CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200740Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 200740	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Cystaran Established/Proper Name: cysteamine ophthalmic solution Dosage Form: Ophthalmic Solution Strengths: 0.44%		
Applicant: Sigma-Tau Pharmaceuticals Inc.		
Date of Receipt: March 4, 2010		
PDUFA Goal Date: October 2, 2012	Action Goal Date (if different):	
Proposed Indication(s): Treatment of corneal cystine crystal accumulation in patients with cystinosis.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 020392, Cystagon	Use in specific populations, (Pregnancy, Nursing Mother) Pharmacodynamics, Pharmacokinetics

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant is using toxicology information using an overexposure to the drug substance. This cannot be achieved with the drug product for either a b1 or a b2, but is instead done with a different dosing regimen and formulation of the active ingredient. The bridge is that the drug substance is chemically the same, determined chemically.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Cystagon	020392	YES

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication, a change in dosage from capsule to ophthalmic solution, and new strength.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☒

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

JUNE GERMAIN
10/02/2012
505b2 assessment

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 14, 2012

To: June Germain, Regulatory Project Manager
Division of Transplant and Ophthalmology Products

From: Christine Corser, Pharm.D.
Division of Professional Drug Promotion

Subject: **NDA #200740**
CYSTARAN (cysteamine ophthalmic solution) 0.44%

As requested in your consult dated September 5, 2012, the Division of Professional Drug Promotion (DPDP) has reviewed the draft labeling for CYSTARAN (cysteamine ophthalmic solution) 0.44% (Cystaran).

DPDP's, PI comments are based on the substantially complete version of the labeling titled, "NDA 200740 track changes PI July 27 2012.doc" which was sent via email from June Germain on September 5, 2012.

DPDP's comments are provided in the attached, clean version of the labeling. If you have any questions about DPDP's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this label.

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

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/s/

CHRISTINE G CORSER
09/14/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	August 27, 2012
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Acting Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Cystaran (Cysteamine Ophthalmic Solution), 0.44%
Application Type/Number:	NDA 200740
Applicant:	Sigma-Tau Pharmaceuticals, Inc
OSE RCM #:	2012-953

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Cystaran (NDA 200740) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On September 3, 2010, the application received a Complete Response due to the manufacturing facilities not being in compliance with current Good Manufacturing Practices (cGMPs). On March 30, 2012, the Applicant addressed the Complete Response Letter and resubmitted NDA 200740.

1.2 PRODUCT INFORMATION

The following product information is provided in the April 13, 2012 proprietary name submission.

- Active Ingredient: cysteamine hydrochloride
- Indication of Use: A cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis
- Route of Administration: Ophthalmic
- Dosage Form: Ophthalmic Solution
- Strength: 0.44% (as free base)
- Dose and Frequency: Instill one drop in each eye, every waking hour
- How Supplied: 15 mL LDPE bottle with an LDPE controlled dropper tip
- Storage: Store in freezer -25°C to -15°C (-13°F to 5°F). Thaw for approximately 24 hrs before use. Thawed bottle can be stored at 2°C to 25°C (36°F to 77°F) for up to 1 week. Do not refreeze. Discard after 1 week of use.
- Container and Closure Systems: 15 mL, round, white, LDPE bottle with a 15 mm, white, LDPE dropper tip and a white polypropylene screw-cap. The American Academy of Ophthalmology (AAO) does not currently have a cap color designated for this particular class of drug; in the absence of a designated cap color, the cap color should be white.

1.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 17, 2012 (Appendix B)
- Carton Labeling submitted August 17, 2012 (Appendix C)
- Insert Labeling submitted August 17, 2012

1.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed the Cystaran label and labeling (OSE # 2010-688) on August 13, 2010. We referenced the review to ensure all of our previous label and labeling recommendations were implemented. On August 16, 2010, it appears a communication regarding the insert and carton labeling as well as the container label was sent to the Applicant, which may have included some of DMEPA's recommendations. The Applicant provided updated labels and labeling on August 30, 2010 and made some minor revisions that addressed some concerns DMEPA had in our previous review, but most recommendations were not implemented. The most notable changes were the Applicant deleted the (b) (4) and relocated the net quantity statement to appear beneath the route of administration statement. Some of the recommendations that were not implemented will be addressed in this review.

