CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

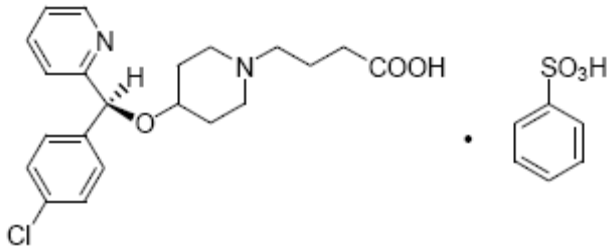
CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 25, 2009
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-288
Applicant	ISTA Pharmaceuticals, Inc.
Date of Submission	November 12, 2008
PDUFA Goal Date	September 12, 2009
Type of Application	505(b)(1)
Name	Bepreve (bepotastine besilate ophthalmic solution) 1.5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Indicated for the treatment of itching associated with allergic conjunctivitis
Recommended:	Recommended for Approval

1. Introduction

Chemical Structure of Bepotastine Besilate



Bepotastine besilate (+)-(S)-4-{4-[(4-Chlorophenyl)(2-pyridyl)methoxy] piperidino} butyric acid monobenzenesulfonate was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. as a treatment for allergic rhinitis. Bepotastine besilate is a histamine H_1 receptor antagonist and has an inhibitory action on eosinophilic infiltration to inflammatory sites.

The support of clinical safety and efficacy for bepotastine besilate ophthalmic solution included 3 clinical studies conducted in the United States under IND 66,864. One safety study (CL-SAF-0405071-P) and two efficacy studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) were performed.

2. Background

An oral preparation of bepotastine besilate [Talion tablets, Mitsubishi Tanabe Pharma Corporation (formerly Tanabe Seiyaku Company, Ltd.)] was approved in Japan in July 2000 as a treatment for allergic rhinitis (10mg p.o. bid for up to 4 weeks). In January 2002, the additional indication of pruritus/itching accompanying urticaria and other skin diseases was approved in Japan. Bepotastine is a new molecular entity in the United States.

Studies CL-S&E-0409071 and CL-SAF-0405071 (7/23/07 SPA response) were performed after submission of a Special Protocol Assessment (SPA). There was an EOP 2 Meeting held on 8/15/07, a SPA Meeting held on 9/17/08, and a pre-NDA Meeting on 8/4/08.

The efficacy endpoints chosen for the phase 3 studies have been widely used in clinical studies of ophthalmic solutions and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products. For an indication for the treatment of allergic conjunctivitis, a demonstration of efficacy is recommeded to include evidence of statistical significance and clinical relevance in the resolution of both ocular itching and redness. In the case of antigen challenge studies or controlled environmental studies, the difference between groups is recommended to be at least one unit on a scale from zero to four.

Table of Currently Available Treatments for Proposed Indication of Itching Associated with Allergic Conjunctivitis

Brand Name	**Name of Drug**	**NDA**
Alocril	Nedocromil	21-009
Acular	Ketorolac	19-700
Optivar	Azelastine	21-127
Alamast	Pemirolast	21-079
Pataday	Olopatanol	21-545
Elestat	Epinastine	21-565

Adverse events for this class of drugs (topical H1 antagonists) are well known. Common side effects seen with this class include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, and taste perversion/bitter taste.

3. CMC

From the two CMC Reviews finalized 7/27/09 and 8/9/09:

Bepotastine besilate is manufactured by Ube Industries and the information for the NDA is submitted through DMF #19966. Bepotastine besilate is a white crystalline powder with (b) (4). It is very soluble in (b) (4) but sparingly soluble in (b) (4). It is stable when exposed to light, and optically active. The S-isomer is the active drug and (b) (4) is controlled as an impurity through synthesis. The distribution coefficient in 1-octanol is higher than in aqueous buffer in the pH 5-9 range. There are 10 potential impurities but only one impurity is above 0.1%. Two potential genotoxic impurities (b) (4) are controlled below (b) (4). Residual (b) (4) is controlled below (b) (4). Bepotastine besilate is stable under long term storage conditions for (25ºC/60% RH) over 5 years.

