

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 200-740
Supporting document/s: 1
Applicant's letter date: 3/4/2010
CDER stamp date: 3/4/2010
Product: Cystaran™ (cysteamine hydrochloride
ophthalmic solution) 0.65% Sterile
Indication: Treatment of corneal cystine crystal
accumulation in cystinosis patients.
Applicant: Sigma-Tau Pharmaceuticals, Inc.
Review Division: DAIOP
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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, the application is approvable.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Results of nonclinical studies for the ophthalmic solution and the degradant consisted of either negative findings or findings of irritation and/or inflammation. The Applicant has included (b) (4) which should be removed. Discussion of (b) (4) are not relevant to the proposed drug product and should be removed as well. Any relevant information regarding ocular irritation or inflammation due to the drug product should come from clinical studies data. However, (b) (4) The remainder of the label should be consistent with that for the reference listed oral product, Cystagon, as this drug is likely to be used in addition to the oral product. Wording should be as specified in 21 CFR 201.57.

The following wording is recommended (based on the most recent draft labeling from supporting document 0007):

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies of ophthalmic cysteamine in pregnant women. **Cystaran should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.**

The following information is from the oral cysteamine product:

Teratogenic Effects: Pregnancy Category C

Teratology studies have been performed in rats at oral doses in a range of 37.5 to 150 mg/kg/day (about 0.2 to 0.7 times the recommended human maintenance dose on a body surface basis) and have revealed cysteamine bitartrate to be teratogenic and fetotoxic. Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly, and exencephaly.

(b) (4)

8.3 Nursing Mothers

The following information is from the oral cysteamine product:

It is not known whether oral cysteamine is excreted in human milk. Because many drugs are excreted in human milk and because of the manifested potential of cysteamine for developmental toxicity in suckling rat pups when it was administered to their lactating mothers at an oral dose of 375 mg/kg/day (2,250 mg/m²/day, 1.7 times the recommended human dose based on body surface area), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (b) (4)

[Reviewer's comment: (b) (4) which is pending for NDA 20-392 for Cystagon, should be added to both labels following Agency review.]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.

Cysteamine was not mutagenic in the Ames test. It produced a negative response in an *in vitro* sister chromatid exchange assay in human lymphocytes but a positive response in a similar assay in hamster ovarian cells.

Repeat breeding reproduction studies were conducted in male and female rats. Cysteamine was found to have no effect on fertility and reproductive performance at an oral dose of 75 mg/kg/day (450 mg/m²/day, 0.4 times the recommended human dose based on body surface area). At an oral dose of 375 mg/kg/day (2,250 mg/m²/day, 1.7 times the recommended human dose based on body surface area), it reduced the fertility of the adult rats and the survival of their offspring.

(b) (4)

1.2 Brief Discussion of Nonclinical Findings

Studies of cysteamine HCl 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 was 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 following ocular administration of cysteamine 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.

2 Drug Information

2.1 Drug – Cystaran™ (cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

2.1.1 CAS Registry Number

156-57-0 (cysteamine HCl)
60-23-1 (cysteamine free base)

2.1.2 Generic Name

Cysteamine hydrochloride

2.1.3 Code Name

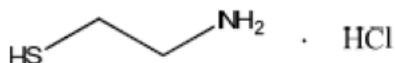
CST
031

2.1.4 Chemical Name

2-Amino-ethanethiol hydrochloride, or
2-Mercaptoethylamine hydrochloride

2.1.5 Molecular Formula/Molecular Weight

Molecular Formula: C₂H₇NS HCl
Molecular Weight: 113.61
77.15 (free base)

2.1.6 Structure**2.1.7 Pharmacologic class**

Aminothiols

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 40,593
NDA 20-392 – Cystagon capsules, reference listed drug

2.3 Clinical Formulation**2.3.1 Drug Formulation**

(Formulation 3)

Component	Amount
Cysteamine	0.65%
Sodium chloride	(b) (4)
Benzalkonium chloride (BAK)	0.01%

The vehicle is purified water, USP.

The pH is adjusted to (b) (4) using HCL and/or NaOH. (b) (4)

2.3.2 Comments on Novel Excipients

N/A

2.3.3 Comments on Impurities/Degradants of Concern

Cysteamine disulfide (cystamine, a dimer) is a degradant formed upon oxidation of the drug substance in solution at room temperature. It was tested for efficacy in patients with negative results. The specification for this degradant in the drug substance is \leq (b) (4) and the Applicant states that it has been qualified at or above that level in clinical trials. In the drug product, this impurity is controlled up to an absolute value of (b) (4) (specification of (b) (4) of the labeled amount of cysteamine HCl (0.65%). The Applicant states that it was qualified in the rabbit ocular toxicity study performed by NEI at concentrations up to (b) (4) cystamine for one month. The NOAEL in that study was (b) (4), so the degradant was only qualified at (b) (4) however, the specifications for this impurity in the drug product are below this value.

Residual solvents in the drug substance include (b) (4). All three are controlled with a specification of not more than (b) (4), which appears to be consistent with ICH Q3C.

The specifications for the drug product also include (b) (4) unspecified impurities.

