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RESEARCH**

APPLICATION NUMBER:

200740Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	200-740
Submission Date(s):	April 2, 2012
PDUFA Date:	October 2, 2012
Brand Name	Cystaran®
Generic Name	Cysteamine HCl 0.65%
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip Colangelo, Pharm.D; Ph. D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Sigma-Tau
Submission Type; Code	Resubmission/Class 2; Type 3–New dosage form; Priority Review
Formulation; Strength(s)	Cysteamine hydrochloride ophthalmic solution; 0.65%
Indication	Treatment of corneal cystine crystal accumulation in cystinosis patients

1. EXECUTIVE SUMMARY

On December 03, 2010, the Agency issued a complete response to the NDA 200-740 submitted on March 04, 2010. The major deficiency identified is that the manufacturing facilities for drug substance and drug products are not in compliance with current good manufacturing practices. In this resubmission, the Applicant submitted a complete, class 2 response to the 03 December 2010 action letter.

There is no additional clinical pharmacology studies submitted in the resubmission, therefore, no substantial review is needed from a clinical pharmacology perspective for the current review cycle. Please refer to Clinical Pharmacology Review on the original submission by Dr. Yongheng Zhang on August 4, 2010, which contained the label recommendations. As the sponsor submitted a new proposed label in the resubmission based on the Agency's previous recommendations, the reviewer updated the label recommendations from a clinical pharmacology perspective.

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Concurrence:

Philip Colangelo, Pharm.D.; Ph.D.
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Division File: NDA 200-740/HFD-520 (CSO/Germain)/HFD-520 (MO/Boyd)/HFD-520
(Chambers)/HFD-880 (Lazor)

2. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear in underlined and/or strikethrough type).

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of cysteamine following ophthalmic administration of (b) (4) cysteamine hydrochloride ophthalmic solution has not been evaluated ~~because ophthalmic exposure compared to systemic exposure is negligible.~~ (b) (4) (b) (4) the majority of the patients in the ophthalmic clinical studies ~~are assumed to have~~ (b) (4) had some degree of renal impairment due to their underlying systemic disease. The total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine; thus, the systemic exposure following ophthalmic administration is expected to be negligible. (b) (4) compared to oral administration.

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/s/

YONGHENG ZHANG
06/21/2012

PHILIP M COLANGELO
06/21/2012

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 200-740
 Drug Name: Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65%
 Applicant: Sigma-Tau
 Indication: Treatment of corneal cystine crystal accumulation in cystinosis patients
 Submission Type: Resubmission/Class 2; Type 3 – New dosage form; Priority Review
 Submission Date: April 2, 2012
 Filing Date: June 1, 2012
 PDUFA Date: October 2, 2012
 OCP Primary Reviewer: Yongheng Zhang, Ph. D.
 OCP Team Leader: Philip Colangelo, Pharm. D., Ph. D.

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<u>Fileability:</u> <i>Is the Clinical Pharmacology section of the application fileable?</i> <i>(if 'NO', please comment as to why it is not fileable)</i>	X			
<i>Fileability Review Components</i>				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No clinical pharmacology studies were conducted or submitted by the sponsor
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See response to Question #1
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See Note
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See response to Question #1
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The sponsor has not requested a waiver for in vivo bioavailability data
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See response to Question #1

Note: In the original submission on April 26, 2012, the to-be-marketed formulation was different from the formulation used in the clinical trials. Per the Agency's request via teleconference on April 28, 2010, the sponsor has since revised the to-be-marketed formulation to be the same as the formulation used on the clinical trials.