Bepotastine besilate was originally developed as an oral tablet dosage form and received approval in Japan in 2000 for allergic rhinitis. Bepotastine besilate ophthalmic solution 1.5% is an aqueous solution to be administered as drops at or near physiological pH range of tears. The formulation contains sodium chloride, monobasic sodium phosphate as dihydrate, benzalkonium chloride, sodium hydroxide and purified water; typically these components are used for adjusting tonicity, preservative action, pH adjustment, buffering capacity and a vehicle for administration. It was demonstrated during the formulation development that sodium chloride, in addition to its use to (b) (4) All excipients are of USP/NF grade. It is manufactured as a (b) (4) solution.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Table of Composition of Bepotastine Besilate Ophthalmic Solution

Components	Function	Amount/mL	(b) (4) Batch Composition	(b) (4) Batch Composition	% w/v
Bepotastine besilate	Active pharmaceutical ingredient	15 mg[1] (b) (4)			(b) (4)
Sodium chloride					(b) (4)
Monobasic Sodium Phosphate, Dihydrate					
Benzalkonium chloride	Preservative	0.05 mg			(b) (4)
Sodium hydroxide	pH adjuster	qs to pH 6.8			(b) (4)
Water for Injection	Solvent	qs			

[1] For Bepreve™ 1.5% drug product
[2] For Bepreve™ 1.0% drug product

PROPOSED REGULATORY SPECIFICATIONS:

(b) (4)

From the CMC Review finalized 7/27/09:

FACILITIES INSPECTIONS:
The overall recommendation from the Office of Compliance is "Acceptable" in EES.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 7/21/09:

The pharmacology/toxicology reviewer has no objection to the approval of this NDA.

Bepotastine besilate in the Bepreve formulation did not cause ocular inflammation or histopathologic changes in rabbits or dogs. There are some data that suggest that Bepreve may have an affinity for melanin binding based on the observation of presence in the iris in an ocular toxicity study and to pigmented tissues in a radiolabeled study. This association with melanin appears to be reversible, reaching levels below limit of detection when given enough time for clearance after dosing (e.g. 30 days after single dose of radiolabeled compound, bepotastine besilate was no longer detected in pigmented tissues).

The pivotal study for the proposed indication was a 26 week study in dogs using 4 and 8X per day dosing with the 1.5% TAU-284 solution. The 4X/day dosing paradigm was determined to be the NOAEL based on decreases in A and B wave amplitude in electroretinograms (ERG) in the 8X/day dose group. When considering systemic exposures seen in this study, the identified NOAEL for ERG endpoints provides a 15X safety factor over that of anticipated systemic exposures seen with topical ocular use in humans. Several short term ocular toxicity studies demonstrated that bepotastine besilate solutions up to 2% in concentration were well tolerated in various animal species. Bepreve also did not demonstrate strong hypersensitivity reactions with repeated use.

Although bepotastine besilate appears to be a substrate for Cyp450 metabolism in rodents, it does not appear to be a target/inhibitor of human CYP450 enzymes. In both rats and dogs, test article is primarily excreted in feces and urine. Additional information may be found in the clinical pharmacology review.

The exec-CAC concluded that bepotastine besilate did not significantly induce neoplasms in 2 year dietary carcinogenicity studies in mice (at margin of exposure relative to human after ophthalmic use of 353) or in rats (at a margin of exposure relative to human of 200) .

Pregnancy category C is recommended for this product due to the observation of a rare skeletal malformation seen in the fertility/early embryo development study in rats at the 1000 mg/kg dose. The approximate margin of exposure for the 200 mg/kg/day NOAEL identified in this study was 3,300X that of anticipated human systemic exposure with topical ocular use. In rats given oral doses of 100 mg/kg/day, an increased incidence of stillborns was observed (~200X human systemic exposure for

ocular use). At the 1000 mg/kg/day dose level in this same study, an increase in stillborns, decreased survival and decreased rate of development were observed in pups. There were no effects observed in rats treated with 10 mg/kg/day (representing a maximal systemic concentration approximately 18 times that anticipated for topical ocular use in humans).

From a radiolabeled study in pregnant rats, it is recognized that bepotastine besilate can rapidly distribute to the yolk sac/placenta and to the fetus. Bepotastine besilate was transferred to the yolk sac/placenta at levels nearly equivalent to maternal maximal plasma concentration; ~33-55% of bepotastine besilate was transferred to the developing fetus. At 24 hours following a single oral administration of 3 mg/kg, ~ 5.9% and 3.1% of maximal plasma TAU-284 concentrations were detected in the brain and liver of the fetus at 24 hours postdose. Bepotastine besilate was also noted to be transferred to milk in lactating rats, with milk concentrations being 1.5 to 2 times maximal plasma concentrations by 1 hour postdose and reaching levels below the limit of detection by 48 hours postdose.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 5/22/09:

The clinical pharmacology information provided by the Applicant is acceptable.