2.4 Proposed Clinical Population and Dosing Regimen

The drug product is to be administered as one drop to both eyes daily once every waking hour in children and adults with cystinosis for the treatment (b) (4) of corneal cystine crystal accumulation.

2.5 Regulatory Background

Cystagon® (cysteamine bitartrate) capsules are approved as an oral treatment for cystinosis. The current application is filed under the provisions of Section 505(b)(2), with Cystagon® capsules as the reference listed drug (NDA 20-392). The current drug product has orphan drug designation and has been granted a priority review. The originally proposed drug name, Cystoran™, was deemed not acceptable by the Agency and was withdrawn. The currently proposed trade name at the time of completion of this review is Cystaran.

3 Studies Submitted

3.1 Studies Reviewed

1. Study no. 97G-1828: 30 day ocular safety study in rabbits
2. NEI January 1994 memo describing a 30-day toxicology study in rabbits of the impurity cysteamine disulfide (cystamine)

3. Kaiser-Kupfer MI *et al.* Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. N. Eng. J. Med. 316:775-779, 1987
4. Jain S *et al.* Range of toxicity of topical cysteamine in rabbit eyes. J. Ocul. Pharmacol. 4(2):127-131, 1988.

3.2 Studies Not Reviewed

Seventy-two additional literature references are provided, but are not reviewed in detail. Where appropriate, information discussed below is based on the Applicant's summaries.

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Patients with the autosomal recessive lysosomal storage disease, cystinosis, lack a functional cystine carrier, resulting in intracellular accumulation of cystine. Cysteamine is an aminothiols that converts cystine to cysteine and cysteine-cysteamine mixed disulfide, both of which can pass through the lysosomal membranes without a functional carrier, and both of which can then be eliminated from the cells of patients with cystinosis. Orally administered cysteamine does not reach the cornea due to lack of blood supply to corneal stromal cells, and does not prevent the ophthalmic complications of cystinosis, including corneal crystals, photophobia, blepharospasm, and eye pain. The Applicant states that cysteamine, topically applied to the eye, will mitigate ocular effects of cystinosis. (n.b. The target clinical population will likely be treated with both the oral and ophthalmic drug products.)

The Applicant cites references of published studies demonstrating that cysteamine can deplete some cells of more than 90% of excess cystine content.

4.2 Secondary Pharmacology

The Applicant cites additional references indicating that cysteamine has protective effects against oxidative injury as a scavenger of free radicals and its protective effect against ionizing radiation. They further state that it is generally accepted that sulfhydryl compounds, such as cysteamine, cysteine, and glutathione, can protect mammalian cells from oxidative damage.

An *in vitro* study demonstrated a small decrease in aqueous outflow via the trabecular meshwork following perfusion of calf eyes with 10 mM cysteamine. However, if eyes

were pretreated with BCNU and 10 mM diamide, perfusion of cysteamine resulted in a large increase in outflow. In pig retina *in vitro*, cysteamine prevented and reversed inhibition of creatine kinase by cystine.

4.3 Safety Pharmacology

No new safety pharmacology studies were performed. The following is based on the Applicant's summary of referenced published studies.

Nervous and Endocrine Systems

Cysteamine was shown to disrupt the neuroendocrine systems involved in the regulation of growth hormone, thyroid-stimulating hormone, and corticosterone secretion. Cysteamine was also shown to lower hypothalamic somatostatin.

Cysteamine affects neuroendocrine regulation of monoamines as well as circulating hormones. Cysteamine was shown to block the synthesis of norepinephrine and epinephrine, through its inhibitory effect on dopamine- β -hydroxylase (DBH). No effect was reported on serotonin or dihydroxyphenylalanine levels. Cysteamine had differential effects on growth hormone (GH) depending on the dose administered. Low-dose cysteamine (100 mg/kg) caused an increase in resting mean plasma growth hormone levels, and partially blocked stress-induced growth hormone suppression, while the high dose (300 mg/kg) had no effect. However, the post-stress increase in plasma growth hormone was blocked by high dose cysteamine, but not by the low dose. Cysteamine treatment resulted in increased resting thyroid-stimulating hormone (TSH) plasma concentrations that were not changed by stress. However, similar to the case for growth hormone, post-stress increases in TSH were blocked by high dose cysteamine.

Intravenous administration of cysteamine was shown to result in hemorrhagic necrosis of the adrenal gland in the rat. This effect was associated with an increase in adrenal dopamine and norepinephrine concentrations, which the Applicant speculates may have resulted in the adrenal damage observed.

Cysteamine also rapidly reduced prolactin concentrations, both *in vitro* and *in vivo*, in pituitary tissue and serum, with the effects being dose-dependent and reversible.

Cysteamine was shown to deplete somatostatin-like immunoreactivity in a dose-dependent manner in the gastrointestinal tract and hypothalamus in rats. The effect was slowly reversible. The Applicant notes that somatostatin inhibits the release of GH and TSH. Intraocular administration of cysteamine to Dutch Belted rabbits resulted in decreased somatostatin-like immunoreactivity in the eye.

Cataract development was observed when cysteamine was administered to neonatal rats.

