

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200740Orig1s000

CHEMISTRY REVIEW(S)



CMC Assessment Section

Establishment Evaluation Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 200740/000 Sponsor: SIGMA TAU PHARMS
Org. Code: 590 9841 WASHINGTON BLVD STE 500
Priority: 3 GAITHERSBURG, MD 20878
Stamp Date: 04-MAR-2010 Brand Name: Cysteamine hydrochloride ophthalmic solu
PDUFA Date: 02-OCT-2012 Estab. Name:
Action Goal: Generic Name: Cysteamine hydrochloride ophthalmic solu
District Goal: 03-AUG-2012 Product Number; Dosage Form; Ingredient; Strengths
001; SOLUTION, DROPS; CYSTEAMINE HYDROCHLORIDE; .65%

FDA Contacts: J. DAVID Project Manager 3017964247
B. SHANMUGAM Review Chemist 3017961457
L. NG Team Leader (HFA-320) 3017961426

Table with 6 columns: Overall Recommendation, Date, By, ID, and Reference Number. Rows include ACCEPTABLE, PENDING, and WITHHOLD statuses with corresponding dates and personnel.

Establishment: CFN: (b) (4) FEI: (b) (4)
DMF No: AADA: I 040593
N 020392
Responsibilities: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-APR-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
 [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-APR-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
 [REDACTED] (b) (4)

DMF No: [REDACTED] (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-AUG-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 2433247 FEI: 2433247
HI TECH PHARMACAL CO INC

DMF No: AMITYVILLE, UNITED STATES 117012801 **AADA:** I 040593
N 020392

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-MAY-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: (b) (4) **AADA:** N 020392
I 040593

Responsibilities: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-APR-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 1835063 FEI: 1000517970
SIGMA-TAU PHARMASOURCE, INC.
INDIANAPOLIS, , UNITED STATES 462682582

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY QAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-SEP-2012

Decision: ACCEPTABLE

Reason: BASED ON FILE REVIEW

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY QAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-MAY-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA: N 020392
040593

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS QAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-APR-2010

Decision: ACCEPTABLE

Reason: BASED ON FILE REVIEW

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

/s/

MARY GRACE LUBAO
10/12/2012

NDA 200-740

CystaranTM (cysteamine ophthalmic solution) 0.44%

Sigma-tau Pharmaceuticals, Inc.

Maotang Zhou, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V**

**CMC REVIEW #1 – Addendum 1
For the Division of Transplant and Ophthalmology Products
(DTOP)**

CMC Review Data Sheet

1. NDA 200-740
2. REVIEW #: 1 – Addendum 1
3. REVIEW DATE: 25-September-2012
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
NDA Resubmission/Class 2	0028	3/30/2012	
Quality Amendment (Response to Agency Questions)	0033	7/17/2012	
Quality Amendment (Response to Information Request)	0034	8/3/2012	
Quality Amendment (Response to Information Request)	0035	8/15/2012	
Labeling/Package Insert Draft	0036	8/17/2012	
Labeling/Package Insert Draft	0038	9/13/2012	
Quality Amendment (Response to Information Request)	0039	9/21/2012	
Labeling/Package Insert Draft	0040	9/24/2012	

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Sigma-Tau
Address: 9841 Washingtonian Blvd., Suite 500
Gaithersburg, MD 20878
Representative: Gianfranco Fornasini, Vice President
Telephone: 301-670-2192

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cystaran™
b) Non-Proprietary Name: Cysteamine hydrochloride
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Ophthalmic

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.44%

13. ROUTE OF ADMINISTRATION: Ophthalmic solution

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

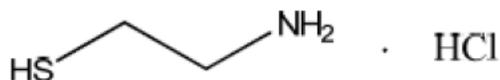
Chemical Name: 2-Amino-ethanethiol hydrochloride; 2-Mercaptoethylamine hydrochloride

Molecular Formula: C₂H₇NS·HCl

CMC Review Data Sheet

Molecular Weight: 113.61; 77.15 (free base)

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			3, 4	N/A	N/A	
	III			3, 4	N/A	N/A	
	III			4	N/A	N/A	
	II			4	N/A	N/A	
	II			4	N/A	N/A	
	III			4	N/A	N/A	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	9/24/2012	M Stock
Pharm/Tox	Acceptable	6/21/2012	Yongheng Zhang
Biopharm	Not required	8/1/2012	Tapash Ghosh
LNC	N/A	9/24/2012	Maotang Zhou
Methods Validation	N/A	8/1/2012	Maotang Zhou
DMEPA*	Acceptable	8/27/2012	Jung Lee
EA	Acceptable	8/1/2012	Maotang Zhou
Microbiology	Acceptable	8/20/2012	Stephen Langille

