

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200740Orig1s000

SUMMARY REVIEW

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products ¹
Subject	Division Director Summary Review
NDA Number	NDA 200740
Related IND	IND 40593
Other NDAs	NDA 20-392 Cystagon (cysteamine bitartrate) Capsules approved 1994 for nephropathic cystinosis
Priority of Standard	Priority
Date of Submission	March 3, 2010
Date of Receipt	March 4, 2010
Complete Response Letter	September 3, 2010
NDA Resubmission Date	March 30, 2012
Date of Receipt	April 2, 2012
PDUFA Goal Date	October 2, 2012
Type of Application	505(b)(2)
Applicant Name	Sigma-Tau Pharmaceuticals, Inc.
Proprietary Name / Established (USAN) Name	Cystaran cysteamine ophthalmic solution
Formulation	Topical ophthalmic solution, 0.44%
Dose	One drop in each eye, every waking hour, daily
Proposed Indication(s)	Treatment of corneal cysteine crystal accumulation in patients with cystinosis
Action for NME	<i>Approval</i>

¹ The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	William Boyd 8/31/2010, Martin Nevitt 9/19/2012
CDTL Review	William Boyd, Wiley Chambers 9/3/2010, 9/26/2012
Deputy Director Review	Wiley Chambers 9/3/2010,
Statistical Review	Mark Gamalo, Yan Wang 8/9/2010
Pharmacology/Toxicology Review	Amy Nostrandt, Wendelyn Schmidt 7/7/2010
Clinical Pharmacology Review	Yongheng Zhang, Charles Bonapace 8/4/2010
Product Quality Review- ONDQA/Branch V, Division II ONDQA/Resubmission Reviews	Xuhong Li, Bala Shanmugam , Rapti Madurawe for Stephen Miller 8/2/2010 Bala Shanmugam , Rapti Madurawe 5/24/2012 Maotang Zhou, Rapti Madurawe 8/24/2012, 9/25/2012
Quality Microbiology Review	Stephen Langille, James McVey 8/3/2010, 8/20/2012
OC/EES	Linda Ng 9/21/2012
Microbiology/Immunology Review	NA
OSI/DGCP	Kassa Ayalew, Jean Mulinde 8/23/2010
OSE/DMEPA Proprietary Name	Deveonne Hamilton-Stokes, Todd Bridges, Denise Toyer, Carol Holquist, 8/10/2010; letter 8/12/2010, and 7/5/2012
OSE/DMEPA Labeling Review	Deveonne Hamilton-Stokes, Todd Bridges, Denise Toyer, Carol Holquist, 8/13/2010 Jung Lee, Jamie Wilkins Parker, Carol Holquist 8/27/2012
OSE/DRISK Labeling Review	Barbara Fuller, Mary Willy, LaShawn Griffiths, 8/11/2010
OPDP/DPDP	Christine Corser, Sheila Ryan 8/11/2010, 9/14/2012
PMHT	Pediatric studies completed
Advisors and Consultants Staff	NA

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

ONDQA = Office of New Drug Quality Assessment

OSI/DGCP=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI))

OC/EES = Office of Compliance/Establishment Evaluation System

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Assessment

OPDP/DPDP=Office of Prescription Drug Prescribing/ Division of Prescription Drug Promotion (formerly DDMAC=Division of Drug Marketing, Advertising and Communication)

PMHT=Pediatric and Maternal Health Staff

Table of Contents:

Table of Contents:.....	3
1. Summary and Recommendations	4
1.1 Deficiencies.....	4
1.2 Post-Marketing Studies:.....	4
1.3 Other Issues.....	4
2. Background	4
2.1 Priority Review	5
2.2 Regulatory Issues	5
2.3 Meetings during development.....	5
3. CMC/Product Quality Microbiology	6
3.1 Drug Substance/Drug Product	6
3.2 Resubmission	7
3.3 Quality Microbiology Sterility.....	8
4. Nonclinical Pharmacology/Toxicology	8
5. Clinical Pharmacology/Biopharmaceutics.....	8
6. Clinical Microbiology/Immunology	9
7. Clinical/Statistical-Efficacy	9
8. Safety	12
8.1 Safety Updates	12
9. Advisory Committee Meeting	12
10. Pediatrics	13
11. Other Relevant Regulatory Issues	13
11.1 Compliance Inspection – OBP and OC	13
11.2 Office of Scientific Investigation (OSI) Audits.....	13
11.3 Debarment certification	13
11.4 Financial Disclosure.....	13
11.5 Other Regulatory Issues.....	13
12. Labeling	14
13. Decision/Action/Risk Benefit Assessment.....	14
13.1 Regulatory Action.....	14
13.2 Recommendation for other Postmarketing Requirements and Commitments.....	14

1. Summary and Recommendations

Based on the review of the original application and this resubmission, Cytaran (cysteamine ophthalmic solution) 0.44% has been found to be safe and effective for the treatment of corneal cystine crystal accumulation in patients with cystinosis. All review disciplines recommend approval of the application, and the Office of Compliance has issued a recommendation of Acceptable during this review cycle, and labeling has been finalized.