Behavioral studies have led to the hypothesis that disruption of somatostatinergic transmission, as evidenced by sustained elevated levels of hippocampal and hypothalamic somatostatin in rats treated with repeated doses of cysteamine, leads to decreased cognitive function in rats. Locomotor function generally was not affected. Persistent gliopathic effects were noted in the hippocampus of treated animals. Other studies demonstrated reversible inhibition or no inhibition of active avoidance behavior,

impaired passive avoidance behavior with decreased retention or no effect on passive avoidance, hyperactivity followed by hypoactivity, inhibition of discrimination learning, induction and suppression of kindled seizures. Results appeared to be dependent on the timing of testing following administration of cysteamine. In general, it was hypothesized that disruption of somatostatinergic transmission affects cognitive function in rats.

The Applicant states that central nervous system effects reported in patients taking oral cysteamine include headache and encephalopathy. Uncommon reports of somnolence and convulsions have also been observed.

Cardiovascular system

Effects on the cardiovascular system in rats have included degeneration of elastic fibers, leading to aortic aneurysm and rupture following treatment with cysteamine for 6 months. (That same study noted adverse effects on the skeleton, including effects on the spine.) The Applicant states that similar effects have not been reported from the clinical literature following several years of dosing in humans and that effects related to the cardiovascular system have only rarely been reported in patients receiving cysteamine.

Renal system

The Applicant states that no toxic effects of oral cysteamine on the renal system were reported following repeat-dose administration to pregnant rats. Histopathological evaluation revealed no adverse effects on renal structural development, even in kidneys from fetuses with growth retardation and malformations.

Gastrointestinal system

In animal studies, oral cysteamine administration rapidly produced perforating duodenal ulcerations that could be prevented by the administration of somatostatin. The mechanism of this effect was thought to be the reduction in somatostatin and marked increase in serum gastrin and gastric acid secretion. Decreased gastric emptying and motility also were suggested as being involved in the gastrointestinal effects observed. The Applicant states that potential for duodenal and gastric ulcerogenic effects has been observed following oral and parenteral administration in rodents but not in monkeys. The Applicant states that effects on the gastrointestinal tract have been reported in patients receiving cysteamine and consist primarily of vomiting, nausea, diarrhea, abdominal pain, breath odor, dyspepsia, and gastroenteritis, as well as, less commonly, gastrointestinal ulcers.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The Applicant indicates that there has been no systemic exposure documented following ocular administration of cysteamine in nonclinical studies. They further state

that clinical data have suggested that ocularly administered cysteamine does not penetrate into the aqueous humor of the eye.

The Applicant also states that, even if assuming 100% bioavailability from the proposed clinical ophthalmic dose, the theoretical plasma concentration observed would be 1.7 µg/mL cysteamine. They further state that this exposure level is less than the concentrations that have been observed following oral administration of the approved reference product, Cystagon. Additionally, the combination of ocular and oral cysteamine has been administered clinically with no potentiation of adverse effects of the oral drug following the addition of ophthalmic cysteamine administration. They conclude that ocular cysteamine administration should not pose a significant safety risk to cystinosis patients.

Some of the summarized published references dealt with pharmacokinetics of cysteamine in nonclinical species:

In pregnant Wistar rats administered 100 mg/kg PO, clearance was altered as compared to non-pregnant animals. Fetal exposure was demonstrated by fetal plasma drug concentrations which exceeded maternal concentrations and neurological effects on the offspring.

Following oral administration of radiolabeled cysteamine to mice, peak organ exposure was within 6 hours and was highest in liver, small intestine, pancreas, and kidney. Lower peak concentrations were noted in heart, lungs, testes, spleen, brain, muscle, and bone marrow, and peaks were seen later (at 12-48 hours) in lungs, testes and bone marrow.

In mice, urinary excretion included equal amounts of parent cysteamine and metabolites taurine and sulfate, plus smaller amounts of cystamine. The Applicant also states that six urinary metabolites were identified in mice following oral administration. Regional metabolism in the brain of the rat has been investigated. In the dog, following an intravenous dose of radio-labeled cysteamine, approximately 4-5% of the administered drug was excreted unchanged in the urine, mostly in the first 2 hours post-administration. The Applicant states that the bulk of cysteamine in clinical patients is excreted as sulfate, and that effects of mortality and growth reduction in nursing rat pups of treated dams suggest that cysteamine is excreted in milk.

The Applicant states that there has been no systemic exposure of cysteamine following ocular administration reported in nonclinical species, but it does not appear that there has been pharmacokinetic monitoring in those species after ocular administration.

6 General Toxicology

6.1 Single-Dose Toxicity

In single dose studies in rodents to support orally administered cysteamine, decreased motor activity and generalized hemorrhage in the gastrointestinal tract and

kidneys were observed. The Applicant states that the gastrointestinal tract was considered to be the main target organ of toxicity in these studies.