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 200-740

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA as revised has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. The inspection of the manufacturing and testing facilities was completed and the Office of Compliance issued an Overall Acceptable Recommendation for this NDA. From the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

NDA 200-740 for Cystaran® (cysteamine ophthalmic solution) was first submitted to the Agency by the applicant on March 4, 2010,. All CMC review issues were resolved during the review of the original NDA by Drs. Xuhong Li and Balajee Shanmugam. However, the NDA was issued a Complete Response (CR) by FDA on September 3, 2010 since the manufacturing facilities failed cGMP inspection.

On March 30, 2012, the applicant resubmitted the application. In the current resubmission, the applicant has replaced [REDACTED] (b) (4) as the drug substance manufacturer and added Sigma-Tau PharmaSource Inc. (STPS) as a second drug product manufacturer, in addition to Hi-Tech.

Drug Substance

Cysteamine HCl drug substance is a [REDACTED] (b) (4). It is prone to oxidation and forms the disulfide, cystamine 2HCl, [REDACTED] (b) (4). The drug substance is manufactured by [REDACTED] (b) (4).

In the resubmission, [REDACTED] (b) (4) has been identified as the drug substance manufacturer. No change in the synthetic scheme has been made and the manufacturing process has remained essentially the same as before. New CMC

Executive Summary Section

information such as some minor changes in the manufacturing process and the stability data from the batches produced at the new facility to support the drug substance manufacturer change from (b) (4) is provided and found to be acceptable (Please refer to CMC Review #1 for more information). The (b) (4) facility has been found to be acceptable by the Office of Compliance.

Drug Product

The drug product is formulated as a sterile solution of strength 0.44% with benzalkonium as preservative. The formulation tested in the clinical studies is essentially the same as the commercial formulation. Each milliliter of Cystaran™ contains: Active: Cysteamine HCl 6.5 mg, equivalent to 4.4 mg cysteamine; Preservative: Benzalkonium chloride 0.1 mg; Inactive Ingredients: Sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Excipients used are compendial grade. The manufacture of the drug product involve (b) (4)

(b) (4) he drug product is recommended to be stored under frozen condition (b) (4) thawed prior to use and stored under refrigerated condition until further use. The supportive freeze-thaw data are provided. It is recommended that containers should be discarded 7-days after opening. Since cysteamine HCl has the potential to (b) (4) (b) (4) The recommended expiry dating, based on evaluation of stability data, is 12-months (b) (4)

In CMC Review #1, the CMC information as provided in the NDA was found to be adequate to assure the identity, strength, purity and quality of the drug product. But the NDA was not recommended for approval from a CMC perspective because an “Acceptable” site recommendation from the Office of Compliance had not been made and labeling issues were still pending at that time (please refer to CMC Review #1 in DARRTS for detail). Since then, the applicant has revised the labeling information per FDA’s recommendation. The applicant has also withdrawn STPS from the NDA as a drug product manufacturer. An “Acceptable” site recommendation from the Office of Compliance has been made for all the manufacturing facilities. Therefore, all outstanding CMC issues have been resolved for the NDA and it is now recommended for approval from a CMC perspective.

B. Description of How the Drug Product is Intended to be Used

The proposed indication of Cystaran™ (cysteamine ophthalmic solution) is for the treatment of corneal cystine crystal accumulation in cystinosis patients. The intended dosing is to instill one drop of Cystaran™ into both eyes (b) (4). The requested expiration dating period of 12-months for product stored in freezer (-25°C to -15°C) is adequately supported by the drug product stability data.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have received “Acceptable” site recommendations from the Office of Compliance. All labels have the required information. Therefore, from the CMC perspective, this NDA is recommended for approval.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

MAOTANG ZHOU
09/25/2012

RAPTI D MADURawe
09/25/2012

NDA 200-740

CystaranTM (cysteamine ophthalmic solution), 0.44%

Sigma-tau Pharmaceuticals, Inc.

