CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200740Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review #2 for NDA 200740

Date	September 24, 2012
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	200740
Applicant	Sigma-Tau Pharmaceuticals, Inc.
Date of Submission	April 2, 2012
PDUFA Goal Date	October 2, 2012
Type of Application	505(b)(2)
Name	Cystaran (cysteamine ophthalmic solution) 0.44%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	treatment of corneal cystine crystal accumulation in patients with cystinosis
Recommended:	Recommended for Approval

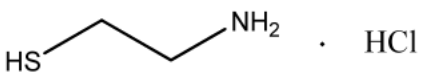
1. Introduction

Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. Cystine accumulation is due to a defective lysosomal cystine transport system and results in tissue-damaging cystine crystal formation within cells of the kidney, bone marrow, pancreas, muscle, brain, and eye. The disease often presents with growth retardation and renal tubular Fanconi syndrome in the first year of life and, if untreated, leads to renal failure by the age of 10 years.

The mainstay of treatment for cystinosis is oral cysteamine. If administered chronically and diligently beginning prior to 2 years of age, oral cysteamine retards or prevents glomerular deterioration and enhances growth in children with nephropathic cystinosis.

Corneal cystine crystals are an ocular manifestation of nephropathic cystinosis that progressively worsens with time and does not spontaneously resolve. In the cornea, cystine crystals generally appear by 1 year of age and are pathognomonic of cystinosis. They initially appear in the central cornea and progress to the full thickness of the peripheral cornea and anterior two-thirds of the central cornea with age. These cystine crystals are considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

Cysteamine HCl Structural Formula:



Molecular Formula: C_2H_7NS HCl

Cysteamine is an aminothiol that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can pass through the lysosomal membrane of patients with cystinosis without a

functional carrier and both of which can then be eliminated from the cell. Oral cysteamine was approved in the United States as Cystagon (cysteamine bitartrate) Capsules in 1994 for the management of nephropathic cystinosis in children and adults. Originally, it was thought that oral cysteamine therapy would prevent the ophthalmic complications of cystinosis, including corneal crystals, photophobia, blepharospasm, and eye pain; however, this did not occur. The absence of a vascular supply to the cornea limits cystine depletion in the eye following oral cysteamine administration.

The lack of effect of oral cysteamine on the ocular effects of cystinosis led to the development of an ophthalmic formulation. Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient.

This application received a Complete Response Letter dated September 3, 2012, which stated:

> Manufacturing facilities for the drug substance and the drug product are not in compliance with current good manufacturing practice. Satisfactory resolution of this deficiency is required before this application may be approved. Please amend the application with facilities that are in compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.

Sigma-Tau Pharmaceuticals, Inc. submitted a Complete Response, received April 2, 2012, which stated:

> The FDA's Complete Response Letter noted that the NDA was not approvable due to the manufacturing facilities for DS and drug product DP not being in cGMP compliance. Upon receipt of FDA's notification, Sigma-Tau identified and selected new manufacturing facilities for production of Cystaran. Sigma-Tau provides with this amendment new CMC information incorporating these new facilities.

2. Background

This is a 505(b)(2) application. The Form 356h submitted by Sigma Tau Pharmaceuticals, Inc., lists Cystagon (cysteamine bitartrate) Capsules (Mylan Pharmaceuticals, Inc.) as the reference listed drug Product.

The information being used by Sigma Tau as the 505(b)(2) information is toxicology information using an overexposure to the drug substance. This overexposure to the drug substance cannot be achieved with the drug product Cystaran for either a 505(b)(1) or a (b)(2) application; overexposure to drug substance is instead done with a different dosing regimen and formulation of the active ingredient. The bridge between Cystaran and Cystagon is that the drug substance is chemically the same (cysteamine) determined chemically.

There are no approved drug products for the prevention and treatment of corneal cystine crystal accumulation in patients with cystinosis. An orphan designation for cysteamine hydrochloride for the

treatment of corneal cystine crystal accumulation in patients with cystinosis was granted in August 1997.

NDA 20-392 for Cystagon (cysteamine bitartrate) Capsules was approved in 1994 for the management of nephropathic cystinosis in children and adults.