The applicant submitted clinical pharmacology data for bepotastine from the Japanese development programs, including a Phase 1 pharmacokinetic (PK) study examining systemic exposure following bepotastine besilate ophthalmic solutions 1.0% and 1.5% instilled as repeated doses (QID) over a 7 day period (Study SNJ-TO-02), as well as data from multiple Phase 1 studies from the oral development program. The clinical pharmacology information provided by the Applicant is acceptable.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 6/17/09:

There are no microbiology deficiencies identified.

(b) (4)

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7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 8/13/2009:

Analyses of Endpoints

Primary Efficacy Variables for Studies ISTA-BEPO-CSO1 and CL-S&E-0409071-P

The primary efficacy variables were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post challenge (0-4 unit [nine step] scale, allowing half unit [one step] increments)
- Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit [9 step] scale, allowing half unit [one step] increments).

To demonstrate clinical significance in a CAC study, the difference between groups should be at least one unit on a scale from 0-4 at a majority of the time points evaluated. This endpoint was duplicated in two trials only at the 8 hours post-dosing CAC with both concentrations of drug (bepotastine 1% and 1.5%). Bepotastine besilate ophthalmic solution 1.5% produced greater clinical response than bepotastine besilate ophthalmic solution 1% in reducing ocular itching at both 8-hour and 16- hour duration-of-action time points versus vehicle. The data support bepotastine 1.5% with bid dosing for the treatment of itching associated with allergic conjunctivitis.

ITCHING

Study ISTA-BEPO-CSO1: Ocular Itching (ITT Population with LOCF)

Visit	**Bepotastine 1% N=36**	**Bepotastine 1.5% N=35**	**Vehicle N=36**
Visit 2			
3 Minutes Post-Challenge	2.52	2.57	2.35
5 Minutes Post-Challenge	2.73	2.81	2.76
7 Minutes Post-Challenge	2.75	2.82	2.81
Visit 3b – 16 Hour			
3 Minutes Post-Challenge	1.44	1.16	2.10
5 Minutes Post-Challenge	1.58	1.34	2.37
7 Minutes Post-Challenge	1.44	1.31	2.27
Visit 4 – 8 Hour			
3 Minutes Post-Challenge	1.15	0.73	2.06
5 Minutes Post-Challenge	1.29	0.80	2.33
7 Minutes Post-Challenge	1.27	0.82	2.23
Visit 5 – 15 minutes			
3 Minutes Post-Challenge	0.56	0.49	1.87
5 Minutes Post-Challenge	0.72	0.71	2.07
7 Minutes Post-Challenge	0.70	0.67	1.95

Visit	**Bepotastine 1%**		**Bepotastine 1.5%**	
	Difference in Mean Itching Grades (Vehicle – Active)	**p-value**	**Difference in Mean Itching Grades (Vehicle – Active)**	**p-value**
Visit 3B (Day 1)-CAC at 16 hours post dosing				
3 min post-CAC	0.7	0.002	0.9	<0.001
5 min post-CAC	0.8	<0.001	**1.0**	<0.001
7 min post-CAC	0.8	<0.001	**1.0**	<0.001
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	0.9	<0.001	**1.3**	<0.001
5 min post-CAC	**1.0**	<0.001	**1.5**	<0.001
7 min post-CAC	**1.0**	<0.001	**1.4**	<0.001
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	**1.3**	<0.001	**1.4**	<0.001
5 min post-CAC	**1.4**	<0.001	**1.4**	<0.001
7 min post-CAC	**1.3**	<0.001	**1.3**	<0.001

Study CL-S&E-0409071-P: Ocular Itching (ITT Population with LOCF)

Visit	**Bepotastine 1% N=44**	**Bepotastine 1.5% N=43**	**Vehicle N=43**
Visit 1-Baseline	0	0	0
10 Minutes post-challenge	3.3	3.22	3.23
Visit 2			
3 Minutes Post-Challenge	2.57	2.51	2.63
5 Minutes Post-Challenge	2.99	2.99	2.9
7 Minutes Post-Challenge	3.05	3.07	3.05
Visit 3b – 16 Hours			
3 Minutes Post-Challenge	1.27	1.23	1.83
5 Minutes Post-Challenge	1.42	1.44	2.15
7 Minutes Post-Challenge	1.19	1.23	2.02
Visit 4 – 8 Hours			
3 Minutes Post-Challenge	0.96	0.89	2.18
5 Minutes Post-Challenge	1.01	0.95	2.27
7 Minutes Post-Challenge	0.94	0.87	2.1
Visit 5 – 15 Minutes			
3 Minutes Post-Challenge	0.42	0.4	1.85
5 Minutes Post-Challenge	0.6	0.46	2.07
7 Minutes Post-Challenge	0.64	0.51	1.93