Maotang Zhou, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V**

**CMC REVIEW OF NDA 200-740
For the Division of Transplant and Ophthalmology Products
(DTOP)**

Table of Contents

CMC Review Data Sheet.....4

The Executive Summary8

I. Recommendations.....8

 A. Recommendation and Conclusion on Approvability..... 8

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 8

II. Summary of CMC Assessments8

 A. Description of the Drug Product(s) and Drug Substance(s)..... 8

 B. Description of How the Drug Product is Intended to be Used..... 10

 C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative.....11

CMC Assessment.....12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....12

 S. DRUG SUBSTANCE..... 12

 S.1 General Information.....12

 S.1.1 Nomenclature..... 12

 S.1.2 Structure..... 12

 S.1.3 General Properties..... 12

 S.2 Manufacture13

 S.2.1 Manufacturers13

 S.2.2 Description of Manufacturing Process and Process Controls..... 14

 S.2.3 Control of Materials..... 18

 S.2.4 Controls of Critical Steps and Intermediates..... 18

 S.2.5 Process Validation and/or Evaluation 20

 S.2.6 Manufacturing Process Development 20

 S.3 Characterization21

 S.3.1 Elucidation of Structure and other Characteristics..... 21

 S.3.2 Impurities..... 21

 S.4 Control of Drug Substance.....21

 S.4.1 Specification 21

 S.4.2 Analytical Procedures 23

 S.4.3 Validation of Analytical Procedures 25

 S.4.4 Batch Analyses 30

 S.4.5 Justification of Specification..... 31

 S.5 Reference Standards or Materials31

 S.6 Container Closure System.....32

 S.7 Stability32

 S.7.1 Stability Summary and Conclusions 32

 S.7.2 Postapproval Stability Protocol and Stability Commitment 36

 S.7.3 Stability Data 36

 P. DRUG PRODUCT 38

P.1	Description and Composition of the Drug Product.....	38
P.2	Pharmaceutical Development.....	39
P.2.1	Components of the Drug Product.....	39
P.2.1.1	Drug Substance.....	39
P.2.1.2	Excipients.....	39
P.2.2	Drug Product.....	39
P.2.2.1	Formulation Development.....	39
P.2.2.2	Overages.....	42
P.2.2.3	Physicochemical and Biological Properties.....	42
P.2.3	Manufacturing Process Development.....	42
P.2.4	Container Closure System.....	43
P.2.5	Microbiological Attributes.....	44
P.2.6	Compatibility.....	44
P.3	Manufacture.....	44
P.3.1	Manufacturers.....	44
P.3.2	Batch Formula.....	45
P.3.3	Description of Manufacturing Process and Process Controls.....	46
P.3.4	Controls of Critical Steps and Intermediates.....	52
P.3.5	Process Validation and/or Evaluation.....	53
P.4	Control of Excipients.....	54
P.4.1	Specifications.....	54
P.4.2	Analytical Procedures.....	54
P.4.3	Validation of Analytical Procedures.....	54
P.4.4	Justification of Specifications.....	55
P.4.5	Excipients of Human or Animal Origin.....	55
P.4.6	Novel Excipients.....	55
P.5	Control of Drug Product.....	55
P.5.1	Specification.....	55
P.5.2	Analytical Procedures.....	57
P.5.3	Validation of Analytical Procedures.....	60
P.5.4	Batch Analyses.....	60
P.5.5	Characterization of Impurities.....	62
P.5.6	Justification of Specification.....	62
P.6	Reference Standards or Materials.....	63
P.7	Container Closure System.....	63
P.8	Stability.....	64
P.8.1	Stability Summary and Conclusion.....	64
P.8.2	Postapproval Stability Protocol and Stability Commitment.....	70
P.8.3	Stability Data.....	70
A.	APPENDICES.....	71
A.1	Facilities and Equipment (biotech only).....	71
A.2	Adventitious Agents Safety Evaluation.....	71
A.3	Novel Excipients.....	71
R.	REGIONAL INFORMATION.....	71
R1	Executed Batch Records.....	71
R2	Comparability Protocols.....	71
R3	Methods Validation Package.....	71
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	71
A.	Labeling & Package Insert.....	71
B.	Environmental Assessment Or Claim Of Categorical Exclusion.....	77
C.	Establishment Evaluation Report.....	78
III.	List Of Deficiencies Communicated and Resolved.....	82

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 200-740
2. REVIEW #: 1
3. REVIEW DATE: 24-August-2012
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
NDA Resubmission/Class 2	0028	30-MAR-2012	
Quality Amendment (Response to Agency Questions)	0033	17-JULY-2012	
Labeling/Package Insert Draft			
Labeling/Package Insert Draft			
Quality Amendment (Response to Information Request)			

7. NAME & ADDRESS OF APPLICANT:

Name: Sigma-Tau
Address: 9841 Washingtonian Blvd., Suite 500
Gaithersburg, MD 20878
Representative: Gianfranco Fornasini, Vice President
Telephone: 301-670-2192