2 DISCUSSION

The proposed established name for the drug product, cysteamine hydrochloride, is based on the salt form. However, USP recommends that the titles of USP monographs for drug products formulated with a salt of an acid or base use the name of the active moiety, and that the strength of the product be expressed in terms of the active moiety unless otherwise justified as described in USP <1121>. In addition, the USP also recommends that the drug product labeling clearly state the specific salt form of the active moiety that is present in the product, and the names and strengths of both the active moiety and specific dosage form. In consideration of this policy which becomes effective May 1, 2013, and because the strength will be expressed as the free base, the recommendation was made to the Division of Transplant and Ophthalmology Products (DTOP) that the drug product established name should be revised to only reference the active moiety. DTOP and ONDQA concurred with this recommendation. The Applicant will be advised to revise the established name to only reference the active moiety on the labels and labeling, which will be consistent with the current strength presentation.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS

The proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to clarify information, and to properly present the established name of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 COMMENTS TO THE APPLICANT

A. Container Label

1. The proprietary name appears in (b) (4) different shades of blue. Present the proprietary name in one color to improve readability of the proprietary name.
2. Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
3. For clarity, a space should be included between a number and the unit of measure. Revise the net quantity statement "15mL" to read "15 mL" (space).
4. The strength statement lacks prominence. Therefore, we request you increase the prominence of the strength statement.
5. The statement "Write discard date here" lacks prominence. Bold and increase the font size of this statement since this product is only stable for 1 week after thawing and it is important to discard the medication after 1 week.
6. The route of administration statement "For Ophthalmic Use Only" lacks prominence. Bold and relocate this statement to appear below the established name and remove the period at the end of the statement.
7. The Rx Only statement is overly prominent. Therefore, we request you debold the Rx Only statement and remove the period at the end of the statement.

B. Carton Labeling

1. See comments A1 through A4.
2. Relocate the route of administration statement "For Ophthalmic Use Only" to appear below the established name.
3. Debold the net quantity statement so it does not have greater prominence than the strength statement.

4. Bold the statements “Discard after 1 week of use, even if there is remaining drug product” and “Avoid touching dropper tip to any surface” on the side panel as this information should be highlighted to users.
5. Debold and relocate the “Rx Only” statement to the PDP.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

(b) (4)

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/s/

JUNG E LEE
08/24/2012

JAMIE C WILKINS PARKER
08/27/2012

CAROL A HOLQUIST
08/27/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: Monday, August 23, 2010

TO: William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 200740

APPLICANT:
Sigma-Tau Pharmaceuticals, Inc.
9841 Washingtonian Blvd. Suite 500,
Gaithersburg, MD 20878
Contact Person: Gianfranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs
Phone # (301) 670-2192

DRUG: Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65%

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: For the (b) (4) treatment of corneal cystine crystal accumulation in children and adults with cystinosis

CONSULTATION REQUEST DATE: April 12, 2010

PDUFA: September 4, 2010

I. BACKGROUND:

The sponsor, Sigma-Tau Pharmaceuticals, Inc, submitted an original New Drug Application (NDA) in the eCTD format for Cystoran™ (cysteamine hydrochloride) 0.65% ophthalmic solution to support labeling claims for the treatment (b) (4) of corneal cystine crystal accumulation in cystinosis patients. The application is being filed under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The investigations describing certain pharmacology, toxicology, and systemic clinical safety of cysteamine are provided in NDA 020329, the currently approved Cystagon@ (cysteamine bitartrate) Capsules application.

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. These cystine crystals are considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis. Nephropathic cystinosis is an autosomal recessive lysosomal storage disorder characterized by renal tubular Fanconi syndrome in the first year of life, growth retardation in children, renal glomerular failure at approximately 10 years of age, hypothyroidism, and a variety of other complications, including photophobia, blepharospasm, and corneal erosions due to cystine crystal formation within the eye.

There is no known cure for cystinosis, although symptomatic replacement of renal losses is standard therapy, and renal transplantation may cure the kidney problem.

To support the approval, the Applicant has provided data from efficacy and safety studies consisting of three clinical trials: 98-EI-0109E, 98-EI-0109S, and STP869294 (Protocols: 86-EI-0062, 92-EI-0230, 94-EI-0116) in support of their request for the indication sought in the NDA. The (b) (4)
was utilized to reviewed medical records, informed consent forms, CRFs, and drug accountability records to assess adherence to the protocol, ensure accuracy of CRF data, and ensure that the study was conducted according to pertinent regulatory requirements.