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/s/

YONGHENG ZHANG
05/14/2012

PHILIP M COLANGELO
05/14/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	200-740
Submission Date(s):	March 4, 2010; April 26, 2010; May 27, 2010
Brand Name	Cystaran™
Generic Name	Cysteamine
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Relevant IND(s)	40,593
Submission Type; Code	Original 505(b)(2) ; Priority review
Formulation; Strength(s)	0.65% cysteamine HCl ophthalmic solution
Indication	Treatment of corneal cystine crystal accumulation in cystinosis patients

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1. EXECUTIVE SUMMARY

Cystinosis patients have a gene mutation that manifests as an absence of an enzyme that is involved with cystine egress from cells. The resultant cystine accumulation is the reason for organ pathology in cystinosis. Cysteamine is an aminothioliol that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can readily pass through the lysosomal membrane of cystinosis patients and facilitates cystine depletion from the cell. The 0.65% cysteamine HCl ophthalmic solution was developed to reduce cystine deposits in the cornea and manage the ophthalmic complications of cystinosis (including corneal crystals, photophobia, blepharospasm, and eye pain), which are not be relieved by the oral administration of cysteamine (Cystagon[®] approved for the management of nephropathic cystinosis in children and adults) because cysteamine is unable to reach ocular tissues in adequate concentrations to deplete cystine due to the lack of blood supply to the corneal stroma cells following oral administration. The proposed dosage and route of administration for 0.65% cysteamine HCl ophthalmic solution is to instill one drop to each eye every waking hour.

The current NDA for 0.65% cysteamine HCl ophthalmic solution included Study STP869294 (CAPTOC) and two randomized, double-masked trials 98-E1-0109E and 98-E1-0109S to demonstrate the safety and efficacy of cysteamine ophthalmic solution in the (b) (4) treatment of corneal cystine crystal accumulation in cystinosis patients. The Applicant did not perform any human pharmacokinetic assessment of cysteamine HCl ophthalmic solution and did not specifically request a waiver of the *in vivo* bioavailability requirement. Based on 21 CFR 320.22 (e), we hereby grant the Applicant a waiver of the *in vivo* bioavailability requirement, because of the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate (Cystagon[®]).

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The active component of 0.65% cysteamine HCl ophthalmic solution, cysteamine, has been previously approved as the orally administered Cystagon[®] for the management of nephropathic cystinosis in children and adults. The Applicant did not perform any human pharmacokinetic assessment of cysteamine following the administration of 0.65% cysteamine HCl ophthalmic solution. It is recognized that the clinical pharmacology characteristics of cysteamine have been adequately established in the previous NDA approval for orally administered cysteamine.

The total daily dose administered ophthalmically for 0.65% cysteamine HCl ophthalmic solution is estimated to be 7.8 mg/day based on a 100 µL dose per hour × 12 waking hours. The recommended daily maintenance dose approved for orally administered cysteamine ranges from 400 mg/day for an infant with body weight < 10 pounds to 2000 mg/day for adults. Therefore, the total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine. Even assuming complete systemic availability, the peak plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine.

From a Clinical Pharmacology perspective, the requirement for submission of evidence of *in vivo* bioavailability can be waived based on the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate (Cystagon[®]).

2. QUESTION BASED REVIEW

Since this submission is a 505(b)(2) NDA for a locally administered product relying upon conclusions drawn by the Agency for a previously approved orally administered product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

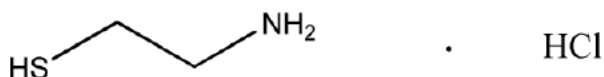
Cysteamine HCl is freely soluble in water. In solution, cysteamine degrades to a dimer (cystamine) and should be stored frozen until prior to use.

Structural Formula: C₂H₇NS • HCl

Molecular Weight: 113.61 Dalton; 77.15 Dalton (free base)

CAS Index Name: CAS-156-57-0; CAS-60-23-1 (free base)

Chemical Structure:



Drug Product:

The drug product is a sterile ophthalmic solution containing 6.5 mg/mL cysteamine HCl as the active ingredient. Cysteamine HCl Ophthalmic Solution is packaged in a 15 mL, opaque, white, low-density polyethylene (LDPE) bottle with a 15 mm white, LDPE controlled dropper tip and closed with a white, polypropylene screw-cap. The materials are opaque to protect the solution from light. The proposed commercial formulation is shown in **Table 2.1.1-1**.