Visit	**Bepotastine 1%**		**Bepotastine 1.5%**	
	Difference in Mean Itching Grades (Vehicle – Active)	**P value**	**Difference in Mean Itching Grades (Vehicle – Active)**	**P value**
Visit 3B (Day 1)-CAC at 16 hours post-dosing				
3 min post-CAC	0.6	0.0055	0.6	0.0051
5 min post-CAC	0.7	0.0006	0.7	0.0021
7 min post-CAC	0.8	0.0001	0.8	0.0003
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	**1.2**	<0.001	**1.3**	<0.001
5 min post-CAC	**1.3**	<0.001	**1.3**	<0.001
7 min post-CAC	**1.2**	<0.001	**1.2**	<0.001
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	**1.4**	<0.001	**1.5**	<0.001
5 min post-CAC	**1.5**	<0.001	**1.6**	<0.001
7 min post-CAC	**1.3**	<0.001	**1.4**	<0.001

REDNESS

Study ISTA-BEPO-CSO1: Clinical Assessment of Conjunctival Redness (ITT Population with LOCF)

Visit	**Bepotastine 1% N=44**	**Bepotastine 1.5% N=43**	**Vehicle N=43**
Visit 2			
7 Minutes Post-Challenge	2.01	2.03	2.10
15 Minute Post-Challenge	2.21	2.29	2.25
20 Minutes Post-Challenge	2.19	2.28	2.25
Visit 3b			
7 Minutes Post-Challenge	1.42	1.63	1.79
15 Minutes Post-Challenge	1.53	1.81	1.81
20 Minutes Post-Challenge	1.47	1.78	1.70
Visit 4			
7 Minutes Post-Challenge	1.26	1.30	1.67
15 Minutes Post-Challenge	1.56	1.47	1.84
20 Minutes Post-Challenge	1.55	1.52	1.84
Visit 5			
7 Minutes Post-Challenge	1.11	1.37	1.91
15 Minute Post-Challenge	1.45	1.65	2.05
20 Minutes Post-Challenge	1.44	1.62	1.95

Time of Post-CAC Observation	**Bepotastine 1%**		**Bepotastine 1.5%**	
	Difference in Mean Redness Grades (Vehicle – Active)	**P value**	**Difference in Mean Redness Grades (Vehicle – Active)**	**P value**
Visit 3B				
7 min post-CAC	0.4	0.012	0.2	0.208
15 min post-CAC	0.3	0.048	0.0	0.755
20 min post-CAC	0.2	0.102	-0.1	0.711
Visit 4				
7 min post-CAC	0.4	0.014	0.4	0.029
15 min post-CAC	0.3	0.071	0.4	0.062
20 min post-CAC	0.3	0.083	0.3	0.137
Visit 5				
7 min post-CAC	0.8	<0.001	0.6	0.004
15 min post-CAC	0.6	<0.001	0.4	0.039
20 min post-CAC	0.5	<0.001	0.3	0.151

Study CL-S&E-049071-P: Clinical Assessment of Conjunctival Redness (ITT Population with LOCF)

Visit	**Bepotastine 1% N=44**	**Bepotastine 1.5% N=43**	**Vehicle N=43**
Visit 1-Baseline	0.52	0.63	0.58
10 minutes post-challenge	2.6	2.68	2.60
Visit 2			
Pre-CAC	0.65	0.67	0.63
7 Minutes Post-Challenge	2.41	2.46	2.40
15 Minute Post-Challenge	2.49	2.59	2.53
20 Minutes Post-Challenge	2.52	2.60	2.50
Visit 3a Pre-CAC	0.61	0.63	0.6
Visit 3b			
7 Minutes Post-Challenge	1.46	1.80	1.89
15 Minutes Post-Challenge	1.6	1.85	1.99
20 Minutes Post-Challenge	1.62	1.87	1.98
Visit 4			
Pre-CAC	0.6	0.69	0.63
7 Minutes Post-Challenge	1.35	1.59	1.8
15 Minutes Post-Challenge	1.57	1.76	1.88
20 Minutes Post-Challenge	1.59	1.77	1.84
Visit 5			
Pre-CAC	0.49	0.60	0.56
7 Minutes Post-Challenge	1.28	1.42	1.85
15 Minute Post-Challenge	1.51	1.59	1.97
20 Minutes Post-Challenge	1.64	1.67	1.87