The indication for the treatment of corneal cysteine crystal accumulation in patients with cystinosis is based on controlled clinical trials conducted by the National Eye Institute since 1986 to present on approximately 300 patients. The recommended dosing regimen is one drop of Cystaran in each eye every waking hour, each day. Based various analyses of the data, the statistical reviewer has noted that response is higher in patients who are judged as having excellent compliance.

The original NDA for this orphan disease was submitted in March 4, 2010, and clinical, statistical, clinical pharmacology, pharmacology/toxicology data and CMC was found acceptable by the review disciplines and draft labeling was sent to the applicant. However, the application received a *Complete Response* letter on September 3, 2010 because the Office of Compliance found that the drug substance (DS) and drug product (DP) facilities were not in compliance. In the resubmission, the company submitted alternative DS and DP facilities. The new (b) (4) facility for manufacture of DS was found to be acceptable. The new Sigma-Tau facility for the DP was found unacceptable, however the deficiencies in the previously unacceptable Hi-Tech facility were addressed and the facility was considered acceptable. Therefore the applicant withdrew the Sigma-Tau facility manufacturing, but retained the endotoxin testing at Sigma-Tau, and OC considered these changes acceptable. As a result, the application now had both acceptable DP and DS facilities and, therefore the application can now be approved. An *Approval* letter will be issued during this review cycle.

Complete details regarding the disease, the product, manufacturing, related NDAs and INDs, and the basis for the approval including efficacy and safety can be found in the primary, team leader, CDTL and Deputy Director Reviews for the original application and resubmission. The following document provides summaries of the issues.

1.1 Deficiencies

None

1.2 Post-Marketing Studies:

None

1.3 Other Issues

None

2. Background

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Disease

Cystinosis is an autosomal recessive lysosomal storage disease characterized by the abnormal accumulation of cystine in multiple organs. It is associated with the formation of hexagonal, colorless crystals in the affected cells and resulting organ damage. The most severe form causes progressive kidney damage (Fanconi syndrome) and renal failure in the first decade of life; the milder or adult form is associated with only visual symptoms such as photophobia due to cystine crystal deposition in the cornea. The marketed oral cysteamine product, Cystagon, is effective in mitigating systemic organ damage, but does not adequately penetrate the eye. Therefore, development of an ophthalmic solution was important to address this unmet need.

Drug

Cystaran (cysteamine ophthalmic solution) 0.44% is an aminothioliol, a cystine-depleting agent, that reduces the accumulation of cystine corneal crystals by converting cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which pass through the lysosomal membrane and the cell.

Oral cysteamine was approved in the United States as Cystagon (cysteamine bitartrate) Capsules NDA 20-392 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; therefore an alternative approach was needed. This led to the development of an ophthalmic formulation.

2.1 Priority Review

There are currently no approved therapies for treating the corneal deposition of cystine.

2.2 Regulatory Issues

The application was submitted under FD&C Act section 505(b)(2).

Orphan Designation

There are about 2000 individual with the disease.² Orphan designation for treatment of corneal cystine crystal accumulation in patients with cystinosis was granted in 1997.

Transfer of Sponsorship

The IND was transferred from William A. Gahl, MD, Ph.D, Clinical Director, National Human Genome Research Institute, National Institutes of Health to Sigma-Tau Pharmaceuticals, Inc. effective on November 20, 2009 (see letter dated February 12, 2010).

2.3 Meetings during development

The medical officer notes that a pre-NDA meeting was held on October 19, 2001.

² <http://en.wikipedia.org/wiki/Cystinosis>

<http://www.cystinosis.org/symptoms-treatments>

3. CMC/Product Quality Microbiology

For details, see complete CMC reviews.