8. DRUG PRODUCT NAME/CODE/TYPE:

CMC Review Data Sheet

- a) Proprietary Name: Cystaran™
b) Non-Proprietary Name: Cysteamine hydrochloride
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Ophthalmic

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.44%

13. ROUTE OF ADMINISTRATION: Ophthalmic solution

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

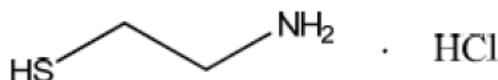
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-Amino-ethanethiol hydrochloride; 2-Mercaptoethylamine hydrochloride

Molecular Formula: C₂H₇NS·HCl

Molecular Weight: 113.61; 77.15 (free base)

Chemical Structure:



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			3, 4	N/A	N/A	
	III			3, 4	N/A	N/A	
	III			4	N/A	N/A	
	II			4	N/A	N/A	
	II			4	N/A	N/A	
	III			4	N/A	N/A	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A
NDA	N/A	N/A

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox	Review in DARRTS	6/21/2012	Yongheng Zhang
Biopharm			
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA*	Review in DARRTS	6/27/2012	Jung Lee
EA	Categorical exclusion (see review)	8/1/2012	Maotang Zhou
Microbiology	Approvable	8/20/2012	Stephen Langille

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 200-740

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product.

An "Acceptable" site recommendation from the Office of Compliance has not been made as of the date of this review.

The labeling issues are still pending as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until all the pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

NDA 200-740 for Cystaran® (cysteamine ophthalmic solution) is a 505(b)(2) application that lists Cystagon (cysteamine bitartrate) Capsules (Mylan Pharmaceuticals, Inc.) as the reference listed drug product. This is a resubmission by the same applicant, Sigma-Tau Pharmaceuticals, Inc.

The NDA was first submitted to the Agency by the applicant on March 4, 2010,. All CMC review issues were resolved in the first review cycle (See CMC review in DARRTS by Dr. Xuhong Li and Dr. Balajee Shanmugam). However, the NDA was issued a Complete Response (CR) by FDA on September 3, 2010 since the manufacturing facilities failed cGMP inspection.

On August 24, 2011, the company requested a six-month extension to amend the application as they were in the process of identifying alternate manufacturing facilities.

On March 30, 2012, the applicant resubmitted the application. In the resubmission, (b)(4) is identified as the drug substance manufacture, replacing

Executive Summary Section

(b) (4) Sigma-Tau PharmaSource Inc. (STPS) has been identified as the manufacturer of the commercial drug product, Cystaran® (cysteamine ophthalmic solution), 0.44%, as an additional facility to Hi-Tech Pharmacal, Inc., (Hi-Tech). The applicant further states that STPS will be the primary source for the manufacture of the drug product. New CMC information to support STPS as a manufacturing site of Cystaran® drug product is provided in the resubmission.

Filing review and IQA of the resubmission were completed by Dr. Balajee Shanmugam and the NDA was found to be complete from a CMC perspective.

Drug Substance

Cysteamine HCl drug substance is a (b) (4). It is prone to oxidation and forms the disulfide, cystamine 2HCl, (b) (4). The drug substance is manufactured by (b) (4).

In the resubmission, the applicant identified (b) (4) to manufacture the commercial source of the drug substance (cysteamine hydrochloride) as a replacement for (b) (4). No change in the synthetic scheme has been made and the manufacturing process has remained essentially the same as before. New CMC information such as some minor changes in the manufacturing process and the stability data from the batches produced at the new facility to support the drug substance manufacturer change (b) (4) is provided and found to be acceptable.

Drug Product

The drug product is formulated as a sterile solution of strength 0.44% with benzalkonium as preservative. The formulation tested in the clinical studies is the same as the commercial formulation. Each milliliter of Cystaran™ contains: Active: Cysteamine HCl 6.5 mg, equivalent to 4.4 mg cysteamine; Preservative: Benzalkonium chloride 0.1 mg; Inactive Ingredients: Sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Excipients used are compendial grade. The manufacture of the drug product involves (b) (4).

The drug product is recommended to be stored under frozen condition (b) (4), thawed prior to use and stored under refrigerated condition until further use. The supportive freeze-thaw data are provided. It is recommended that containers should be discarded 7-days after opening. Since cysteamine HCl has the potential to (b) (4), (b) (4). The recommended expiry dating, based on evaluation of stability data, is 12-months (b) (4).

The applicant did not discuss their control strategy in the NDA. Based on this reviewer's evaluation of the NDA information, the following control strategies are used by the

Executive Summary Section

applicant

(b) (4)

(b) (4)

Taking into consideration of the (b) (4) of cysteamine HCl, the CMC information as provided in the NDA is deemed to be adequate to assure the identity, strength, purity and quality of the drug product.