A November 10, 2010, teleconference was held with Sigma-Tau. Sigma-Tau stated that they had been advised that NEI/NIH planned to discontinue the current treatment program in December 2010 and that the program termination procedure has been initiated by NEI/NIH. Sigma Tau further stated that the current proposal by NEI/NIH (b) (4) Sigma-Tau had intended to support the continuation of the program at NEI/NIH until the GMP issues regarding the NDA were resolved. Sigma-Tau was concerned that (b) (4) The Division agreed that (b) (4) The Division stated that there was no legal mechanism for a provisional approval of the NDA even under special restrictions and oversights. Sigma-Tau asked the Division if they had any recommendation on how to proceed with NEI/NIH. The Division encouraged additional communication with NEI/NIH.

Subsequently, Sigma-Tau continued to provide cysteamine eye drops for the treatment program at NEI/NIH.

3. CMC

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

The original commercial formulation proposed in the NDA had (b) (4) sodium chloride (b) (4) (b) (4) The Division, in a teleconference with Sigma-Tau on April 28, 2010, informed the company that the commercial formulation should be identical to the formulation used in the clinical trials. The company agreed to revise the NDA commercial formulation to match formulation 3, and accordingly sodium chloride was revised (b) (4) (see following table). The revised formulation results in a (b) (4)

The drug product will be packaged in 15 mL LDPE round bottles with a white LDPE controlled drop dispenser and a white propylene cap. Container closure parts are (b) (4)

From the CMC review completed 8/24/12:

As per USP <1121>, the USP recommends that the labeled strength be expressed in terms of the parent acid or base for drug products formulated with a salt. Sigma-Tau has agreed to change the strengths in the label to be expressed in the drug product as cysteamine free base. Consequently the concentration in the commercial formulation will be expressed as 0.44% instead of 0.65%.

Table 2.3.P.2-2. Comparison of IND Clinical Formulations and NDA Stability and Commercial Formulations

Component	Clinical NIH Formulation 2	Clinical NIH Formulation 3	NDA Primary Stability Formulation	NDA Supportive Stability Formulation	NDA Commercial Formulation
Cysteamine HCl	6.5 mg[a]	6.5 mg[a]	6.5 mg	6.5 mg	6.5 mg
Sodium Chloride	(b) (4	(b) (4)			(b) (4)
Benzalkonium Chloride		0.1 mg			
Hydrochloric Acid					
Sodium Hydroxide					
Purified Water					(b) (4)

Table 2.3.P.1-1. Components of Cysteamine HCl Ophthalmic Solution

			Quantity	
Component	**Function**	**Reference to Quality Standards**	**% w/v**	**mg/mL**
Cysteamine HCl	Active ingredient	In-house (*Section 3.2.S.4.1*)	0.65	6.5
Benzalkonium Chloride (b) (4)	Preservative	NF		(b) (4)
Sodium Chloride	(b) (4)	USP		
Hydrochloric Acid		NF		
Sodium Hydroxide		NF		
Water for Injection		USP		(b) (4)

PROPOSED SPECIFICATIONS:

Table 2.3.P.5-1. Release and Stability Specifications for Cysteamine HCl Ophthalmic Solution			
Test	**Release Acceptance Criteria**	**Stability Acceptance Criteria**	***Analytical Procedures**
Description	Clear, colorless solution	Clear, colorless solution	*ACM-2300*
pH	4.00–4.60	3.80–4.80	ACM-2300 (USP <791>)
Osmolality	360–420 mOsmol/kg	360–420 mOsmol/kg	*ACM-1832*
Deliverable Volume	Meets requirements	NA	ACM-2300 (USP <698>)
Particulate Matter	(b) (4)		*ACM-2307* (USP <789>, Microscopic)
(b) (4)	(b) (4)		*ACM-2306*
Identification UPLC	The retention time of the cysteamine HCl peak in the chromatogram of the test sample preparation corresponds to the cysteamine HCl peak in the chromatogram of the standard preparation.	NA	*ACM-2302*
UV-Vis	The UV-vis spectrum (between (b) (4) nm) for the cysteamine HCl in the product sample preparation concordant with the UV-vis spectrum of cysteamine HCl in the cysteamine HCl standard preparation.	NA	
Cysteamine HCl	(b) (4)		
Specified Impurities/Degradation Product (b) (4)			*ACM-2302*