During the review of the original NDA, all chemistry review issues were resolved as summarized in the reviews by Dr. Xuhong Li for drug substance (DS) and by Dr. Balajee Shanmugam for drug product (DP) showing the product has sufficient assurance of identity, strength, purity and quality. The basis for the CR in the first cycle was failed GMP inspection of DS and DP manufacturing facilities.

3.1 Drug Substance/Drug Product

Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient. Cysteamine is an aminothiols that converts cystine to cysteine-cysteamine mixed disulfide, both of which can pass through lysosomal membranes of patients with cystinosis. The details of the manufacturing can be found in the CMC reviews. The product contains benzalkonium chloride 0.1 mg (0.65%).

Cysteamine HCl is [REDACTED] (b) (4)

[REDACTED] It is to be stored [REDACTED]
 [REDACTED] Expiry is set at [REDACTED] (b) (4) [REDACTED] (b) (4)

The product is packaged in 15 mL LDPE round bottles with a white LDPE controlled drop dispenser and a white propylene cap. The product is thawed before use, should be refrigerated on opening, and discarded 7 days after opening.

The National Institute of Health evaluated several formulations as summarized below:

Table. Summary of Formulation History

Date Used	Cysteamine HCl (w/v) ^a	pH Adjustment ^b	Benzalkonium Chloride	[REDACTED] (b) (4)	Clinical Formulation
Before June 1998	0.11%	[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)	1
June 1998 to April 1990	0.55%	[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)	2
April 1990 to April 1991	0.55% ^c	[REDACTED] (b) (4)	[REDACTED] (b) (4)	[REDACTED] (b) (4)	2
April 1991 to May 1992	0.55% ^c	[REDACTED] (b) (4)	0.01% ^d	[REDACTED] (b) (4)	3
May 1992 to current	0.55% ^c	[REDACTED] (b) (4)	0.01% ^d	[REDACTED] (b) (4)	3

^a All batches were made with saline as diluent
^b pH was adjusted with HCl or NaOH
^c [REDACTED] (b) (4)
^d Some lots continued to be formulated without benzalkonium chloride (BAK) for patients with sensitivity to BAK

The to-be-marketed formulation was matched closely to Formulation 3 which was used in the NIH trials between 1991-present (table below). During a teleconference on April 28, 2010

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Sigma-Tau was informed the content of sodium chloride for the market formulation needed to match the amount in Formulation 3 on which clinical trials were conducted. Thus the quantity was changed (b) (4). In the CMC review, there is also an explanation that the NIH calculation of cysteamine HCl concentration (b) (4) and the correct concentration used in Formulation 3 and intended for commercial distribution is 0.65%, not 0.55%.

Table. Comparison of IND, Clinical and Commercial Formulations

Component	Clinical NIH Formulation 2	Clinical NIH Formulation 3	NDA Commercial Formulation 2
Cysteamine HCl	6.5 mg ^a	6.5 mg ^a	6.5 mg
Sodium Chloride	(b) (4)	(b) (4)	(b) (4)
Benzalkonium Chloride		0.1 mg	0.1 mg
Hydrochloric acid			(b) (4)
Sodium Hydroxide	(b) (4)		(b) (4)
Purified Water			(b) (4)

Product characteristics -

- 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.

3.2 Resubmission

In the resubmission, the applicant identified new DS and DP manufacturing facilities: The drug substance was initially manufactured by (b) (4) which failed GMP inspection during the original review of the NDA. In this resubmission, (b) (4) was identified as the new manufacturer for the drug substance and the CMC reviewer reported that there were no changes in the drug substance synthetic scheme and the manufacturing process remained essentially the same, therefore much of the information from the initial facility were applicable. Six month stability data were sent, and CMC determined that the batches from (b) (4) are deemed to be more relevant than those from Farchemia to set expiry for the (b) (4) DS because of (b) (4) Retest period of (b) (4) was set for DS.

The drug product was initially manufactured at the Hi-Tech facility, which also failed GMP inspection during the original review cycle. In the resubmission Sigma-Tau Pharma Source

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

(STPS) was identified as an additional manufacturer for the drug product. Again the DP manufacturing process remained essentially the same. The DP formulation proposed for the resubmission is identical to the formulation in the original submission. In addition to the active cysteamine hydrochloride, the drug product contains benzalkonium chloride (preservative), sodium chloride (b) (4), hydrochloric acid and sodium hydroxide (for pH adjustment), and water (b) (4) (b) (4) All excipients are of USP/NF grade.

3.3 Quality Microbiology Sterility

The container closure system is (b) (4)
(b) (4) There are no deficiencies identified.