An "Acceptable" site recommendation from the Office of Compliance has not been made and labeling issues are still pending as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until the pending issues are resolved.

B. Description of How the Drug Product is Intended to be Used

The proposed indication of Cystaran™ (cysteamine ophthalmic solution) is for the treatment of corneal cystine crystal accumulation in cystinosis patients. The intended dosing is to instill one drop of Cystaran™ into both eyes (b) (4). The requested expiration dating period of 12-months for product stored in freezer ($-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$) is adequately supported by the drug product stability data.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

However, the labeling issues are still pending and a site recommendation form the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are resolved.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

MAOTANG ZHOU
08/24/2012

RAPTI D MADURawe
08/24/2012

Initial Quality Assessment Branch V Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products

NDA: 200-740

Applicant: Sigma-Tau Pharmaceuticals

Stamp Date : 30 March, 2012

Proposed Trademark: Cystaran®

Established Name: Cysteamine Hydrochloride

Dosage Form: Ophthalmic Solution

Route of Administration: Topical

Strength: 0.44%

Indication: Treatment (b) (4) of corneal crystal accumulation
in Cystinosis patients

Reviewer : Maotang Zhou

Microbiology Reviewer: Stephen Langille

CMC Lead : Bala Shanmugam

	YES	NO
Acceptable for filing:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter:	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues

Summary

The NDA for Cystaran® (cysteamine hydrochloride ophthalmic solution) submitted March 04, 2010 was issued a Complete Response on September 03, 2010 since the manufacturing facilities failed GMP inspection. On August 24, 2011 the company requested an extension of six-months to amend the application as they were in the process of identifying alternate manufacturing facilities. All chemistry review issues were resolved in the first review cycle (please see CMC review in DARRTS – team review by Xuhong Li [drug substance] and Balajee Shanmugam [drug product]). The drug product is formulated as a sterile preserved solution.

The filing review determined that the application is complete from Quality perspective. (b) (4) is identified to manufacture the drug substance, replacing (b) (4). Similarly, Sigma-Tau Pharmasource is identified to manufacture the drug product, replacing Hi-Tech Pharmacal, Inc.

Drug Substance

Manufacturer: (b) (4)
Stability samples are stored at: (b) (4)

- The NDA provides an updated section of Module 3.2.S. While the drug substance synthesis has remained largely unchanged some minor changes have been implemented to improve the safety, technical and quality aspects of the process. (b) (4)
- Section 3.2.S.2.6 also provides a comparison of the impurities. The data submitted indicates that no new impurities are formed in the batches manufactured by (b) (4) and this should be confirmed on review of the NDA resubmission. *Additionally, the analytical methods should be verified to ensure it remains the same.*
- Batch analysis data for three batches manufactured by (b) (4) has been submitted. The commercial production scale is expected to be approximately (b) (4) Table 3.2.S.4.4-2 provides a comparison of the old and new DS batches
- The resubmission provides 6-months stability data under accelerated ($40 \pm 2^\circ \text{C}$ / $75\% \pm 5\% \text{RH}$), long-term ($25 \pm 2^\circ \text{C}$ / $60\% \pm 5\% \text{RH}$) and refrigerated conditions for 3 batches manufactured at (b) (4) the new drug substance manufacturing facility. As supportive stability, data from batches manufactured at (b) (4) Farchemia have been provided.
- The specification proposed for the (b) (4) (b) (4) (b) (4) (b) (4) However, the revised specification propose (b) (4) (b) (4) (b) (4) (b) (4) *The revised limits conform to ICH Q3C (R5).*

Drug Product

Manufacturer: Sigma-Tau PharamaSource, Inc (*new manufacturer*)

- The formulation and the manufacturing process remains unchanged to the information presented in the original NDA submission. (b) (4)
- LOAs for the DMFs (b) (4) have been provided. *The adequacy of the DMFs needs to be verified.*
- DMF (b) (4) is a CBER DMF and it should be determined if this DMF needs review (b) (4)
- Data for five batches manufactured at commercial scale (b) (4) at Sigma-Tau facility has been submitted.
- DP specification remains the same and now includes test for preservative challenge and bacterial endotoxins.
- The container closure system provided in the original NDA remains unchanged.
- The new manufacturing facility is supported by a maximum of 6-9- months stability data provided for 5 batches stored under accelerated ($5 \pm 3^\circ \text{C}$; upright and inverted), freezer long-term ($-20 \pm 5^\circ \text{C}$; upright and inverted) and $-70 \pm 5^\circ \text{C}$; upright and

inverted. Assay in general shows a downward trend but remains within the proposed limits.