Table 2.3.P.5-1. Release and Stability Specifications for Cysteamine HCl Ophthalmic Solution

Test	Release Acceptance Criteria	Stability Acceptance Criteria	*Analytical Procedures
Individual Unspecified Impurities/Degradation Products	(b) (4)		
Total Specified and Unspecified Impurities/Degradation Products of Cysteamine HCl			
Benzalkonium Chloride			*ACM-2301*
(b) (4)			
Sterility	Meets requirements	Meets requirements	*ACM-0071* (USP <71>)
Preservative Challenge[a]	Meets requirements	Meets requirements	USP <51>
Bacterial Endotoxin	(b) (4)		*ACM-0073* (USP <85>)

[a] = Preservative Challenge testing will only be conducted on the validation batches.
NA = Not applicable.

A freeze-thaw study was conducted on Cystaran (cysteamine ophthalmic solution) 0.44%. Results indicate that the product remains within specification after three freeze-thaw cycles.

A simulated usage study was conducted to mimic patient use conditions. Results indicate that the product remains within specifications after 7 days of simulated use, regardless if the bottles were kept refrigerated or at room temperature conditions

FACILITY INSPECTIONS

A teleconference was held between Sigma-Tau and representatives from DTOP, ONDQA, and OC on 9/18/12. Sigma-Tau is aware that it is not currently in compliance for Sigma-Tau drug product manufacturing. They propose to:

1) withdraw themselves a drug product manufacturer n an amendment and retain Hi-Tech as sole drug product manufacturer, and
2) retain their endotoxin testing for drug product manufactured at Hi-Tech.

Amendment was received on 9/21/12 with these revisions to the application.

Manufacturing facilities for the drug substance and the drug product are in compliance with current good manufacturing practice.

(b) (4)

[redacted]

4. Nonclinical Pharmacology/Toxicology

There is no new nonclinical Pharmacology/Toxicology information included in this resubmission. See the original Pharmacology/Toxicology review dated 7/7/2010.

5. Clinical Pharmacology/Biopharmaceutics

There is no new nonclinical Clinical Pharmacology information included in this resubmission. See the original Clinical Pharmacology review dated 8/4/2010.

A second Clinical Pharmacology was completed dated 6/21/2012 which recommends revision to Section 8.6 of the package insert:

8.6 Renal Impairment

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

These recommendations are not included in the final labeling of the product. The statement regarding systemic use of cysteamine in the final labeling is very clinically relevant since all patients are on oral

cysteamine, and it should not be removed; renal impairment is essentially a certainty from the systemic cystinosis, and thus use of (b) (4) is not as accurate as the current wording.

6. Sterility Assurance

See the original Product Quality Micro review dated 7/7/2010. There were no microbiology deficiencies identified.

A second Product Quality Micro review was completed on 8/20/12:

NDA 200-740 is recommended for approval from the standpoint of product quality microbiology.

Sterility, endotoxin, and preservative testing will be conducted at release. Preservative effectiveness testing will be conducted during development. The benzalkonium chloride content at release must be (b) (4) of the content specified on the label.

The package insert states that the drug product should be kept frozen prior to use and refrigerated during use. The package insert also states that the drug product is preserved with benzalkonium chloride and should be discarded one week after initiation of use.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 8/31/2010:

Analyses of Primary Endpoints

STP869294 (CAPTOC)

Table 12. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT Population)			
		Total Eyes (N = 322)	
Time Point	**N[b]**	***n* (%)**	**95% CI[c]**
Response at Any Time During Study[a]	321	98 (30.5%)	[25.5, 35.9%]
Eyes with CCCS ≥1.00 at Baseline	291	94 (32.3%)	[27.0, 38.0%]
Eyes with CCCS <1.00 at Baseline	30	4 (13.3%)	[3.8, 30.7%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	291		
Year 1		27 (9.3%)	[6.2, 13.2%]
Year 2		51 (17.5%)	[13.3, 22.4%]
Year 3		72 (24.7%)	[19.9, 30.1%]
Year 4		80 (27.5%)	[22.4, 33.0%]
Year 5		85 (29.2%)	[24.0, 34.8%]
Year 6[d]		87 (29.9%)	[24.7, 35.5%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 19 may be found in *Table 14.2.1.1*.
Source: *Table 14.2.1.1*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, the response rate in the mITT population was 13% (4/30) [95% CI: (4, 31)]. For eyes with a higher baseline CCCS of ≥1, the response rate was 32% (94/291) [95% CI: (27, 38)].