Comment: The reviewers recommend approval from a CMC and Quality Microbiology Sterility perspective and have made labeling revisions. The Office of Compliance has recommended that manufacturing facilities are “acceptable,” during the current review cycle.

4. Nonclinical Pharmacology/Toxicology

For details, see pharmacology /toxicology review by Drs. Nostrandt and Schmidt.

Studies of cysteamine hydrochloride ophthalmic solution 0.1-10% included one GLP study conducted by the Applicant and two studies from the peer-reviewed scientific literature.

In the GLP-compliant study in rabbits, 2 drops of 0.55% cysteamine ophthalmic solution were administered hourly for 8 hours per day for 30 days to the right eye of 12 rabbits/sex. No findings of irritation, corneal disruption, or ocular histopathology were reported.

In published studies in rabbits, gross and/or microscopic signs of irritation or inflammation were seen following ocular administration of cysteamine at concentrations of 1% and higher when administered hourly for 8 consecutive hours for 4 weeks, while eyes treated with 0.1% or 0.5% cysteamine for 3 months were reported to be normal.

Topical doses over 0.65 cysteamine HCl caused inflammation, thus higher clinical concentrations were not pursued. Oral cysteamine caused duodenal ulcers and perforation in rats.

Comment: The reviewers recommend approval from a pharmacology/toxicology perspective and have made labeling revisions.

5. Clinical Pharmacology/Biopharmaceutics

For details, see clinical pharmacology review by Dr. Yongheng Zhang. This review also provides details comparing the five formulations studies in clinical trials, including different concentrations, presence of preservative, and storage conditions.

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Formulations Used in Clinical Studies (from Dr. Zhang)

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

Per the Clinical Pharmacology Review dated 8/4/2010:

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

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

Comment: The reviewer recommends approval from the clinical pharmacology perspective; no phase 4 studies are requested.

6. Clinical Microbiology/Immunology

Not applicable

7. Clinical/Statistical-Efficacy

For complete details, see clinical reviews by Drs. Nevitt, Boyd, and Chambers and statistical review by Drs. Gamalo and Wang.

Cystaran is a sterile ophthalmic solution containing 6.5 mg of cysteamine hydrochloride, equivalent to 4.4 mg of cysteamine as the active ingredient. The clinical trials were done with multiple formulations (see above); the proposed marketed formulation is the same as

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Formulation 3 tested in these trials. The concentration reported as the cysteamine hydrochloride 0.65% is higher than the 0.44% concentration which is based on the active ingredient, cysteamine.

Three studies, mainly conducted or overseen by NIH/NEI were provided and summarized the experience with cysteamine since 1986; a detailed history of these is provided in the statistical review.

The earliest studies were placebo controlled (one eye drug, other eye placebo) but after an effect was seen with cysteamine in these trials, the placebo control was stopped. Subsequently, five different formulations with different characteristics and storage conditions were tested in comparative trials. In addition, patients with cystinosis who receive Cystaran topically will also be expected to receive the oral Cystagon (cysteamine bitartrate) Capsules. The adverse event profile of Cystagon Capsules is reflected in the approved labeling; the most frequent adverse reactions seen with the oral product involve the gastrointestinal and central nervous systems. Adverse reactions were not collected systematically, but were often listed by investigators. The adverse reaction rates may therefore be underestimated. The most common events (> 5%) were vomiting 35%, anorexia 31%, fever 22%, diarrhea 16%, lethargy 11%, and rash 7%. Less common events involving various organ systems are also listed in labeling.

Of the formulations tested by NIH, Sigma-Tau's product matches Formulation 3. A brief summary of the studies and results is provided below.

Study STP869294 (CAPTOC)

The development of cysteamine HCl was done at NEI from March 1986 until July 2005. Over the years, investigators evaluated different ophthalmic formulations and concentrations in patients (see tables above as well as statistical and clinical pharmacology reviews for details). NEI then conducted a combined analysis of all 247 patients treated with cysteamine HCl and refers to this overview as CAPTOC (Study STP869294).

The patients in this analysis had a clinical history consistent with cystinosis, could be receiving oral treatment with Cystagon (cysteamine bitartrate) Capsules, were from birth to 60 years in age, and had to be willing to comply with study procedures and have photographs of the cornea taken for evaluation.