- Supporting stability data for a maximum of 18-25 months have been submitted for batches manufactured at Hi-Tech Pharmacal.
- *Please ensure that the strength is expressed as the free base in the label*
- The requested shelf-life is 12-months when stored in the freezer and is recommended to be discarded 1-week after opening.

Comments and Recommendation:

Based on the perusal of this NDA resubmission, it is determined to be complete from CMC perspective.

Balajee Shanmugam Ph.D.
 CMC Lead
 Branch V
 Division of Pre-Marketing Assessment
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

See DARRTS
Date

Rapti Madurawe Ph.D.
 Branch Chief
 Branch V
 Division of Pre-Marketing Assessment
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

See DARRTS
Date

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/s/

BALAJEE SHANMUGAM
05/24/2012

RAPTI D MADURawe
05/24/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 200-740

Supplement Number and Type:

**Established/Proper Name:
Cysteamine Hydrochloride
Ophthalmic Solution**

**Applicant: Sigma-Tau
Pharmaceuticals Inc.**

Letter Date: 30-March-2012

Stamp Date: 11-April-2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		The facilities have been identified with contact information (See Section 1.1.2)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Yes, as noted in item 5 of this review, the required information has been submitted.</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>		✓	<p>The readiness of the facilities is provided in Section 1.1.2 of the NDA.</p>

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	✓		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	✓		The submission under review is a resubmission in response to the CR issued (letter dated 3 September 2010) for the original NDA. The company has provided a new DS manufacturing facility with adequate CMC data to support the new manufacturer. There is no change in the synthesis of the DS from the scheme reported in the original NDA.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See item 12
14.	Does the section contain information regarding the characterization of the DS?			See item 12
15.	Does the section contain controls for the DS?			See item 12
16.	Has stability data and analysis been provided for the drug substance?	✓		The NDA provides 6-months accelerated, 6-months intermediate and 6-months long-term stability data for three batches manufactured at the new facility. Additionally, data for batches from previous manufacturers' presented in the original NDA is provided as supportive stability data. The data is acceptable since the manufacturing process remains same.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		As indicated in item 12, this submission is a resubmission. A new additional manufacturing facility is identified in the resubmission. Adequate data is provided to support the new manufacturing facility.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	✓		
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		The NDA provides adequate stability data for three batches stored at long-term and accelerated storage conditions. The requested expiration date is 12-months.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		✓	NA
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		✓	NA

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	✓		Yes. Product Quality Microbiology will provide an evaluation.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		Yes, as noted above, DMFs have been referenced for the drug substance and container closures. LOA's have been provided from the respective DMF holders.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	20-Apr-09	
	III			21-May-09	
	III			12-Aug-10	
	II			22-Dec-11	
	II			31-Jan-12	
	III			22-Feb-12	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		✓	

{See appended electronic signature page}

Balajee Shanmugam
CMC Lead
Division of Pre-Marketing Assessment, DNDQ II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe Ph.D.
Branch Chief
Branch V
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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/s/

BALAJEE SHANMUGAM
04/13/2012

RAPTI D MADURawe
04/16/2012

NDA 200-740

**Cystaran™
(cysteamine hydrochloride
Ophthalmic Solution), 0.65% sterile**

Sigma-tau Pharmaceuticals, Inc.

Xuhong Li¹ and Balajee Shanmugam²

¹Division of New Drug Quality Assessment II, Post-Marketing Branch VI

²Division of New Drug Quality Assessment II, Pre-Marketing Branch V

ONDQA

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	6
The Executive Summary	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment.....	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE.....	12
S.1 General Information.....	12
<i>S.1.1 Nomenclature</i>	<i>12</i>
<i>S.1.2 Structure</i>	<i>12</i>
<i>S.1.3 General Properties</i>	<i>12</i>
S.2 Manufacture	13
<i>S.2.1 Manufacturers</i>	<i>13</i>
<i>S.2.3 Control of Materials</i>	<i>19</i>
<i>S.2.4 Controls of Critical Steps and Intermediates</i>	<i>19</i>

