamine (LD product), even assuming complete systemic availability, the plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the plasma concentration of cysteamine following oral administration, therefore, it is acceptable that the Applicant has not conducted in vivo bioavailability studies for the proposed drug product. It is scientifically justified that the current application relies on the systemic safety of the LD per 21 CFR 320.24(b)(6).

In Vitro Formulation Bridging:
The clinical and commercial formulations have different compositions. Based on comparable pH, osmolality and viscosity values, in vitro bridging between the clinical and commercial formulations has been established.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 211302 for the proposed Cystadrops® (cysteamine hydrochloride ophthalmic solution) 0.37%, is recommended for **APPROVAL**.

BIOPHARMACEUTICS REVIEW

1. Biowaiver request

In the Type B pre-NDA meeting scheduled on 05/15/2018, the Applicant asked the question about the biowaiver, as:

Question 12: The systemic exposure of cysteamine following topical ophthalmic administration of CYSTADROPS is expected to be low in comparison to exposures observed following orally administered cysteamine bitartrate (i.e., CYSTAGON). Does the FDA agree that a waiver of the in vivo bioavailability requirement can be granted for CYSTADROPS?

Clinical Pharmacology's Response: yes

Note that the preliminary comments were conveyed on 05/09/2018[1], but the pre-NDA meeting was withdrew/cancelled on 05/14/2018[2].

In the current NDA, the Applicant submitted a formal biowaiver request to waive the in vivo bioavailability studies of the proposed drug product.

Reviewer's Assessment:
The Applicant did not conduct human pharmacokinetic assessment following topical administration of the proposed drug product. The clinical pharmacology characteristics of cysteamine have been adequately established in the LD product. Similar to other topically administered ocular products, some systemic absorption is likely to occur but at very low levels. The proposed drug product will be available as a viscous eye-drop solution containing 5.6 mg/mL of cysteamine hydrochloride (*i.e.*, 0.55% cysteamine hydrochloride), equivalent to 3.8 mg/mL of cysteamine (free base) as the active pharmaceutical ingredient (*i.e.*, 0.37% cysteamine). At the proposed dose regimen of 1 drop of the 0.55% formulation per eye, 4 times daily during waking hours, the dose of cysteamine base is 1.52 mg/day (assuming 1 drop = 50 µL). Taking into account the dose regimen prescribed for the oral LD product, the recommended daily dose of cysteamine from the proposed drug product is no more than approximately 0.4% of the highest recommended daily oral dose of cysteamine for the treatment of cystinosis in any age group. Even assuming complete systemic availability, the plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the plasma concentration of cysteamine following oral administration. It is scientifically justified that the current application relies on the systemic safety of the LD per 21 CFR 320.24(b)(6).

[1] Preliminary comments dated 05/15/2018:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80496745&_afrRedirect=74164865685062
[2] Meeting cancellation dated 05/14/2019:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8049fb44&_afrRedirect=74136621624993

2. In vitro formulation bridging

The composition and batch information and physical-chemical characters of the clinical and commercial formulations are presented in Tables 1 and 2 below.

Table 1: Batch information of the clinical and commercial formulations
(*from Table 20 of M.3.2.P.2, page 29*)

	First pilot clinical formula	Second pilot clinical formula	Commercial formula
Components: centesimal formula (w/w)			
Cysteamine hydrochloride	(b) (4)		0.55 %
Carmellose sodium			(b) (4)
Benzalkonium chloride			
Disodium edetate			
Citric acid monohydrate			
Sodium hydroxide			
Hydrochloric acid (b) (4)			
(b) (4)			
Water for injections			
			(b) ( )
Batches			
Used in OCT-1 clinical study	F7179; F8148.	F9145; F10101; F10147; F11103; F11167; F11216.	-
Used in CHOC clinical study	-	F11204.	-
ATU Study	-	Various lots	-
Used for Manufacturing process validation and stability studies	-	-	F18160, F18161, F18188, F16121, F16143, F16144

Table 2: Comparative batch analysis results of the clinical and commercial formulations (*from Table 21 of M.3.2.P.2, page 30*)

TESTS	F7179	F8148	F9145	F10101	F10147	F11103	F11167	F11216	F11204	F16121	F16143	F16144
FORMULATION	*1st pilot*		*2nd pilot*							*Commercial*		
GENERAL CHARACTERISTICS												
Appearance (Viscous limpid solution)	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
TESTS												
pH									(b) (4)	5.3	5.2	5.2
Viscosity (mPas at $7s^{-1}$)										2400	2380	2180
Osmolality (mOsm/kg)										357	358	357
Density										-	-	-
IDENTIFICATION												
Cysteamine hydrochloride	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
ASSAY												
Cysteamine hydrochloride (g/100g)									(b) (4)	0.54	0.55	0.55
Disodium edetate (g/100g)												(b) (4)
Benzalkonium chloride (g/100g)										0.010	0.010	0.010
IMPURITIES												
												(b) (4)
Any other impurity * (each) (RRT, %)												(b) (4)
Total impurities (%)												
MICROBIOLOGICAL CONTROL												
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile

Reviewer's Assessment:

The clinical and commercial formulations of the proposed drug product differ only slightly in the amount of carmellose sodium and are considered to have comparable pH and osmolality. Note that the proposed pH and osmolality specifications (pH: (b) (4), osmolality: (b) (4) mOsm/kg) are (b) (4) than the USP chapter <771> recommendations for ophthalmic products (e.g., pH is 3.0 to 8.6, osmolality is 171 to 1711 mOsm/kg).

Regarding the proposed viscosity specification of (b) (4) to (b) (4) mPas at 7s-1, Biopharmaceutics has conveyed the following Information Request (IR) to the Applicant on 09/23/2019:

Justify the proposed viscosity range of (b) (4) to (b) (4) mPas at 7s-1. Explain the source of the difference between the viscosity of the 2nd pilot formulation ((b) (4) to (b) (4) mPas at 7s-1) and the commercial formulation (2180 to 2400 mPas at 7s-1). Justify why you think that this difference will or will not affect the in vivo performance of the proposed drug product.

In the response dated 10/17/2019, the Applicant repeated the same explanations as provided in the original submission, as (a) the proposed viscosity range came from the data of clinical and commercial batches; (b) from the non-clinical data (*Figures 5 and 6 of non-clinical data provided in M.3.2.P.2.2, page 37-38*), it appears that rabbit corneal

C_{max} and corneal AUC are not affected by the viscosity in a range of 2345 and 9920 cP (*data are not presented in this review*), so that the in vivo performance is expected not being affected by the viscosity data range of 2345 to 9920 $mPa.s^{-1}$.

Considering (i) the clinical and commercial batches have viscosity data in the range of 2900-4200 $mPa.s^{-1}$ (from Table 2 above); (ii) the six commercial/registration batches have viscosity data ranging from 2180 to 3200 $mPa.s^{-1}$ (from Tables 3 and 4 below), all data are in the proposed viscosity range of (b) (4) to (b) (4) $mPa.s^{-1}$. USP <771> has no recommended viscosity data range, because viscosity is not a compendial test but is part of the proposed specification of the drug product. Therefore, from a Biopharmaceutics perspective, the clinical and commercial formulations are considered to have acceptable viscosities.

Table 3: Six commercial/registration batches of the proposed drug product
(*from Table 1 of M.3.2.P.5.4, on page 2*)

Batch number	**F16121**	**F16143**	**F16144**	**F18160**	**F18161**	**F18188**
Place of manufacture	BACCINEX					
Date of manufacture	27/01/2016	22/03/2016	04/04/2016	25/04/2018	26/04/2018	27/06/2018
Batch size	(b) (4)					
API manufacturer	(b) (4)			RECORDATI		
API batch number	17412503P1583 17412501P1555	17412602P1696		17100394		
Use of the batch	Commercial (non-USA), validation, supportive stability			Commercial: validation, stability		

Table 4: Comparative batch analysis results for the six commercial/registration batches of the proposed drug product
(*from Table 2 of M.3.2.P.5.4, on page 3*)

CONTROLS	**SPECIFICATIONS**	**F16121**	**F16143**	**F16144**	**F18160**	**F18161**	**F18188**
Tests							
Appearance	Viscous limpid solution	Complies	Complies	Complies	Complies	Complies	Complies
pH	(b) (4)	5.1	5.2	5.2	5.2	5.2	5.0
Viscosity at 7 s^{-1}		2460	2380	2180	2620	2800	3200
Osmolality		357	358	357	356	359	358
Minimum Fill					Complies		Complies
Identification							
Cysteamine hydrochloride	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Assays							
Cysteamine hydrochloride	(b) (4)	0.55	0.55	0.55	0.54	0.54	0.55
EDTA		(b) (4)					
Benzalkonium chloride		0.010	0.010	0.010	0.009	0.009	0.009
Degradation products							
							(b) (4)
Any other impurity (each, by RRT)							(b) (4)
Total impurities							

CONTROLS	**SPECIFICATIONS**	**F16121**	**F16143**	**F16144**	**F18160**	**F18161**	**F18188**
Microbiology							
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile

Note that the CMC reviewer will assess the information of the two proposed API sources ((b) (4) and Recordati)[3].

Overall, this Reviewer considers that the clinical and commercial formulations have comparative pH, osmolality and viscosity, therefore, in vitro bridging between the clinical and commercial formulations has been established.

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Mei Ou

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Elsbeth Chikhale

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/s/

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