The primary end point in these studies was a reduction in Corneal Cystine Crystal Score (CCCS) in eyes with high CCCS at baseline, and a lack of increase in CCCS in eyes with low CCCS 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 is ≥ 1.00 or CCCS does not increase by at least 1.00 unit at any time during the study when baseline CCCS is < 1.00 . This was assessed by slit lamp photography in conjunction with a photography-based scoring system. The scale went from 0 to 3.00 units, and slit-lamp photographs were evaluated in increments of 0.25 units.

Secondary efficacy variables included improvement in corneal haziness, photophobia, and foreign body sensation. Dark adaptation and color perception were also assessed.

The 247 patients evaluated over the years ranged from 0.2 to 49.6 years (mean 13.8 years) and included males and females. Race or nationality for these patients was not provided.

Protocol 98 EI0109E

This was a 1 year multicenter double masked trial to compare Formulation 3 (NEI) and Formulation 5 in patients with cystinosis. Sixteen patients between 2.7 and 12 years of age (mean age 6.49 years) being treated with Cystagon were enrolled, including male and female, all were Caucasian.

Protocol 98 EI0109S

This was a 6 month multicenter double masked trial to evaluate the safety of Formulation 5 in patients already on Formulation 3 (NEI) > 1 year of age. Twenty patients 6 to 28 years of age (mean 12 years) were enrolled, including male and female, all were Caucasian.

Literature Review

The clinical reviewer summarized the submitted publications reporting on the use of cysteamine eye drops. Some of the authors reported outcomes showing some promise of efficacy and safety with cysteamine, a few reported patient symptom improvements. When reported, the frequency of eye drop administration ranged from 3, 4, 5, and 6 or up to 8 times per day; more frequent administration seemed to result in better clinical response.

Results:

Based on the clinical studies and literature, cystine deposits in the eye of patients with cystinosis do not resolve spontaneously, and over time are associated with symptoms of photophobia, recurrent corneal erosions, secondary blepharospasm and loss of visual acuity.³ Per the clinical and statistical reviews, treatment with cysteamine resulted in improvement of 9% of patient eyes at 1 year, up to 30% at 6 years in STP869294. The response was 9/18 (50%) in study 98 EI0109S and 10/15 (67%) in study 98 EI0109E; Formulation 3 was effective compared to Formulation 5. Approximately 30-50% of patients with scores of ≥ 1 responded, and 13% to 33% of patients with scores of < 1 responded. The statistical review noted that patients with excellent compliance had a response of 42.1% and patients who were considered non-compliers had a response of 15.2% [page 6], therefore, strict adherence to treatment is important. The reviewer also noted that “*the reduction of CCCS can be transient at some time during the study and may not be maintained at the end of the study. In fact, among the 94 response eyes, there were only 22 eyes that had sustained reduction; the proportion of eyes with sustained response was 7.5% (95% CI: 4.5%, 10.6%) and the proportion of eyes with transient responses was 24.7% (95% CI: 19.8%, 29.7%).*”

Assessment of corneal haze, photophobia and foreign body sensation was done at baseline and annually. At baseline, 19%, 13% and 25% of patients had no symptoms (reported as “None”), and by year 6, 32%, 31%, and 55% of patients had scores of “None” for these categories, respectively.

³ Transient spontaneous resolution of 1 unit may be detected in 7% of follow-up examinations in a 12 month period, but is not sustained (Gahl, 2000)

NDA 200740 Cystaran (cysteamine ophthalmic solution) 0.44%

Indication: treatment of corneal cystine crystal accumulation in patients with cystinosis

Comment:

The clinical and statistical reviewers conclude that substantial evidence of safety and efficacy has been provided to support approval of the application.

8. Safety

See detailed safety review in the clinical reviews by Drs. Nevitt, Boyd and Chambers.

Patients in STP860294 had been treated for 5.8 ± 5.5 years, 4 patients had been treated for 19 years. The most common adverse reactions included photophobia (67%), conjunctival hyperemia (28%), ocular pain and irritation (19%). Less frequently events in 2% to 9% of patients included tearing, blurred vision, keratitis, dry eye, itching, blindness, blepharitis, eyelid erythema or edema.

Benign hypertension, potentially related to the oral cysteamine (Cystagon) was reported in 8 patients.

8.1 Safety Updates

From May 1, 2010 through December 30, 2011, a total of 112 cystinosis patients were exposed to cysteamine ophthalmic solution: 102 returning patients and 10 new patients. Adverse events (AEs) were reported in 69/112 (62%) patients. One patient died, this was a 23.7 year old female who had been on study for since 1989 (20 years), died of uremia and pericarditis and death was not considered related to drug.

One 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.