6.2 Repeat-Dose Toxicity

1. Study title: 30-day ocular safety study in rabbits – sponsor specified

Study no.:	97G-1828
Study report location:	Electronic submission, section 4.2.3.2.1
Conducting laboratory and location:	Toxikon Corporation, Bedford, MA
Date of study initiation:	Not provided; amended report date 5/18/98
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Cysteamine HCl Ophthalmic solution 0.55%, lot no. 702-032, purity not provided

Key Study Findings

No signs of irritation or corneal disruption were seen at the only dose tested, 0.55%. No remarkable ocular histopathological findings were reported.

Methods

Doses:	Control eye drops or cysteamine HCl ophthalmic solution 0.55%
Frequency of dosing:	Hourly for 8 consecutive hours daily for 30 days
Route of administration:	Topical to the cornea of the eye
Dose volume:	2 drops
Formulation/Vehicle:	Not specified in report; elsewhere in the application it is stated to be Formulation 5, 0.55% cysteamine (b) (4)
Species/Strain:	New Zealand White rabbits (non-naïve)
Number/Sex/Group:	12/sex
Age:	10-12 weeks
Weight:	2.2-2.6 kg
Satellite groups:	None
Unique study design:	The test article was applied to the right eye of each animal, and the control was applied to the left eye.
Deviation from study protocol:	None reported

Observations and Results

Mortality

There were no deaths.

Clinical Signs

Animals were observed for clinical signs daily. Eyes were examined twice daily by a toxicologist and rated for ocular irritation using the Draize scale.

No clinical signs were reported. No signs of ocular irritation were reported in test or control eyes.

Body Weights

Animals were weighed on Day 1 and Day 30. All animals gained weight over the course of the study.

Ophthalmoscopy

Prior to treatment and on the fifth and thirtieth days of treatment, eyes were examined with a slit lamp and fluorescein staining. No signs of irritation or fluorescein staining were reported.

Gross Pathology

On Day 30, at least 8 hours following the end of treatment, animals were euthanized by injection (agent not specified). No gross necropsy was performed.

Histopathology

Adequate Battery

Eyes were collected and placed in 10% formalin. The cornea, conjunctivae, iris, retina, and optic nerves were prepared for microscopic evaluation.

Peer Review

No

Histological Findings

No remarkable findings were reported.

Stability and Homogeneity

The stability report indicates that the drug substance (b) (4)

2. Study title: Ocular toxicity of cysteamine disulfide in rabbits

Study no.:	Not provided
Study report location:	Electronic submission, section 4.2.3.7.6.1
Conducting laboratory and location:	National Eye Institute, NIH, Bethesda, MD
Date of study initiation:	Not provided; memo date is 1/27/94
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Cysteamine disulfide, no other information provided

Key Study Findings

The study appeared to have been limited to assessment of ocular irritation. Adverse reactions were dose related in incidence, severity, and duration. Trace to moderate conjunctivitis was seen in all groups, but no statistically significant differences were noted by T-test. That assessment excluded the one early decedent in which both eyes were treated with 2% cysteamine disulfide and exhibited marked conjunctivitis. Blepharitis was seen in test article-treated groups only, with the highest incidence and severity (moderate) at the high dose (2%). The high dose was statistically different from the other treatments for blepharitis. Findings at the mid-dose, 1.0% cysteamine disulfide, were slight to mild. Findings at the low dose, 0.5%, were similar to vehicle control.

Methods

Doses:	2 drops per eye of vehicle control (0%), 0.5%, 1.0%, or 2.0% cysteamine disulfide
Frequency of dosing:	Hourly for 8 consecutive hours, 7 days per week for 4 weeks
Route of administration:	Topical to the eye
Dose volume:	2 drops (approximately 0.1 mL)
Formulation/Vehicle:	“Benzalkonium chloride 1:10,000 in sodium chloride”
Species/Strain:	Rabbit; strain not provided
Number/Sex/Group:	There were 4 different treatments, and 12 animals/sex, for a total of 48 eyes. Treatment was randomized by eye, therefore each animal could receive a control and test article treatment, or two different test article treatments. The number of eyes treated in each group were 13 for control, 12 for 0.5% cystamine, 11 for 1% cystamine, and 12 for 2% cystamine.
Age:	Not provided
Weight:	Not provided
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None reported

Observations and Results

Mortality

Rabbit no. 16 had marked lid reactions in both eyes and was euthanized in the second week. Both eyes of that animal were treated with the high dose (2%).

Clinical Signs

Ocular observations were made weekly by NEI clinical ophthalmologists. External ocular photography was performed. Ophthalmoscopy does not appear to have been performed.

Beginning in the second week of administration, inflammation of the eye lids was noted, with dose-related incidence and severity.

In the high dose-treated eyes, a total of 10 of 12 eyes showed adverse reactions. At Week 2, 7 of 12 had reactions ranging from very slight congestion in the eyelid margin to marked hyperemia, accompanied by erosion, scabbing or hair loss of the eye lid. Rabbit no. 16 had marked lid reactions in both eyes (both treated with the 2% concentration of the test article) and was euthanized. Treatment was discontinued for a

third eye exhibiting a marked reaction. Of the 9 remaining eyes in that group, 4 exhibited slight to moderate reactions in Week 3. Treatment was discontinued for the moderately inflamed eye. Of the remaining 8 eyes, 5 exhibited slight to moderate reactions in Week 4.