The most common adverse reactions of Cystoran™ include the following: headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision, pain behind the eye, or pain with eye movement. The proposed recommended dosing regimen for CYSTORAN™ is one drop of Cystoran™ in both eyes daily, every waking hour.

The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Brief descriptions of the studies inspected are provided below:

Study 98 EI-0109E: A Multicenter, Randomized, Double-Masked, Comparative Efficacy Trial of Two Formulations of Ophthalmic Cysteamine Solution in the Treatment of Corneal Cystine Crystal Accumulation in Naïve Ocular Cystinosis Patients

Study 98 EI-0109E was to be a Phase 3, double-masked, multicenter clinical trial to be conducted by the NEI Clinical Center of NIH, Bethesda, MD, and two additional clinical research centers - the University of Michigan and the University of California, San Diego. Protocol 98 EI-0109E, was to be initiated and coordinated by NEI and National Institute of Child Health and Human Development under collaboration with NIH. The NEI Clinical Center sites were to enroll 15 subjects in the United States under the direction of the principal investigator at each study center (Site 01 – National Eye Institute, Clinical Center, Site 02 – University of Michigan Health System, Department of Pathology, Site 03 – University of California, San Diego Medical Center).

The primary objective of this efficacy study was to assess the proportion of eyes with a reduction in corneal cystine crystal score (CCCS) in the eye treated with Formulation 3 (the same ophthalmic cysteamine formulation proposed as Cystoran) in comparison with companion eyes treated with Formulation 5 (0.55% cysteamine, (b) (4) in naïve ocular cystinosis subjects. The treatment period was to be 1 year. In this study, 15 subjects (up to 7 per site) were to be randomized to receive Formulation 3 in one eye and Formulation 5 in the other eye. Study investigators and all clinic staff were to be masked to treatment assignments. The study was to be opened to cystinosis subjects 2-12 years of age (inclusive) who had never used cysteamine eye drops. The treatment period was to be 1 year, with study visits to the clinic every 3 months. Telephone contacts with subjects were to be made during the treatment period at 1 week, 2 weeks, and 1 month. Efficacy assessments were to be taken at baseline and 3 months, 6 months, 9 months, and 12 months after treatment. In addition, the subject or parent/guardian was asked to keep a daily calendar recording the subject's ocular status regarding side effects in each eye. These calendars were to be reviewed by the study site staff twice during the first week and once at 2 weeks and 4 weeks.

Study 98 EI-0109S: A Single-Center, Randomized, Double-Masked, Comparative Safety and Efficacy Trial of Two Formulations of Ophthalmic Cysteamine Solution in the Treatment of Corneal Cystine Crystal Accumulation in Ocular Cystinosis Patient

Study 98 EI-0109S was to be a 6 month single center, randomized, double-masked, safety and efficacy trial of ophthalmic cysteamine solution in the treatment of corneal cystine crystal accumulation in 20 ocular cystinosis subjects. The study was to be initiated and coordinated by NEI and National Institute of Child Health and Human Development under collaboration with NIH. The NEI Clinical Center site was to enroll 20 subjects in the United States under the direction of the principal investigator. The study was to be conducted at the NEI under the direction of Muriel Kaiser, M.D.

The primary objective of this study was to estimate the proportion of cystinosis subjects experiencing an SAE in the eye treated with the formulation of ophthalmic cysteamine solution (Formulation 5) that had been developed with longer room temperature stability.

STP869294: Combined Analysis of Patients Treated with Ophthalmic Cysteamine (CAPTOC)

STP869294 or CAPTOC (Combined Analysis of Patients Treated with Ophthalmic Cysteamine) was a combined analysis of three historically controlled single center studies to demonstrate the safety and efficacy of cysteamine ophthalmic solution in the treatment of corneal cystine crystals in 247 cystinosis subjects who were concurrently receiving oral cysteamine. The CAPTOC report comprises Protocol 86-EI 0062, Protocol 92-EI-0230, and Protocol 94-EI-0116.

The primary end point for CAPTOC was a reduction of CCCS in eyes with high CCCS (≥1.00) at baseline and a lack of increase in CCCS in eyes with low CCCS (<1.00) at baseline. A response was defined as a decrease from baseline of at least ≥1.00 unit in CCCS at any time during the study when baseline CCCS was ≥1.00, or CCCS did not increase by at least 1.00 unit at any time during the study when baseline CCCS was <1.00.