Values highlighted in yellow in this table and subsequent tables were revised in the May 20, 2010, submission.[1]

1 Per the May 20, 2010, submission: Upon review of the study data and the SAS program coding used to generate the initial analysis outcomes, Sigma-Tau confirmed the discrepancy between the CCCS response rates observed by FDA and those reported by Sigma-Tau. These differences were attributed to the manner in which missing values were handled in the response rate calculations. The Sigma-Tau analysis provided that patient eyes with one or more missing change-from-baseline CCCS values, due to missing post-baseline CCCS's, would be assigned as a response to treatment. This resulted in some patient eyes being regarded as responders when in fact there were no data to support that outcome. Sigma-Tau confirmed that when excluding any missing eye-year assessments of change-from-baseline CCCS values from the response rate calculations, the response outcome as observed by FDA was verified. In an effort to facilitate the review process, Sigma-Tau performed a new analysis based on FDA's method. The revised efficacy datasets and analyses have been amended in the STP869294 CSR and replace the original analyses.

Table 13. Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT-1 Population)			
		Total Eyes (N = 184)	
Time Point	**N[b]**	***n* (%)**	**95% CI[c]**
Response at Any Time During Study[a]	183	53 (29.0%)	[22.5, 36.1%]
Eyes with CCCS ≥1.00 at Baseline	156	49 (31.4%)	[24.2, 39.3%]
Eyes with CCCS <1.00 at Baseline	27	4 (14.8%)	[4.2, 33.7%]
Cumulative Response Rates by Year (Eyes with CCCS ≥1.00 at Baseline)[a]	156		
Year 1		11 (7.1%)	[3.6, 12.3%]
Year 2		22 (14.1%)	[9.1, 20.6%]
Year 3		33 (21.2%)	[15.0, 28.4%]
Year 4		40 (25.6%)	[19.0, 33.2%]
Year 5		43 (27.6%)	[20.7, 35.3%]
Year 6[d]		45 (28.8%)	[21.9, 36.6%]

[a] = A response was defined as a decrease from baseline of at least 1.00 unit in CCCS at any time on study when baseline was ≥1.00, or CCCS did not increase at least 1.00 unit at any time on study when baseline CCCS was <1.00.
[b] = Percentages were based on the number of total eyes evaluated.
[c] = Clopper and Pearson 95% CI for percentage.
[d] = Cumulative response rates for Year 7 through Year 19 may be found in *Table 14.2.1.2*.
Source: *Table 14.2.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 11.4.1.1 Primary End Point

For eyes with a lower baseline CCCS of <1, the response rate in the mITT-1 population was 15% (4/27) [95% CI: (4, 34)]. For eyes with a higher baseline CCCS of ≥1, the response rate was 32% (49/156) [95% CI: (24, 39)]. This is consistent with the mITT population results.

98 EI0109E

Table 7. Proportion of Eyes with Reduction in CCCS of 1 Unit or More (Per-Protocol Population)

	Formulation 5		Formulation 3		
Time Point	***n* (%)[a]**	**95% CI[b]**	***n* (%)[a]**	**95% CI[b]**	***p*-Value[c]**
Any Time During Study	2 (13.3%)	1.7-40.5	10 (66.7%)	38.4-88.2	0.0047[d]
Month 3	2 (13.3%)	1.7-40.5	4 (28.6%)[e]	8.4-58.1	0.0833[f]
Month 6	2 (14.3%)[e]	1.8-42.8	7 (50.0%)[e]	23.0-77.0	0.0253[d]
Month 9	1 (7.1%)[e]	0.2-33.9	8 (57.1%)[e]	28.9-82.3	0.0082[d]
Month 12	1 (6.7%)	0.2-31.9	7 (46.7%)	21.3-73.4	0.0143[d]