<i>S.2.5 Process Validation and/or Evaluation</i>	20
<i>S.2.6 Manufacturing Process Development</i>	20
S.3 Characterization	21
<i>S.3.1 Elucidation of Structure and other Characteristics</i>	21
<i>S.3.2 Impurities</i>	21
S.4 Control of Drug Substance	21
<i>S.4.1 Specification</i>	21
S.4.2 Analytical Procedures	23
3.2.S.4.2.1 <i>Appearance</i>	23
3.2.S.4.2.2 <i>Identification</i>	23
3.2.S.4.2.3 <i>Clarity of Solution</i>	24
P DRUG PRODUCT	37
P.1 Description and Composition of the Drug Product	37
P.2 Pharmaceutical Development	38
<i>P.2.1 Components of the Drug Product</i>	38
<i>P.2.1.1 Drug Substance</i>	38
<i>P.2.1.2 Excipients</i>	38
<i>P.2.2 Drug Product</i>	38
<i>P.2.2.1 Formulation Development</i>	38
<i>P.2.2.2 Overages</i>	42
<i>P.2.2.3 Physicochemical and Biological Properties</i>	42
<i>P.2.3 Manufacturing Process Development</i>	42
<i>P.2.4 Container Closure System</i>	42
<i>P.2.5 Microbiological Attributes</i>	43
<i>P.2.6 Compatibility</i>	44
P.3 Manufacture	44
<i>P.3.1 Manufacturers</i>	44
<i>P.3.2 Batch Formula</i>	44
<i>P.3.3 Description of Manufacturing Process and Process Controls</i>	45
<i>P.3.4 Controls of Critical Steps and Intermediates</i>	49
<i>P.3.5 Process Validation and/or Evaluation</i>	50

P.4	Control of Excipients	50
P.4.1	<i>Specifications</i>	50
P.4.2	<i>Analytical Procedures</i>	51
P.4.3	<i>Validation of Analytical Procedures</i>	51
P.4.4	<i>Justification of Specifications</i>	51
P.4.5	<i>Excipients of Human or Animal Origin</i>	51
P.4.6	<i>Novel Excipients</i>	51
P.5	Control of Drug Product	51
P.5.1	<i>Specification(s)</i>	51
P.5.2	<i>Analytical Procedures</i>	53
P.5.3	<i>Validation of Analytical Procedures</i>	58
P.5.4	<i>Batch Analyses</i>	69
P.5.5	<i>Characterization of Impurities</i>	72
P.5.6	<i>Justification of Specification(s)</i>	72
P.6	Reference Standards or Materials	76
P.7	Container Closure System	76
P.8	Stability	77
P.8.1	<i>Stability Summary and Conclusion</i>	77
P.8.2	<i>Postapproval Stability Protocol and Stability Commitment</i>	82
P.8.3	<i>Stability Data</i>	82
A	APPENDICES	87
A.1	Facilities and Equipment (biotech only)	87
A.2	Adventitious Agents Safety Evaluation	87
A.3	Novel Excipients	87
R	REGIONAL INFORMATION	87
R1	Executed Batch Records	87
R2	Comparability Protocols	87
R3	Methods Validation Package	87

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1	88
A. Labeling & Package Insert.....	88
B. Environmental Assessment Or Claim Of Categorical Exclusion	89
III. LIST OF DEFICIENCIES TO BE COMMUNICATED	89
IV. MISCELLANEOUS	91

Chemistry Review Data Sheet

1. NDA 200-740
2. REVIEW #: 1
3. REVIEW DATE: 24-March-2009
4. REVIEWERS: Xuhong Li and Balajee Shanmugam
5. PREVIOUS DOCUMENTS: NA
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	04-March-2010
IR Response	09-April-2010
IR Response	26-April-2010
IR Response	06-May-2010
IR Response	13-May-2010
Amendment	25-May-2010
IR Response	27-May-2010
IR Response	11-June-2010
IR Response	09-July-2010
IR Response	13-July-2010
IR Response	19-July-2010
IR Response	30-July-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Sigma-Tau
Address: 9841 Washingtonian Blvd., Suite 500, Gaithersburg,
MD 20878
Representative: Gianfranco Fornasini, Vice-President
Telephone: (301) 670-2192

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cystaran™
- b) Non-Proprietary Name (USAN): Cysteamine hydrochloride
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Ophthalmic

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.65%

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

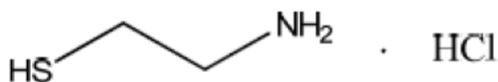
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-Amino-ethanethiol hydrochloride

2-Mercaptoethylamine hydrochloride



Molecular formula: C₂H₇NS HCl

Molecular weight: 113.61; 77.15 (free base)

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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	[REDACTED]	(b) (4)	4	Adequate	05-May-2010	N/A
	III			3 and 4	Adequate	28-April-2010	N/A
	III				3 and 4	Adequate	30-April-2010