Two domestic clinical investigators, Drs. Gahl (Muriel Kaiser) and Monte, and the sponsor and CRO were inspected.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	**Protocol # and # of Subjects:**	**Inspection Date**	**Final Classification**
William A. Gahl, M.D., Ph. D./ Muriel Kaiser, M.D. National Institutes of Health National Eye Institute Building 10, Clinical Center 10 Center Drive Bethesda, MD 20892	98-EI-0109E / Site #1, Site # (n=5) 98-EI-0109S/site # 9/20 STP869294 (86-EI-0062 , 94-EI-0116, 92-EI-0230) / NEI Clinical Center /247	6/3/2010-7/8/2010	Pending (Interim classification: VAI)
Monte A. Del Monte, M.D University of Michigan Medical School M7301 Medical Sciences Building I Box 0624 Ann Arbor, MI 48109-0624	98-EI-0109E / site 02 /6	6/ 10/ 2010 - 7/13/2010	Pending (Interim classification: VAI)

Sponsor: **Sigma-Tau Pharmaceuticals, Inc.** 9841 Washingtonian Blvd. Suite 500, Gaithersburg, MD 20878 Contact Person: Gianfranco Fornasini, Ph.D. Senior Vice President, Scientific Affairs Phone # (301) 670-2192	98-EI-0109E / Site #1, Site # (n=5) 98-EI-0109S/site # 9/20 STP869294 (86-EI-0062 ,94-EI-0116,92-EI-0230) / NEI Clinical Center /247 98-EI-0109E / site 02 /6	August 17, 2010	*Pending (Interim classification: NAI)

(b) (4)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.
* Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

1. **William A. Gahl, M.D., Ph. D./ Muriel Kaiser, M.D**.
   National Institutes of Health
   National Eye Institute
   Building 10, Clinical Center
   10 Center Drive
   Bethesda, MD 20892

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between 6/3/2010- 7/8/2010.

A total of 272 subjects were enrolled into the 3 studies (98-EI-0109E, 98-EI-0109S, STP869294) and 50 medical records were reviewed.

The inspection evaluated informed consent and included review of source documents. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Gahl's/ Kaiser's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

i. Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]. For example,

- There was no documented evidence of test article administration for the duration of the Study 98-EI-0109S (safety) for two subjects (Subject #09009 and Subject #09011)

  DSI Reviewer Comments: *The EIR shows that administration of the investigational drug had been documented by the subjects' parents.*
  In response to Form FDA 483, the CI also presented documentation (ophthalmic evaluation) that indicates that medication was dispensed to the above subjects. The subject interview questionnaires also indicate that the above subjects received the test article.

  While test article administration was not documented per protocol as for other enrolled subjects, alternate source data (diary entries, drug dispensation records, ophthalmic evaluation records, and subject interview questionnaires) support that study drug, as randomized, was administered to the subjects; therefore, the finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

- There is no documented evidence of initial test article administration and observation for at least one day of medication as inpatients – as indicated by protocol 98-EI-0109E (efficacy) – for subjects #01-001, #01-003, #01-004, and #01-005.

  DSI Reviewer Comments: *The EIR shows that administration of the investigational drug on the first day had been documented by the subjects' parents. In response to Form FDA 483, the CI presented documentation showing that the above subjects were seen at the NIH Clinical Center for one day at the start of the study without being formally admitted as inpatients.*

While the clinical investigator did not document that the "inpatient" dose administered at the clinical site was given, the subjects' parents' entry in the diary and interview questionnaires can be used to confirm study drug administration to the subjects listed above for doses not captured by the clinical investigator. Although the clinical investigator failed to adequately document the first dose administered as an "in patient" (clinical research center) on the first day according to the investigational plan, which is a regulatory violation, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

- There is no documented evidence of test article administration and observation for at least one day at the Clinical Center – as indicated by Protocol 98-EI-0109S (safety), Amendment #2 dated 1/12/1999 – for 8 out of 20 subjects: 09013, 09014, 09015, 09016, 09017, 09018, 09019, and 09020.