[a] = Percentages are based on the number of eyes with non-missing values at the corresponding time point.
[b] = Clopper and Pearson 95% CI for percentage.
[c] = Results from McNemar's Test.
[d] = Statistically significant (p <0.05).
[e] = The number of eyes evaluated at this time point was only 14 as opposed to 15.
[f] = Note: At Month 3, Patient 3003 is excluded from the McNemar Test due to the fact that a valid assessment was not available for both eyes.
Source: *Table 14.2.1.1.1*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109E, 11.4.1 Analysis of Efficacy

This study evaluated ocular cystinosis patients who had a baseline CCCS ≥1. The response rate in the Per Protocol population was 67% (10/15) [95% CI: (38, 88)] with Formulation 3. The response rate was 13% (2/15) [95% CI: (2, 41)] with Formulation 5.

98 EI0109S

Table 11.	**Proportion of Eyes with Reduction in CCCS of 1 Unit or More at Month 6 (Per-Protocol Population and Subset of Patients 2–12 Years of Age)**				
	Formulation 5		**Formulation 3**		
	***n* (%)**	**95% CI[b]**	***n* (%)**	**95% CI[b]**	***p*-Value[c]**
Per-Protocol Population (*n* = 18)					
Eyes With a CCCS ≥1 Unit at Baseline	8 (44.4%)	N/A	9 (50.0%)	N/A	N/A
Eyes With a Reduction in CCCS ≥1 Unit[a]	0 (0.0%)	0.0-36.9	3 (33.3%)	7.5-70.1	0.0833
Patients 2–12 years of Age (*n* = 8)					
Eyes With a CCCS ≥1 Unit at Baseline	3 (37.5%)	N/A	4 (50.0%)	N/A	N/A
Eyes With a Reduction in CCCS ≥1 Unit[a]	0 (0.0%)	0.0-70.8	0 (0.0%)	0.0-60.2	N/A

[a] = Percentages are based on the number of eyes with a CCCS of ≥1 at baseline.
[b] = Clopper and Pearson 95% CI for percentage.
[c] = Results from McNemar's Test.
N/A = Not applicable.
Source: *Table 14.2.1.1.1* and *Table 14.2.1.1.1a*.

Source: December 17, 2009, Clinical Study Report, 98 EI0109S, 11.4.1 Analysis of Efficacy

The majority of these patients in this study (12/20) had a baseline CCCS ≤1. The response rate in the Per Protocol Population with Formulation 3 was 33% (3/9) [95% CI: (8, 70)].

Although the focus of this study was on safety as defined by SAEs in eyes treated with Formulation 5, an increase in CCCS and/or a worsening of the ocular signs and symptoms of cystinosis could also be a safety concern. Although no decision on how to analyze these data was made a priori, the efficacy assessments were collected as per protocol.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

8. Safety

From the original Medical Officer Review dated 8/31/2010:

Studies STP869294 (CAPTOC), 98 EI0109E, and 98 EI0109S were utilized to evaluate safety.

Pooled adverse event data was not submitted in the new drug application.

For the purposes of labeling the adverse event profile of cysteamine hydrochloride ophthalmic solution 0.44%, the data from STP869294 (CAPTOC) was utilized. CAPTOC enrolled 247 subjects; the trial duration was 19 years.

The adverse event profiles seen in 98 EI0109E, and 98 EI0109S are consistent with STP869294 (CAPTOC).

Overall Exposure at Appropriate Doses/Durations

STP869294 (CAPTOC)

Because compliance was not analyzable in CAPTOC, the safety analyses were based on the assumption that all patients were on active treatment with ophthalmic cysteamine. As a conservative effort, these analyses actually encompassed times where patients may have been treated with cysteamine, placebo, or cystamine. The Table below provides the summary of study duration that details average treatment duration, minimum and maximum treatment duration, and how many patients were receiving treatment every year. For the Safety Population, the mean (±SD) treatment duration for the 247 patients was 5.8 ± 5.54 years. There were 4 patients that had been receiving treatment for the maximum duration of 19 years.