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a	n/a	n/a
EES	Inspection scheduled	-	-
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	Not requested		
DMETS	Acceptable of Proprietary name	05-25-2010	
EA	Categorical exclusion	30-APR-2010	B. Shanmugam
Microbiology	n/a	n/a	S. Langille

The Chemistry Review for NDA 22-358

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product. The labels have adequate information as required. However, a recommendation from the Office of Compliance on the site acceptability has not yet been made as of the date of this review. Therefore, from CMC perspective, this NDA is not recommended for approval until the site acceptability is established.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Cysteamine is an aminothiols that converts cystine to cysteine-cysteamine mixed disulfide, both of which can pass through lysosomal membranes of patients with cystinosis.

Cysteamine HCl drug substance is a (b) (4) (b) (4)

(b) (4) It is prone to oxidation and forms the disulfide, cystamine 2HCl, (b) (4)

The drug substance is manufactured by (b) (4)

(b) (4)

The structure of the drug substance is confirmed by Elemental analysis, Infrared (IR) Spectroscopy, ^1H Nuclear Magnetic Resonance (NMR) Spectroscopy, ^{13}C NMR Spectroscopy and Mass Spectrum.

The specification is adequately developed for the drug substance. Appearance, (b) (4) assay and impurity (specified related substances and unspecified impurity) are controlled both at release and during stability studies. In addition, identity, clarity of solution, solution pH, (b) (4) and residual solvents are also controlled at release.

The drug substance is packaged in (b) (4)

(b) (4) Nine months of stability data at $5 \pm 3^\circ\text{C}$ and $25 \pm 2^\circ\text{C}/60\% \text{RH}$ and six months of

Executive Summary Section

data at $40 \pm 2^\circ\text{C}/75\%$ RH demonstrated that the drug substance is stable at both the proposed storage condition (5°C) and $25 \pm 2^\circ\text{C}/60\%$ RH. The applicant proposes that the drug substance to be stored at 5°C and with a retesting time of (b) (4)

The drug product is formulated as a sterile solution of strength 0.65% with benzalkonium as preservative. Each milliliter of Cystaran™ contains: Active: Cysteamine HCl 6.5 mg; Preservative: Benzalkonium chloride 0.1 mg; Inactive Ingredients: Sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Excipients used are compendial grade. The manufacture of the drug product involves (b) (4)

The drug product is recommended to be stored under frozen condition (b) (4) thawed prior to use and stored under refrigerated condition until further use. It is recommended that containers should be discarded 7-days from opening. Since cysteamine HCl has the potential to (b) (4) The recommended expiry dating, based on evaluation of stability data, is 12-months.

B. Description of How the Drug Product is Intended to be Used

Cystaran™ (cysteamine HCl) proposed indication is for the treatment of corneal cystine crystal accumulation in cystinosis patients. The intended dosing is to instill one drops of Cystaran™ into both eyes (b) (4)

The requested expiration dating period of (b) (4) for product stored in freezer (-25°C to -15°C) is not adequately supported by the drug product stability data and therefore an expiry dating of 12-months was recommended by the Agency and accepted by the applicant.

C. Basis for Approvability or Not-Approval Recommendation

The physicochemical properties of the drug substance have been adequately characterized. The manufacturing process and controls have been adequately described. The submitted stability data supports stability of the drug substance. The proposed retest period of (b) (4) with storage at 5°C is acceptable.

The components and composition of the drug product have been adequately specified and the manufacturing process adequately described. All issues regarding drug substance and drug product specifications have been negotiated and resolved with the company. Product quality microbiology recommends approval of the NDA. The applicant will continue to monitor the stability of the drug substance and drug product.

Based on the recommendation made by Product Quality Microbiology team to include a test for endotoxin to the drug product specification, the applicant complied and added this test. Additionally, the company informed the Agency via email on July 23rd to add an endotoxin testing site. As of the date of this review, Office of Compliance has not made a recommendation on the acceptability of the various facilities which are part of this NDA. From CMC perspective, this NDA can not be approved acceptability of the facilities is established by the Office of Compliance.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

{see Electronic Signature Page}

B. Endorsement Block

Xuhong Li/Balajee Shanmugam/Date: Same date as draft review
Stephen Miller (Acting Branch Chief)/Date

C. CC Block

Fariba Izadi/Date

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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

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

/s/

BALAJEE SHANMUGAM
08/02/2010
CMCReview

RAPTI D MADURAWA
08/02/2010
(signed on behalf of Stephen Miller, secondary reviewer)