In mid-dose treated eyes, a total of 4 of 11 eyes showed adverse effects. Two of 11 eyes exhibited mild hyperemia of the eye lid at Weeks 2 and 3. By the fourth week, 2 of 11 eyes exhibited very slight congestion in the eyelid margin.

In low dose treated eyes, 3 of 12 eyes exhibited trace or mild hyperemia of the eyelid at Weeks 2 and/or 3.

Findings in the control group were limited to trace or mild hyperemia of the eyelid in 1 of 13 eyes at Weeks 2 and 3.

Histopathology

Adequate Battery

Ocular tissues were examined at the end of 4 weeks. This was adequate for this test article as used. However, examination did not include more than the surface of the eye.

Peer Review

Unknown

Histological Findings

Rabbit no. 16 had marked lid reactions in both eyes (both treated with the high dose) and was euthanized in the second week; histopathology of the eyelids and conjunctivae was performed at that time. Histopathological findings in both eyes were of marked conjunctivitis and mild to moderate blepharitis.

Rabbits #9 and #2 (both treated with the high dose) developed blepharitis and had eyelid biopsies performed in the second and third week, respectively (left eyes only). Biopsies revealed moderate blepharitis in both sampled eyes. Duplicate tissue samples were collected from these eyes at the end of the study in which blepharitis appeared to have resolved.

The remaining animals were euthanized at the end of the 4 week study, and histopathology of the eyelids and conjunctivae in those animals was performed at that time. Pathological findings were reported as grading for conjunctivitis and blepharitis. In general, findings were dose-related in incidence and severity. Conjunctivitis was seen in all groups, while blepharitis was seen in test article-treated groups only. Conjunctivitis was most often seen in the tarsal conjunctiva, but involved other areas in a few of the test article-treated eyes and was diffuse in two high dose-treated eyes.

In the high dose group, all 12 eyes exhibited pathological findings of conjunctivitis at the time of necropsy, ranging from trace to moderate at the end of the study, and graded as marked for the two eyes from early decedent no. 16. Pathological findings of moderate blepharitis were noted in the two eyes from early decedent no. 16, as well as

those from rabbit nos. 2 and 9 at earlier biopsy, but not from the latter two at the end of the study. In the remaining 8 eyes, five had pathological findings of trace to moderate blepharitis at the end of the study.

In the mid-dose group, 8 of 11 eyes exhibited pathological findings of conjunctivitis, ranging from mild to moderate. Only three of those eyes exhibited pathological findings of blepharitis, graded as mild.

In the low dose group, 9 of 12 eyes exhibited pathological findings of conjunctivitis, ranging from trace to moderate. Only two of those eyes exhibited pathological findings of blepharitis, graded as trace.

In the control group, 11 of 13 eyes exhibited pathological findings of conjunctivitis, ranging from trace to moderate. None of those eyes exhibited pathological findings of blepharitis.

Statistical analysis was by T-test. There were no significant differences noted for conjunctivitis, but the high dose was statistically different from the other treatments for blepharitis.

Studies from the published scientific literature

1. Kaiser-Kupfer MI *et al.* Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. *N. Eng. J. Med.* 316:775-779, 1987

As a preliminary experiment to a clinical study, the authors investigated 0.11% (10 mM) and 0.55% (50 mM) cysteamine eye drops prepared under sterile conditions in normal saline without preservatives. The test article was applied to one eye in 8 albino rabbits every hour for 8 hours daily for 21 days, while normal saline drops were applied to the other eye. The animals were examined daily for conjunctival injection and other adverse ophthalmologic effects. At the end of the study, the ocular tissues were examined histologically. No differences between test article-treated eyes and saline control eyes were reported.

2. Jain S *et al.* Range of toxicity of topical cysteamine in rabbit eyes. *J. Ocul. Pharmacol.* 4(2):127-131, 1988.

In a series of three experiments, the authors investigated multiple concentrations of cysteamine eye drops prepared under sterile conditions in normal saline without preservatives, administered every hour for 8 hours daily. In the first experiment, 5% cysteamine eye drops were applied to the left eye and 10% cysteamine eye drops were applied to the right eye of 10 albino rabbits. In this experiment, dosing of the 10% cysteamine eye drops was discontinued after 10 days, while dosing of the 5% test article was continued for 4 weeks. In the second experiment, concentrations of 1% and 2% were applied to the right and left eyes, respectively, of 10 albino rabbits as described above for 4 weeks. In the third experiment, concentrations of 0.1% and 0.5% were applied to the right and left eyes, respectively, of 18 albino rabbits for 3 months. The animals were examined daily for conjunctival injection and other adverse ophthalmologic effects. External ocular photography was performed to document any changes. At the end of the study, ocular tissues were examined histologically.