  DSI Reviewer Comments: *The EIR shows that administration of the investigational drug for these doses been documented by the subjects' parents; although, dosing was not documented by the clinical investigator. In response to the Form FDA 483, the CI presented documentation showing that the above subjects were seen at the NIH Clinical Center for one day at the start of the study without being formally admitted as inpatients. The subjects' parents' entry in the diary and interview questionnaires can be used to confirm that study drug was administration to the subjects listed above for the dose administrations not adequately documented by the clinical investigator.*

  Although the clinical investigator failed to adequately document test article administration according to the investigational plan, which is a regulatory violation, as alternate source documents are available to document study drug administration, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

- Failure to adequately document investigational drug disposition with respect to quantity and use by subjects; the formulation type of each bottle returned (current or new formulation); and to which eye (left or right) the returned bottles were assigned. The drug accountability records for study 98-EI0109 (both safety and efficacy) do not document the final disposition of investigational drug returned by subjects to the clinic.

  DSI Reviewer Comments: *Dr. Gahl's response (received August 16, 2010) to the Form FDA 483 issued acknowledges the above observation and corrective actions to prevent similar occurrences in future studies appear to be adequate.*

  The drug accountability records for study 98-EI0109 did specify bottles of test article were labeled for each subject for each eye. As the above observations were more related to drug reconciliation rather than adequate drug dispensation, the findings are unlikely to impact data reliability.

ii. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. For example, subjects showing non-compliance with study dosing schedule were not discontinued from study (Subject #01005 and Subject #09011) by the Clinical Investigator.

DSI Reviewer Comments: *There was no provision in the study protocol that required that subjects be discontinued for noncompliance; therefore, DSI does not consider this to be a regulatory violation. The observation does not impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study. The subjects' noncompliance was reported in the NDA submission.*

- **There is no documented evidence of clinical laboratory analyses of blood and urine samples in 18 subjects that was required per protocol 98-EI-0109S (safety).**

DSI Reviewer Comments: *While these specimens were not collected, safety labs were collected in other studies supporting this NDA and are available to the review division. The review division will need to determine the potential impact, if any, that missing safety data from this study has on safety analyses and conclusions.*

- **There is no documented evidence of administration of the "Visual Functioning Questionnaire" at baseline for subject #09012, as required by protocol 98-EI-0109S (safety).**

DSI Reviewer Comments: *The clinical investigator failed to administer Quality of Life questionnaire (VFQ) to one subject. However, the finding was isolated in nature and unlikely to impact overall reliability of efficacy and safety data from the site.*

iii. Failure to include the purposes of the research, and the expected duration of the subject's participation in Informed Consent Document (ICD). Specifically, the Informed Consent Document for Study 98-EI-0109, Safety and Efficacy Trial of a Proposed NDA Formulation of Topical Cysteamine in the Treatment of Corneal Cystine Crystal Accumulation in Cystinosis, does not indicate the expected duration of the subject's participation in the study.

DSI Reviewer Comments: *The ICD (all Versions) had been reviewed and approved by the IRB. The ICD does provide the purpose for the study as it indicates that the purpose of the study is to determine whether a new formulation of cysteamine eye drops will help reduce the number of crystals present in the cornea. The Informed Consent Form of study 98-EI-0109, Safety and Efficacy Trial of a Proposed NDA Formulation of Topical Cysteamine in*

the Treatment of Corneal Cystine Crystal Accumulation of Cystinosis did not, however, indicate the expected duration of the subject's participation in the study.

c. Assessment of data integrity:

Although regulatory violations at this site, it is unlikely based on the nature of the violations and the availability of alternative source documentation to confirm subject dosing, that they significantly affect the overall reliability of safety and efficacy data from the site. The review division will need to determine the potential impact, if any, that missing safety data from study 98-EI-0109S has on safety analyses and conclusions.

2. Monte A. Del Monte, M.D
University of Michigan Medical School
M7301 Medical Sciences Building I Box 0624
Ann Arbor, MI 48109-0624

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811 between June 10, 2010 and July 13, 2010.

A total of 6 subjects were screened, enrolled and completed the study.
The inspection included review of records for 5 subjects who were randomized. There were no Serious Adverse Events (SAEs) or deaths during the study. The following items were reviewed for verification: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequacy of adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Del Monte's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator. The following regulatory violations were observed during the inspection:

i. Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(1)]. Specifically, Drug Accountability records for subject #s 001, 003, 004, 005 were inaccurate and incomplete.