On August 24, 2012, the 120 Day Safety Update was submitted, and no new or unexpected information was found.

The labeling will state that in controlled clinical trials of six months to 19 years duration (b) (4) in approximately 300 patients, the most frequently reported ocular adverse reactions occurring in $\geq 10\%$ of patients were sensitivity to light, redness, and eye pain/irritation, headache and visual field defects.

Comment:

The safety information from the clinical trials will be reflected in the labeling.

9. Advisory Committee Meeting

The application was not presented before an Advisory Committee; there were no scientific issues that were considered to need the input of the Advisory Committee.

10. Pediatrics

Pediatric patients were included in the trials that established the safety and efficacy of the product.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection – OBP and OC

During the first review cycle, OC found that manufacturing facilities were not in compliance; specifically the Hi-Tech plant involved in the manufacture of the DP was out of compliance as was the (b) (4) DS facility. During the current cycle, re-inspection of the Hi-Tech plant was in compliance with cGMP, however, the inspection of the newly-added Sigma-Tau facility was out of compliance. During a teleconference on September 18, 2012, the applicant was informed that there were outstanding cGMP violations identified at the Sigma-Tau facility that precluded approval of the application, but the applicant confirmed that the Hi-Tech facility made DP and was in compliance. Therefore, the applicant withdrew the Sigma-Tau facility from the application, but retained the Sigma-Tau facility to serve as the endotoxin testing site. It was noted during the telecon that once the 483 violations were addressed, the applicant could add the Sigma-Tau facility as a DP manufacturer as a CMC supplement, and as part of the review FDA would re-inspect the facility. The new (b) (4) facility in lieu of the (b) (4) facility for DS manufacture was acceptable. Dr. Linda Ng of OC recommended that facilities were Acceptable.

11.2 Office of Scientific Investigation (OSI) Audits

The protocols inspected were Protocol 98-EI-0109E, Protocol 98-EI-0109S, and Protocol STP869294. Two domestic clinical investigators, Drs. Gahl and Monte, and the applicant and CRO were inspected. OSI found that the efficacy and safety data were generally considered reliable, and some questions regarding missing data and discrepancy in drug bottle counts were discussed with the reviewers. Based on the discussions and consideration of additional data (diaries, drug records, and patient questionnaires), the missing data and bottle count the reviewers recommended that the discrepancies are not expected to impact the safety evaluation and risk/benefit considerations. The inspections of the applicant, Sigma-Tau, and the contract research organization, (b) (4) were classified as NAI.

11.3 Debarment certification

Sigma-Tau Pharmaceuticals, Inc. (STP) certified that they did not or will not use services of any debarred individual [as required under FD&C Act Section 306]. In addition, no person affiliated with the application was convicted of an offense under the same section.

11.4 Financial Disclosure

Per Form 3454, listed clinical investigators did not have covered financial arrangements with the applicant, no equity interest or received significant payments.

11.5 Other Regulatory Issues

The application was issued a *Complete Response* letter in the first cycle due to noncompliance with cGMP at the manufacturing sites. These issues were resolved in this review cycle.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the discipline reviewers, DMEPA, DRISK, and OPDP/DPDP. A decision was made that a patient package insert was not needed since there was nothing new or novel to administering this topical eye drop.

- **Package insert (PI):** The PI is written in PLR format and has been reviewed and appropriate revisions incorporated.
- **Carton and Container Labels:** The labels are acceptable.
- **Proprietary Name:** After rejecting the name “Cystoran” because it was found unacceptable [REDACTED] (b) (4) [REDACTED] DMEPA found the name “Cystaran” conditionally acceptable as stated in the letter issued August 12, 2010 and a second letter July 5, 2012 (which is within 90 days of the PDUFA goal date of October 2, 2012).

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The manufacturing facility deficiencies included in the September 3, 2010 *Complete Response* letter have been addressed. As noted in Section 11.1 of this document, all facilities are in compliance and a recommendation of Acceptable has been issued by OC.

The safety and efficacy of the product based on adequate and well-controlled studies was established during the original review and is reflected in the Sections 7 and 8 of this document. The labeling was commented on by all disciplines and consulting groups. In the current review cycle, the new items included the resolution of the manufacturing deficiencies and the safety update.

All disciplines recommend approval of the application, labeling has been completed, and there are no outstanding issues. The application will be issued an *Approval* letter.

13.2 Recommendation for other Postmarketing Requirements and Commitments

None

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

/s/

RENATA ALBRECHT
10/02/2012