Adverse effects at the 10% concentration resulted in discontinuation of that dose after 10 days of treatment. Five of the 10 eyes at that concentration had mild to moderate hyperemia and thickening of both upper and lower eye lids. These findings resolved within 7-10 days after cessation of treatment. No clinical signs were reported at any of the lower concentrations. On microscopic examination, findings of inflammatory reaction were limited to lymphocytic infiltration of the limbal subepithelial connective tissue in eyes completing the course of treatment. This was graded as moderate to marked in 3 of 10 eyes treated with 5% cysteamine, mild in 3 of 10 eyes treated with 5%. 6 of 10 eyes treated with 2%, and 4 of 10 eyes treated with 1% cysteamine. Findings were considered to be normal in 4 of 10 eyes each at 2% and 5% cysteamine and in 6 of 10 eyes treated with 1% cysteamine, as well as all eyes (18) treated with 0.1 or 0.5% cysteamine for 3 months. In the eyes treated with 10% cysteamine for 10 days that were examined histologically 2.5 weeks after discontinuation of treatment, the only change noted was mild neovascularization in the peripheral cornea. Otherwise, at all test article concentrations, the corneal epithelium was reported to be normal, and intraocular tissues were negative for any pathological changes.

Additional information from the Applicant's summary:

Gastric and duodenal ulcers were observed following single and repeat subcutaneous administration of ≥ 200 mg/kg in rats.

The oral toxicity of cysteamine was evaluated in a 13 week (feeding) rabbit study (100 mg/kg/day), a 4 week study in two monkeys (150 mg/kg/day), and a 1 year study in five monkeys (20-150 mg/kg/day). The Applicant states that no gastrointestinal effects were observed in these studies; however, the no observed effect level could not be established. Bone marrow effects were observed in another 9 week rabbit study and in the 1 year monkey study. Other studies in rats confirmed the potential for duodenal and gastric ulcerogenic effects and cataract development. In addition, it has been reported that oral administration of cysteamine in rats rapidly and selectively depletes the gastrointestinal tract, hypothalamus, and plasma of immunoreactive somatostatin.

A dose range-finding study was conducted in nonpregnant Wistar rats to establish the doses for a reproductive and developmental toxicity study. Five female Wistar rats per group were administered 0, 75, 150, 225, 300, and 375 mg/kg/day cysteamine (as phosphocysteamine) PO in a 10% (w/v) aqueous solution for 4 days. Statistically significantly decreased body weight and food consumption were observed at 375 mg/kg/day on Day 4 and at ≥ 300 mg/kg/day on Day 5, with a trend toward decreased body weight apparent at 225 mg/kg/day. At termination on Day 5, inflammation of the duodenum with small focal mucosal hemorrhages was observed in two 375 mg/kg/day rats. Corresponding microscopic findings included increased lymphocyte proliferation in the lamina propria, and focal inflammation, increased lymphocyte proliferation, and congestion in the mucosa. The NOAEL appeared to be 225 mg/kg/day.

A study in Wistar rats, in which 3 mg/day cysteamine was administered in the drinking water, demonstrated skeletal and cardiovascular toxicity. Vertebral bodies were collapsed at the thoracolumbar junction and the midthoracic region, resulting in

kyphosis. Longitudinal dissection of the aorta was seen grossly; degeneration of elastic fibers led to aortic aneurism and rupture.

Cysteamine has also been shown to induce hemorrhagic adrenocortical necrosis in the rat. It has been hypothesized that the pathogenesis of this lesion is related to depletion of glutathione and increased dopamine concentration in the adrenals, followed by capillary endothelial damage, embolization, and hemorrhage into the adrenal cortex.

Cysteamine has been shown to stimulate accumulation of peroxidase-positive inclusions in cultured astroglial cells. Cysteamine was also said to induce the synthesis of a stress protein (heme oxygenase) in rat liver, and it has been hypothesized that this may also be the mechanism of biogenesis of these inclusions.

7 Genetic Toxicology

No new genetic toxicity studies were performed.

Cysteamine HCl was described as negative in the Ames bacterial reverse mutation assay and the *Saccharomyces* mitotic gene conversion assay. A rat liver chromosome assay was described, using an RL₁ epithelial-type cell line from a 10-day old (b) (4) rat, which was positive for a variety of chromatid and chromosomal aberrations following exposure to 5-400 µg/mL cysteamine HCl.

Cysteamine treatment resulted in dose-related increased incidence of sister chromatid exchange (SCE) in cultured Chinese Hamster Ovary (CHO) cells, with a peak frequency at 10⁻⁴M. Addition of copper ion enhanced this effect. The Applicant states that copper ion is known to catalyze the auto-oxidation of thiols, and that the SCE induction by thiols is assumed to be due to the formation of hydrogen peroxide. In contrast no significant SCE induction was found in an experiment in human lymphocytes. In cultured Chinese hamster V79 cells, catalase inhibited SCE induction by cysteamine and by hydrogen peroxide.

An *in vivo* assay was conducted in the Chinese hamster. No increase in the frequency of chromosomal aberrations was seen in bone marrow cells at 6 or 24 hours following 2 days of dosing with 100 or 200 mg/kg cysteamine. Similarly, cysteamine bitartrate was stated to be negative in the mouse micronucleus assay.

8 Carcinogenicity

No carcinogenicity studies have been performed for cysteamine.

9 Reproductive and Developmental Toxicology

No new studies to evaluate the potential of cysteamine for reproductive and developmental toxicology have been performed. The Applicant provides the following information from the scientific literature and for the approved product Cystagon.