DSI Reviewer Comments: *This should have been recorded adequately. FDA regulations require an investigator to adequately record the receipt, preparation, use and/or disposition of the investigation product, and this information should have been*

adequately documented. Specifically, the review of the EIR shows discrepancies in drugs issued compared with drug vials returned for the Subject # s 001, 003, 004, 005. The drug dispensation appeared adequate and drug accountability issues were limited to drug reconciliation. The discrepancies in drugs issued compared with drug vials returned, however, were minor accounting for ≤10% of the total dose administered to each of the subjects as in the table below.

Subject	Bottles Drug Issued	Bottles Drug Returned/ Lost / Explained	Discrepancy
001	120	114	-6
003	120	118	-2
004	120	123	+3
005	120	108	-12

Dr Del Monte's response (submitted on July 22, 2010 and received August 20, 2010) to the Form FDA 483 issued acknowledged that the 4 subjects identified above had incorrect drug accountability records as result of human error.

ii. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, the Case Report Form TERM Date of Study Drug discontinuation occurred after the date documented as week 52 for the following subjects #s 001, 002, 003, 004, 005.

DSI Reviewer Comments: *It appears that the listed subjects may have continued to receive therapy beyond week 52 (the primary efficacy time point), but there is not specific evidence that suggests the 52 week efficacy data reported for these subjects are inaccurate. Dr Del Monte's response (submitted on July 22, 2010 and received August 20, 2010) to the Form FDA 483 issued acknowledged that 5 of the six subjects identified above had incorrect drug accountability records as result of human error.*

c. Assessment of data integrity:

Based on DSI's review of the Form FDA 483, the EIR and associated exhibits, and Dr. Del Monte's response to the issued Form FDA 483, DSI considers primary efficacy and safety data from this site to be acceptable, provided The review division concurs that the discrepancies in drug bottles issued compared with drug bottles returned (accounting for ≤10% of the total number of bottles/doses administered) is within acceptable limits for total potential doses administered.

3. Sigma-Tau Pharmaceuticals, Inc.
9841 Washingtonian Blvd. Suite 500,
Gaithersburg, MD 20878

a. What was inspected?

This sponsor inspection was conducted in accordance with Compliance Program 7348.811 on August 17, 2010. This was a directed inspection; the FDA investigator specifically evaluated sponsor/monitor obligations as related to the conduct of Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294, the pivotal studies submitted in support the indication sought in the NDA.

Review of records included, but was not limited to, sponsor organization and associated contracted firms, data handling and entry, clinical investigator selection and training procedures, monitor selection processes, monitoring procedures and activities, site-specific data, quality assurance activities, adverse event reporting, and study drug reconciliation. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of the Sponsor/Applicant, Sigma-Tau Pharmaceuticals, Inc., did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. Assessment of data integrity:

Based on the FDA field investigator's preliminary report of the inspection, Sigma-Tau Pharmaceuticals, Inc adequately fulfilled sponsor/monitor obligations in the conduct of Protocol 98-EI-0109E , Protocol 98-EI-0109S and Protocol STP869294.

<u>Note</u>: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

(b) (4)

(b) (4)

[redacted]

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The preliminary classification of Clinical Investigator inspections of Dr. William A. Gahl and Dr. Monte A. Del Monte, are Voluntary Action Indicated (VAI). While DSI considers primary safety and efficacy data from these sites to be generally reliable in support of the requested indication, the review division will need to determine the potential impact of the following observations on approvability of the application:

- At Dr. Gahl's site, the potential impact, if any, that missing safety data from study 98-EI-0109S has on safety analyses and conclusions.
- At Dr. Del Monte's site, whether discrepancies in drug bottles issued compared with drug bottles returned accounting for ≤10% of the total number of bottles or doses potentially administered is within acceptable limits for total potential doses administered.