Table 14.1.5.1

Summary of Study Duration
ITT Population

	Total (N=247)
Duration on study (years)	
n	247
Mean	5.8
S.D.	5.54
Median	4.5
Min, Max	0.0, 19.0
Patients on study by year	
Baseline	247 (100.0)
1	180 (72.9)
2	176 (71.3)
3	153 (61.9)
4	137 (55.5)
5	128 (51.8)
6	113 (45.7)
7	102 (41.3)
8	94 (38.1)
9	85 (34.4)
10	74 (30.0)
11	63 (25.5)
12	55 (22.3)
13	47 (19.0)
14	34 (13.8)
15	25 (10.1)
16	15 (6.1)
17	10 (4.0)
18	7 (2.8)
19	4 (1.6)

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.1 Extent of Exposure

Subject Disposition

STP869294 (CAPTOC)

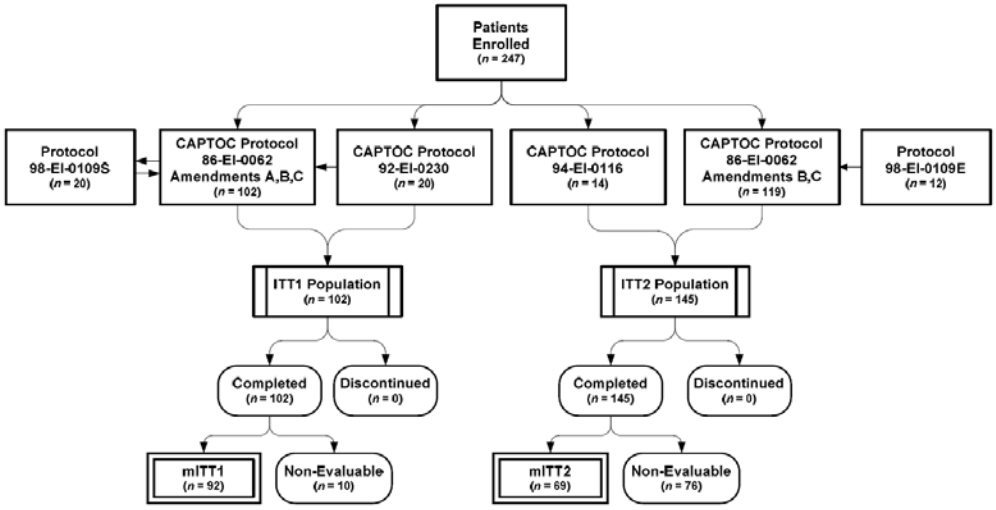


Figure 2. Patient disposition overview.

ITT-1 and ITT-2 populations labeled in this figure are for descriptive purposes only to delineate the discontinuation of placebo treatment. No efficacy analyses were performed on ITT-1 and ITT-2 populations.

Adverse Events

CAPTOC

Table 23. Summary of the Incidence of the Most Common (≥2.0%) Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population	
System Organ Class Preferred Term[a]	**Total (N = 247) *n* (%)**
Number of Patients With at Least One AE	**169 (68.4)**
Eye Disorders	**166 (67.2)**
Photophobia	157 (63.6)
Conjunctival Hyperaemia	69 (27.9)
Eye Pain	48 (19.4)
Ocular Hyperaemia	43 (17.4)
Eye Irritation	42 (17.0)
Lacrimation Increased	21 (8.5)
Keratitis	19 (7.7)
Optic Disc Disorder	18 (7.3)
Vision Blurred	17 (6.9)
Dry Eye	13 (5.3)
Eyelid Oedema	12 (4.9)
Retinal Disorder	11 (4.5)
Conjunctivitis	10 (4.0)
Eye Pruritus	10 (4.0)
Blindness	7 (2.8)
Corneal Epithelium Disorder	6 (2.4)
Blepharitis	5 (2.0)
Erythema of Eyelid	5 (2.0)
General Disorders and Administration Site Conditions	**40 (16.2)**
Instillation Site Irritation	30 (12.1)
Instillation Site Pain	17 (6.9)
Adverse Drug Reaction	2 (0.8)[b]
Instillation Site Erythema	5 (2.0)