9.1 Fertility and Early Embryonic Development

No evidence of impairment of fertility or reproductive performance was observed in male and female rats following oral administration of 75 mg/kg/day (HED = 12.5 mg/kg) cysteamine. The fertility of adult rats and the weight gain and survival of offspring were reduced following oral administration of 375 mg/kg/day (HED = 62.5 mg/kg) cysteamine.

9.2 Embryonic Fetal Development

The Applicant notes that embryofetal effects have been observed in rats at 100 mg/kg/day and in rabbits at 50 mg/kg/day (HED \approx 16 mg/kg for both), however, neither data nor details from a rabbit study were provided. (Reviewer's comment: (b) (4) appears to be pending for NDA 20-392 for Cystagon.) The reported NOAEL in rats was 75 mg/kg/day (HED \approx 12.5 mg/kg/day). Adverse effects in rats included intrauterine death, intrauterine growth retardation, and developmental anomalies. Teratogenic effects included cleft palate, kyphosis, rib and vertebral anomalies, heart ventricular septal defects, microcephaly, and exencephaly.

9.3 Prenatal and Postnatal Development

Pre- and post-natal developmental toxicology studies have been performed to specifically examine effects on the central nervous system and the kidney. Doses up to 75 mg/kg/day did not affect development of kidney function in the rat. A dose of 100 mg/kg/day to rats resulted in a delayed onset of the auditory startle reflex in pups. Pregnancy altered clearance of cysteamine in maternal circulation. Peak fetal plasma concentrations were seen 1 hour following the maternal peak and fetal peak concentrations "greatly exceeded" maternal concentrations. Fetal brain somatostatin was decreased for up to 8 hours post-dose.

Developmental toxicity (reduced growth, increased mortality) in suckling offspring was observed when 375 mg/kg/day cysteamine was orally administered to the lactating dams. Studies *in vitro* and *in vivo* demonstrated that cysteamine rapidly reduced prolactin concentration in pituitary tissue in a dose-dependent and reversible fashion. A study of daily subcutaneous injections of cysteamine to neonatal rats revealed delayed growth, eye opening, and sexual development in pups. Dense bilateral cataracts developed that were evident at eye opening and were permanent. The cataracts were not observed when cysteamine administration was delayed until post-natal day (PND) 10, or when cysteamine was administered to adult rats. It was hypothesized that the mechanism of cataract formation was by cysteamine induction of protein cross-linking by abnormal disulfide bonds.

10 Special Toxicology Studies

The ophthalmic solutions were considered to be non-irritating following ocular administration every hour, 8 consecutive hours daily, of either Cysteamine Hydrochloride Ophthalmic Solution 0.55% (treated) or placebo for Cysteamine Hydrochloride 0.55% Ophthalmic Solution (untreated) in albino rabbits for 30 days (see repeat dose toxicity study reviewed above above).

The Applicant cites a published mechanistic study in which the cytotoxicity of cysteamine was investigated. It was shown that cysteamine produces hydrogen peroxide and inhibits glutathione peroxidase. Cysteamine appeared to stimulate production of cellular glutathione, but this may reflect an accumulation of cysteamine to levels that inhibit glutathione peroxidase.

Oral or subcutaneous administration of cysteamine resulted in acute perforating duodenal ulcers in a published study in rats. A single oral dose of 100 mg resulted in 70% mortality within 48 hours with all animals exhibiting evidence of duodenal ulcers. A dose of 100 mg SC was immediately lethal, while 50 mg SC resulted in 70% mortality within 48 hours, with perforating ulcers seen in half of the animals. Another study demonstrated a specific decrease in total duodenal mucosal HCO₃-ATPase activity in cysteamine-treated rats that was not seen in other segments of the intestines. This and a decrease in carbonic anhydrase activity were transient and associated with ulcer formation. Additional studies in rats: 1) demonstrated depression of sympathetic innervation and increased parasympathetic fiber activity associated with cysteamine-induced ulcers, 2) suggested that the hepatoduodenal branch of the vagus nerve may play a role in cysteamine-induced duodenal ulcers, 3) demonstrated selective inhibition of alkaline phosphatase isoenzymes in the duodenal mucosa prior to any visible signs of ulcer formation following cysteamine treatment, and 4) suggested a role for iron in the pathogenesis of cysteamine-induced ulcers. A study in rats, discussed above under Safety Pharmacology, demonstrated that cysteamine is a relatively specific depletor of tissue somatostatin.

11 Integrated Summary and Safety Evaluation

In a 30-day rabbit study, there were no observations noted in any animals following ocular administration of Cysteamine Hydrochloride 0.55% Ophthalmic Solution (treated) or placebo for Cysteamine Hydrochloride 0.55% Ophthalmic Solution (untreated) every hour, for 8 consecutive hours daily, for 30 days. The cysteamine hydrochloride ophthalmic solution was considered to be a nonirritant to the ocular tissue of albino rabbits under the study conditions. It should be noted that the cysteamine ophthalmic formulation administered in this 30-day study did not evaluate the planned clinical concentration of 0.65%. The Applicant states that two drops of the Cysteamine Hydrochloride 0.55% Ophthalmic Solution, administered hourly for 8 consecutive hours, resulted in a greater local exposure to cysteamine when compared with the planned clinical dose regimen of one drop of the 0.65% cysteamine hydrochloride ophthalmic solution administered hourly during waking hours. However, it is unclear whether or not

the entire 2 drop dose volume would stay in the rabbits' eyes, and clinical applications may result in more than eight daily applications.