The preliminary classification of the sponsor/applicant, Sigma-Tau Pharmaceuticals, Inc. and the CRO, (b) (4) [redacted] are No Action Indicated (NAI), based on preliminary communications with the FDA field investigator. The preliminary classifications for these entities are based on the preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

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/s/

KASSA AYALEW
08/23/2010

JEAN M MULINDE
08/23/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	August 13, 2010
To:	Wiley Chambers, MD, Acting Director Division of Anti-Infective and Ophthalmology Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Deveonne Hamilton-Stokes RN, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Cystaran (Cysteamine HCL) Ophthalmic Solution 0.65%
Application Type/Number:	NDA 200740
Applicant/sponsor:	Sigma-Tau Pharmaceuticals, Inc.
OSE RCM #:	2010-688

CONTENTS

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis evaluated the proposed container label, carton labeling and insert labeling for Cystaran Ophthalmic solution (NDA 200740) and identified vulnerabilities that could lead to medication errors.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels and carton labeling submitted May 25, 2010 and revised insert labeling submitted August 5, 2010. See Appendix A and B for images of proposed container labels and carton labeling.

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 3.1, Comments to the Division, contains our recommendations for the package insert labeling, and patient package insert labeling for discussion during the labeling meetings. Section 3.2, Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations for the container labels and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Brantley Dorch, at 301-796-0150.

3.1 COMMENTS TO THE DIVISION

1. According to CFR 201.57 (a)(7), the storage conditions and detailed patient information is generally not found in the Dosage and Administration section. However, if the review team determines that this information should stay in the Dosage and Administration section, revise the order of the sentences so that the storage information does not appear in between the administration information. Revise the order to appear as:

   Instill one drop of Cystaran in each eye, every waking hour.

   Thaw for approximately 24 hours before use.

   Store thawed bottle at (b) (4) or below for up to 1 week. Do not refreeze.

   Do not touch dropper tip to any surface, as this may contaminate the solution.

   Discard after 1 week of use.

   (b) (4)

2. In Section 2, revise the sentence: (b) (4) to read: "Store thawed bottle (b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[redacted] for up to 1 week. Do not refreeze."

3. In Subsection 17.1 (Storage of bottles), revise #6 to read: "Store thawed bottle [redacted] for up to 1 week. Do not refreeze."

[redacted]

3.2 COMMENTS TO THE APPLICANT

A. Container Label

1. Delete [redacted] Additionally, present the proprietary name in one color font.
2. As currently presented, the established name does not appear to be one half the size of the proprietary name. Ensure the prominence of the established name is in accordance with 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3. Relocate the product strength to appear below the established name and dosage form, in the location the word "Sterile" currently appears. Additionally, increase the prominence of the product strength commensurate with the established name and proprietary name.
4. Include the statement "Discard after:_____" to appear on the principle display panel of the container label, in order that patients may record and readily see the discard date. You may need to delete [redacted]
5. Relocate the route of administration to appear below the product strength.
6. Revise the storage conditions to be consistent with the insert labeling. Additionally since proper storage is important to the stability of this drug, we recommend that the storage conditions be more concise and easier to read. The information may appear more concise, for example, by formatting with bullets:
   - Store in freezer ……
   - Store at [redacted]
7. Decrease the prominence of the Rx only statement by removing the bolding.

B. Carton Labeling

1. See comments A1 through A6.
2. Decrease the prominence of the net quantity statement by removing the bold font from the statement. As currently presented, it is more prominent than the product strength. Additionally, relocate the net quantity statement so that it appears beneath the route of administration statement “For Ophthalmic Use Only.”
3. Relocate the statement “Discard one week after opening” to the principle display panel.
4. The side panel that includes the active ingredients and storage information appears cluttered. Relocate the storage instructions, the shake well before each use and avoid touching dropper tip to any surface statements to the panel that will contain the UPC code, in order to increase the visibility of this important information.

2 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 PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

DEVEONNE G HAMILTON-STOKES
08/13/2010

DENISE P TOYER
08/13/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information*****

Date: August 11, 2010

To: Fariba Izadi, Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising, and Communications

Subject: Cystaran™ (cysteamine hydrochloride ophthalmic solution) 0.65%
NDA: 200740

DDMAC has reviewed the proposed product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran™ (cysteamine hydrochloride ophthalmic solution) 0.65%, dated 8/5/2010, and we offer the following comments. Please feel free to contact me at (301) 796-2653 with any questions or clarifications.

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

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/s/

SHEILA K RYAN
08/11/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 11, 2010
To:	Wiley Chambers, M.D., Acting Director **Division of Anti-Infective and Ophthalmology Products (DAIOP)**
Through:	Mary Willy, PhD, Deputy Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Barbara Fuller, RN, MSN, CWOCN Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Instructions for Use)
Drug Name(s):	Cystaran (cysteamine hydrochloride) ophthalmic solution
Application Type/Number:	NDA 200740
Applicant/sponsor:	Sigma-Tau Pharmaceuticals, Inc.
OSE RCM #:	2010-1614

1 INTRODUCTION

This review is written in response to a request by the Division of Anti-Infective and Ophthalmology Products (DAIOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Instructions for Use (IFU) for Cystaran (cysteamine hydrochloride) ophthalmic solution.