Table 23.	**Summary of the Incidence of the Most Common (≥2.0%) Ocular Adverse Events (*n* and %) for the Treatment Period: Safety Population**
System Organ Class Preferred Term[a]	**Total (N = 247) *n* (%)**
Infections and Infestations	**11 (4.5)**
Eye Infection	5 (2.0)

[a] = All AE terms were coded using MedDRA Dictionary Version 9.0.
[b] = There were a total of 7 patients experiencing adverse drug reactions; 2 ocular and 5 non-ocular. Although when separated out, ocular adverse drug reactions occurred in less than 2.0% of the population (0.8%), it continues to be included in this table because of its relevancy to the drug and indication. Please see below and *Table 24* for additional details.
Note: A patient experiencing multiple occurrences of an AE is counted only once within each system organ class and within each preferred term.
Source: *Table 14.3.1.2*.

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.2.2.3 Non-Ocular Adverse Events

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

Deaths

Eighteen deaths were reported in the three studies comprising the CAPTOC analysis. Two of the patient deaths (Patient 374973 and Patient 835249) were reported to FDA in IND Safety Reports.

Five patients (Patients 221252, 315632, 352157, 727697, and 883818) died with no cause provided.

Table 28. Cause of Death in Patients by Preferred Term: Safety Population	
Patient Number (*n* = 18)	**Cause of Death[a]**
221252	No cause given
221478	Central nervous system lymphoma
268427	Therapeutic response unexpected (complications due to dialysis); Azotaemia
288466	Neuropathy; Azotaemia
292824	Pneumonia
315632	No cause given
352157	No cause given
374973	Renal failure
419131	Cardiac arrest; Peritonitis
665494	Congenital neurological disorder; Sudden infant death syndrome; Aspiration
717581	Respiratory failure
724841	Sepsis; Pneumonia aspiration
727697	No cause given
736117	Endocarditis; Sepsis
835249	Intestinal obstruction; Gastrointestinal infection; Renal failure
883818	No cause given
893478	Colon injury
997414	Myopathy; Depression
[a] = All AE terms were coded using MedDRA Dictionary Version 9.0. Source: *Appendix 16.2.7.1.5*	

Source: May 6, 2010, Clinical Study Report Amendment, CAPTOC, 12.3.2.1 Deaths

The Case Report Forms (CRFs) for all 18 patients were reviewed. For the five patients where no cause was provided, there was additional information in the CRFs for two.

Patient 21252 apparently rejected her renal allograft and refused dialysis. Patient 352157 was found unresponsive and died despite vigorous resuscitation attempts.

There were no deaths in 98 EI0109S and 98 EI0109S.

Safety Update

As part of the April 4, 2012, resubmission, a safety update covering the period from May 1, 2010, to December 30, 2011, was submitted. During this safety update period, a total of 112 cystinosis patients were exposed to cysteamine ophthalmic solution: 102 returning patients, and 10 new patients.

Summary of the Incidence of the Most Common (≥ 2.0%) Adverse Events (n and %) for the Study Update Safety population	
System Organ Class Preferred Term	**May 1, 2010 to December 30, 2011 (N=112)**
Number of patients with at least one AE	69 (62%)
Eye Disorders	59 (53%)
Photophobia	54 (48%)
Eye pain	5 (5%)
Ocular Hyperemia	3 (3%)
Eye Irritation	4 (4%)
Nervous System Disorders	22 (20%)
Headache	19 (17%)
Benign Intracranial Hypertension	5 (5%)
General Disorders and Administration Site Conditions	7 (6%)
Instillation site pain	5 (5%)

Note: A patient experiencing multiple occurrences of an AE is counted only within each system organ class and within each preferred term.

During the safety update reporting period from May 1, 2010, to December 30, 2011, one patient died. The patient death occurred on (b) (6) in a female 23.7 years of age due to uremia and pericarditis. The patient was in the study for 20 years, with the first assessment on (b) (6) when the patient was 2½ years of age, and the last assessment was on May 27, 2009. The death was considered unrelated to Cystaran.