Table 2.1.1-1: Composition of Drug Product

Components	Function	% w/v
Cysteamine	Active ingredient	0.65
Benzalkonium chloride	Preservative	0.01
Sodium chloride	(b) (4)	(b) (4)
Hydrochloric acid	Adjust pH	
Sodium hydroxide	Adjust pH	
Purified water	(b) (4)	
(b) (4)		

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Corneal cystine crystals are an ocular manifestation of nephropathic cystinosis that progressively worsens with time and does not spontaneously resolve. In the cornea, cystine crystals generally appear by 1 year of age and are pathognomonic of cystinosis. They initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two-thirds of the central cornea with age. Cysteamine is an aminothiols that converts cystine to cysteine and cysteine-cysteamine mixed disulfides, both of which can readily pass through the lysosomal membrane of cystinosis patients, therefore facilitates cystine depletion from the cell. The 0.65% cysteamine HCl ophthalmic solution is indicated for the (b) (4) treatment of corneal cystine crystal accumulation in children and adults with cystinosis.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

0.65% cysteamine ophthalmic solution with one drop instilled to each eye every waking hour.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical pharmacology studies were submitted in this NDA.

The current NDA included Study STP869294 (CAPTOC) and two randomized, double-masked trials 98-EI-0109E and 98-EI-0109S to demonstrate the safety and efficacy of cysteamine ophthalmic solution in the treatment of corneal cystine crystals in cystinosis patients. The primary endpoint in these studies was the reduction in corneal cystine crystal score (CCCS).

The CAPTOC report comprises National Eye Institute (NEI) Protocols 86-EI-0062, 92-EI-0230, and 94-EI-0116. The formulations used in these studies are summarized in **Table 2.2.1-1**. The primary objective of Protocol 86-EI-0062 initially was to evaluate the safety and efficacy of Formulation 1 or 2 versus placebo. However, this objective was revised to compare treatment versus natural history of disease progression, when effective treatment outcomes observed in eye receiving active treatment supported the NEI decision to discontinue the use of placebo. The primary objective of Protocol 92-EI-0230 was to evaluate the safety and efficacy of cysteamine ophthalmic solution plus the preservative BAK (Formulation 3) with that of cysteamine ophthalmic solution alone (Formulation 2). The primary objective of Protocol 94-EI-0116 was to evaluate the safety and efficacy of cysteamine ophthalmic solution (Formulation 4 with cysteamine, which is the disulfide degradant of cysteamine) in comparison to that of Formulation 3.

In both Studies 98-EI-0109E and 98-EI-0109S, patients were randomly assigned to receive Formulation 3 in one eye and Formulation 5 (freezing not required) in the companion eye.

Table 2.2.1-1: Formulations Used in Clinical Studies

Ophthalmic Formulation	Active Ingredient	Inactive Ingredient
1	Cysteamine HCL (0.11%)	(b) (4)
2	Cysteamine HCL (0.65%)	(b) (4)
3	Cysteamine HCL (0.65%)	Sodium chloride (b) (4) Benzalkonium chloride, 0.01% (b) (4)
4	Cystamine 2 HCL	(b) (4)
5	Cysteamine HCL	(b) (4)

2.2.2. *What is the basis for selecting the response endpoint (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics and how are they measured in clinical pharmacology and clinical studies)?*

The primary response endpoint is based on the corneal cystine crystal score (CCCS). This score was derived from slit-lamp photographs of the cornea taken by certified photographers following a standard protocol to assess the extent of corneal crystal accumulation. Masked graders then reviewed the photographs and assigned a score, using a scale ranging from 0.00 (clarity at the center) to 3.00 (greatest recognizable crystal density) in 0.25 increments. This method has been used successfully in numerous studies to semiquantitatively assess and document the accumulation of corneal cystine crystal accumulation in cystinosis patients over time and considered to be an appropriate and acceptable measurement of treatment effect. Previous clinical studies have established that a reduction in corneal cystine crystals is considered beneficial to cystinosis patients.