On March 4, 2010 Sigma-Tau Pharmaceuticals, Inc submitted an original New Drug Application (NDA) for Cystaran (cysteamine hydrochloride) ophthalmic solution for the treatment (b) (4) of corneal cystine crystal accumulation in cystinosis patients. The NDA was filed under the provisions of Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act with request for Orphan Drug Designation.

Please let us know if DAIOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Cystaran (cysteamine hydrochloride) ophthalmic solution Prescribing Information (PI) submitted March 4, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on August 5, 2010.
- Draft Cystaran (cysteamine hydrochloride) ophthalmic solution Instructions for Use (IFU) submitted on March 4, 2010, revised by the review division throughout the review cycle and received by DRISK on August 5, 2010.

3 RESULTS OF REVIEW

In our review of the IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated IFU is appended to this memo. Any additional revisions to the PI should be reflected in the IFU.

Please let us know if you have any questions.

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

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/s/

BARBARA A FULLER
08/11/2010
DRISK Final Review of NDA 200740 Cystaran (cysteamine HCl) IFU

MARY E WILLY
08/11/2010
I concur

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200740 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Cystoran Established/Proper Name: Cysteamine Hydrochloride Ophthalmic Solution Dosage Form: Ophthalmic Solution Sterile Strengths: 0.65%		
Applicant: Sigma-Tau Pharmaceuticals. Inc Agent for Applicant (if applicable):		
Date of Application: March 3, 2010 Date of Receipt: March 4, 2010 Date clock started after UN:		
PDUFA Goal Date: September 04, 2010	Action Goal Date (if different): September 04, 2010	
Filing Date: May 17, 2010	Date of Filing Meeting: April 12, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3 P		
Proposed indication(s)/Proposed change(s): Treatment of corneal cystine crystal accumulation in cystinosis patients.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): IND 040593				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	x			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	x			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		x		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		x		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		x		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		x		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		x		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		x		7 years of orphan drug exclusivity

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	x			
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	x			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		x		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #		x		

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	x			No relevant patent
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	x			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			x	All Electronic NDA

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		x		Orphan Designation
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			x	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			x	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			x	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		x		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	x			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	x			
Is the PI submitted in PLR format?	x			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			x	Not applicable at this time.
REMS consulted to OSE/DRISK?			x	No REMS planned for this application
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	x			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	x			Ophan drugs

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		x		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 19, 2001 ***If yes, distribute minutes before filing meeting***	x			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		x		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: 04-12-2010

BLA/NDA/Supp #: 200740

PROPRIETARY NAME: Cysteamine hydrochloride ophthalmic solution

ESTABLISHED/PROPER NAME: Cystoran

DOSAGE FORM/STRENGTH: ophthalmic solution 0.65%

APPLICANT: SIGMA-TAU

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):Treatment of corneal cystine crystal accumulation in cystinosis patients.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Fariba Izadi	Y
	CPMS/TL:	Maureen Dillon Parker	N
Cross-Discipline Team Leader (CDTL)	William Boyd		Y
Clinical	Reviewer:	William Boyd	Y
	TL:	William Boyd	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Yongheng Zhang	Y
	TL:	Charles Bonapace	N
Biostatistics	Reviewer:	Mark Gamalo	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Nostrandt	Y
	TL:	Wendy Schmidt	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Balajee Shanmugam	Y
	TL:	Steven Miller	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Langille	N
	TL:	James McVey	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Deveonne Hamilton-Stokes	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalew	Y
	TL:		

Other reviewers Ron Wassel	OSE/ Safety Evaluator	
Other attendees Brantley Dorch Wiley Chambers Daphne Lin	 OSE PM Acting Division Director Deputy Division Director	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☒ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No Comments	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

disease	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: IR and comments to be sent	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: IR and comments to be sent	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: IR and comments to be sent	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Wiley A. Chambers **21st Century Review Milestones (see attached):** None **Comments**: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Other

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARIBA IZADI
05/27/2010