During the current safety update one ocular serious adverse event (SAE) of blindness was reported and no non-ocular SAEs were reported. The SAE of blindness was considered by the investigator as not related to cysteamine and due to progressive decline in the cornea that had started before the administration of cysteamine drops.

This patient entered into the cysteamine HCL ophthalmic solution protocol in January 1997, at which time her vision was 20/160 in the right eye and 20/80 in the left, the reduction was resulting from a severe corneal epitheliopathy (filaments and disrupted epithelium) in the setting of a heavy crystal burden in the cornea from cystinosis. The patient was started on cysteamine ophthalmic solution, which over the ensuing years, caused the corneal crystal density to decline and brought the patient relief from ocular pain. However, her vision continued to deteriorate as her corneal epithelium remained disrupted, eventually leading to corneal neovascularization and calcification.

On August 24, 2012, the 120 Day Safety Update was submitted to the application covering the dates from January 1, 2012, to August 14, 2012. There was no change to the Cystaran safety profile.

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%, dosed every hour while awake, is safe for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The safety and effectiveness of Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% in pediatric patients have been established for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Cystinosis often presents with growth retardation and renal tubular Fanconi syndrome in the first year of life and, if untreated, leads to renal failure by the age of 10 years.

11. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology, Clinical, Biostatistics, and CMC recommend approval of this new drug application.

OSI

An Office of Scientific Investigations (OSI) audit was requested, and subsequently completed on August 23, 2010. The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Two domestic clinical investigators, Drs. Gahl (Muriel Kaiser) and Monte, and the applicant and CRO were inspected. See the original CDTL Review dated 9/3/2010 for more detail.

The classification of the sponsor/applicant, Sigma-Tau Pharmaceuticals, Inc. and the CRO, (b) (4) are No Action Indicated (NAI).

FINANCIAL DISCLOSURE
The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA
In the original review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations on the packaging configuration and the package insert labeling in a separate review and during labeling meetings held on August 4 and 13, 2010.

DMEPA completed a second review of the proposed proprietary name, Cystaran, and concluded that it was acceptable in a review dated 7/5/12.

Although the labeling for this product was finalized with the exception of the established name in the original review cycle, DMEPA completed a second review on 8/27/12

DPDP
In the original review cycle, the Division of Professional Drug Promotion (DPDP) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DPDP was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review.

Although the labeling for this product was finalized with the exception of the established name in the original review cycle, DPDP completed a second review on 9/14/12.

DRISK
In the original review cycle, the Division of Risk Management (DRISK) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44%. DRISK was invited to the two labeling meetings held on August 4 and 13, 2010, and provided a separate review. A decision was made at the second labeling meeting not to include a Patient Package Insert with the Cystaran labeling because there was nothing new or novel regarding the administration of this ophthalmic solution to the eyes.

BIOSTATISTICS
Per the Biostatistics consultative review finalized 8/9/2010:

The three studies demonstrate that cysteamine ophthalmic solution (Formulation 3) reduces formation of corneal crystals. This reduction however is temporary. Strict adherence to therapy is essential to the efficacy of Formulation 3.

12. Labeling

NDA 200740, Cystaran (cysteamine hydrochloride ophthalmic solution) 0.44% is recommended for approval for the treatment of corneal cystine crystal accumulation in patients with cystinosis with the attached labeling.

The labeling found in the Appendix at the end of this CDTL review (package insert and carton and container labeling submitted on 9/24/12) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 200740, Cystaran (cysteamine ophthalmic solution) 0.44% is recommended for approval for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Cystaran (cysteamine ophthalmic solution) 0.44% reduces the accumulation of cystine corneal crystals considered partly responsible for clinical symptoms of photophobia, recurrent corneal erosions, and secondary blepharospasm that complicate longstanding cystinosis.

The most common ocular adverse events in CAPTOC occurring in ≥ 10 % of patients were sensitivity to light, redness, and eye pain/irritation.

The benefits of using this drug product outweigh the risks for the above indication.

Pharmacology/Toxicology, Biostatistics, Clinical, Clinical Pharmacology, CMC, and Product Quality Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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

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

/s/

WILLIAM M BOYD
09/26/2012

WILEY A CHAMBERS
09/26/2012