2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

No pharmacokinetic data for cysteamine ophthalmic solution 0.65% was submitted in the current application.

2.2.4. *Exposure-Response*

2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

Two dosing strengths of cysteamine HCl, 0.11% (Formulation 1) and 0.65% (Formulation 2 and 3) were evaluated in the clinical studies. The higher strength (i.e. 0.65%) was found to be more effective in removing corneal cystine crystals in older children.

2.2.4.2. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

In albino rabbits, cysteamine eye drops in concentrations at 0.1%, 0.5%, 1%, 2%, 5% and 10% were tested in 21-day and 3-month tolerability studies (*refer to the Pharmacology/Toxicology*

review by Dr. Amy Nostrandt dated on July 7, 2010, page 19). A mild to marked inflammatory response was observed at cysteamine concentrations at 1% and above. No evidence of inflammation was observed in rabbit eyes treated with 0.1% or 0.5% cysteamine every hour for eight hours each day for 3 months.

In clinical studies, two dosing strengths of cysteamine HCl, 0.11% (Formulation 1) and 0.65% (Formulation 2 and 3), were evaluated. Both strengths were well tolerated. The most frequently reported ocular AE with the incidence higher than 15% was photophobia (64% of the patient population), followed by conjunctival hyperaemia (28%), eye pain (19%), ocular hyperemia (17%) and eye irritation (17%). There were no AEs or safety findings that were unexpected or inconsistent with this patient population.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The sponsor has not evaluated the efficacy of cysteamine ophthalmic solution with concentrations greater than 0.65%. However, preclinical data with albino rabbits demonstrated a dose-response relationship for safety (an inflammatory reaction in rabbit eyes) following administration of $\geq 1\%$ cysteamine ophthalmic solution every hour for 8 hours each day for 3 months but not with 0.5% cysteamine ophthalmic solution (*see Section 2.2.4.2*). Thus, the dose-response relationship for efficacy in clinical studies (*see Section 2.2.4.1*) supports the selected dose strength of 0.65%.

2.2.5. What are the PK characteristics of the drug?

The Applicant did not perform any human pharmacokinetic assessment of cysteamine HCl ophthalmic solution and did not specifically request a waiver of the *in vivo* bioavailability requirement. Based on 21 CFR 320.22 (e), we hereby grant the Applicant a waiver of the *in vivo* bioavailability requirement because of the expected low systemic exposure of cysteamine following ophthalmic administration of cysteamine solution in comparison to exposures observed following orally administered cysteamine bitartrate as described below.

The total daily dose of 0.65% cysteamine HCl ophthalmic solution is estimated to be 7.8 mg/day based on a 100 μ L dose per hour \times 12 waking hours. The recommended daily maintenance dose approved for orally administered cysteamine ranges from 400 mg/day for an infant with body weight <10 pounds to 2000 mg/day for adults. Therefore, the total daily ophthalmic dose is less than 2% of the recommended oral daily dose of cysteamine. Even assuming complete systemic availability, the peak plasma concentration of cysteamine following ophthalmic administration is expected to be substantially less than the peak plasma concentration following oral administration of cysteamine.

2.3. Intrinsic Factors

Not applicable.

2.4. Extrinsic Factors

Not applicable.

2.5. General Biopharmaceutics

Not applicable.

2.6. Analytical Section

Not applicable.

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for detail.

4. APPENDICES

4.1. Proposed Package Insert (Annotated label, version 3/4/2010)

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICA LS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

YONGHENG ZHANG
08/04/2010

CHARLES R BONAPACE
08/04/2010