Additional nonclinical data are available in the public domain to support the safety of repeat administration of cysteamine eye drops. A mild to moderate inflammatory response was observed pathologically at doses of 1.0 and 2.0% cysteamine following ocular administration every hour for 8 consecutive hours daily for 1 month. A similar dosing regimen for 3 months in duration resulted in no clinical signs of toxicity to the conjunctiva or cornea and no histopathological evidence of inflammation following administration of 0.1 and 0.5% cysteamine eye drops.

Although there has been no systemic cysteamine exposure reported following ocular administration in nonclinical species (it is unclear whether or not systemic exposure has been evaluated), cysteamine has been orally administered for the treatment of nephropathic cystinosis, and there is clinical experience and safety data for pediatric and adult cystinosis patients. During this time, oral cysteamine has not been effective in reducing corneal crystals or the accompanying secondary symptoms of photophobia, blepharospasm, and eye pain. This is thought to be due to the lack of blood supply to the corneal stromal cells, thus limiting availability of cysteamine to the eye following oral administration. The ophthalmic cysteamine solution has been clinically administered for the treatment of corneal cystine crystal accumulation in pediatric and adult cystinosis patients. Clinical data have suggested that cysteamine does not penetrate into the aqueous humor of the eye. The planned clinical dose is one drop of the Cysteamine Hydrochloride 0.65% Ophthalmic Solution administered in each eye, every hour, during consecutive waking hours. This concentration falls between concentrations associated with no significant ocular irritation and some degree of adverse effect in nonclinical studies.

Based on an assumption of 100% bioavailability of the cysteamine hydrochloride dose administered in the 30-day repeat-dose ocular toxicity study in rabbits, theoretical plasma concentrations and safety margins relative to the exposure following clinical administration of the approved Cystagon drug product have been calculated and are presented in the Applicant's table below. Under this assumption, there would be a 13-fold safety margin relative to the highest clinical exposure (4.0 µg/mL), which was observed following a single oral cysteamine bitartrate dose equivalent to 1.05 g of cysteamine free base in healthy volunteers.

Table 1 Administration of Cysteamine Ophthalmic Solution Safety Margins Relative to Approved Oral Cystagon Doses

Species	Parameter	Duration	Dose Level	Cmax (µg/mL)	Safety Margin ^a
Rabbit	Ocular	Repeat dosing, 30 days	16 drops/day, equivalent to 5.5 mg/day ^b	54.6 ^c	13.65
Human, Planned Clinical Dose	Ocular	Repeat dosing	20 drops/day, equivalent to 8.0 mg/day ^d	1.7 ^e	—
Human, Healthy Volunteers	Oral	Single dose	Cysteamine bitartrate dose equivalent to 1.05 g of cysteamine free base	4.0	—
Human, 11 Pediatric Patients with Nephropathic Cystinosis	Oral	Repeat dosing, >1 year	225 to 550 mg of cysteamine bitartrate, every 6 hours daily	2.6	—

^a Safety margin calculated relative to the highest clinical exposure (4.0 µg/mL), which was observed following a single oral dose in healthy volunteers.

^b Two drops of the Cysteamine Hydrochloride 0.55% Ophthalmic Solution were administered every hour, 8 consecutive hours daily, for 30 days. This would result in a total of 16 drops of solution administered daily. Calculations were based on the following: one drop of solution is equivalent to 1 minim and there are 16.2 minim in 1 mL (Remington's Pharmaceutical Sciences, 18th edition, 2007). The dosing regimen would result in a total daily dose of 1 mL Cysteamine Hydrochloride 0.55% Ophthalmic Solution, which is equivalent to 0.0055 g/day cysteamine hydrochloride.
Reviewer's comment: Another pharmaceutical definition of a drop has been 1/20th (0.05) mL

^c Based on 100% bioavailability of the 0.0055 g dose, assuming a total blood volume of 56 mL/kg in the 1.8 kg rabbit.

^d One drop of the Cysteamine Hydrochloride 0.65% Ophthalmic Solution to be administered in each eye (total of two drops) every hour during waking hours. Assuming 10 administration intervals per day, this would result in a total of 20 drops of solution administered daily. Calculations were based on the following: one drop of solution is equivalent to 1 minim and there are 16.2 minim in 1 mL (Remington's Pharmaceutical Sciences, 18th edition, 2007). The dosing regimen would result in a total daily dose of 1.23 mL Cysteamine Hydrochloride 0.65% Ophthalmic Solution, which is equivalent to 0.008 g/day cysteamine hydrochloride.

^e Based on 100% bioavailability of the 0.008 g dose, assuming a total blood volume of 4700 mL.

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/

AMY C NOSTRANDT
07/07/2010
includes label review

WENDELYN J SCHMIDT
07/07/2010