Time of Post-CAC Observation	**Bepotastine 1%**		**Bepotastine 1.5%**	
	Difference in Mean Redness Grades (Vehicle – Active)	**P value**	**Difference in Mean Redness Grades (Vehicle – Active)**	**P value**
Visit 3B				
7 min post-CAC	0.4	0.005	0.1	0.547
15 min post-CAC	0.4	0.017	0.1	0.388
20 min post-CAC	0.4	0.041	0.1	0.500
Visit 4				
7 min post-CAC	0.5	0.001	0.2	0.107
15 min post-CAC	0.3	0.036	0.1	0.360
20 min post-CAC	0.3	0.103	0.1	0.591
Visit 5				
7 min post-CAC	0.6	0.001	0.4	0.003
15 min post-CAC	0.5	0.002	0.4	0.011
20 min post-CAC	0.2	0.148	0.2	0.225

Neither concentration of bepotastine provides a clinically significant reduction in redness compared to vehicle at any study visit during the treatment period.

Secondary Efficacy Variables for Studies ISTA-BEPO-CSO1 and CL-S&E-0409071-P

Ocular symptom scores:

- Ciliary and episcleral redness evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit (nine step) scale, with half unit (one step) increments allowed)
- Chemosis evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit (one step) scale, with half unit (one step) increments allowed)
- Lid swelling evaluated by the subject at 7, 15, and 20 minutes post challenge (0-3 unit scale, whole unit increments only)
- Tearing evaluated by the subject at 7, 15, and 20 minutes post challenge (graded absent or present)
- Ocular mucous discharge evaluated by the investigator at 7, 15, and 20 minutes post challenge (graded absent or present)

Non-ocular symptom scores:

- Rhinorrhea, ear or palate pruritus, nasal pruritus, and nasal congestion evaluated by the subject at 7, 15, and 20 minutes post challenge (0-4 unit scale, whole unit increments only)
- A composite score of rhinorrhea, ear or palate pruritus, nasal pruritus, and nasal congestion evaluated by the subject at 7, 15, and 20 minutes (0-16 unit scale)

None of the secondary endpoints achieved clinical success (i.e., both statistical and clinical significance) as defined in the trial protocol in either study.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Bepreve (bepotastine besilate ophthalmic solution) 1.5% experienced a statistically and clinically significant response in the reduction of ocular itching. The data support Bepreve (bepotastine besilate ophthalmic solution) 1.5% administered twice a day for the treatment of itching associated with allergic conjunctivitis.

There is **not** substantial evidence that patients receiving Bepreve (bepotastine besilate ophthalmic solution) 1.5% experienced a statistically and clinically significant response in the reduction of ocular redness. The data does **not** support Bepreve (bepotastine besilate ophthalmic solution) 1.5% administered twice a day for the treatment of redness associated with allergic conjunctivitis.

8. Safety

From the original Medical Officer Review dated 8/13/2009:

Three studies are used to support the safety and efficacy of bepotastine. The main support for the safety of bepotastine besilate 1.5% comes from Study CL-SAF-0405071. The patient exposure and safety assessments were adequate.

Treatment Duration (Safety Population) for Study CL-SAF-0405071

Treatment Group	Mean Treatment Duration (Days, +/- sd)
Bepotastine besilate 1.5% (N=572)	40.4 (6.7)
Age 3-9 (N=47)	42.0 (0.4)
Age 10-17 (N=40)	41.2 (5.6)
Age >=18 (N=485)	40.1 (7.1)
Vehicle (N=286)	40.6 (6.5)
Age 3-9 (N=25)	42.0 (0.4)
Age 10-17 (N=15)	42.1 (0.3)
Age >= 18 (N=246)	40.3 (6.9)

*Treatment duration was defined as the number of days between the first and last instillation of masked investigational product.

No patient or subject deaths occurred during the conduct of the two Phase 3 clinical studies and the additional safety study that form the basis of this application.

Study ISTA-BEPO-CSO1: Patient Disposition

	Bepotastine 1%	Bepotastine besilate 1.5%	Vehicle
Randomized	36	35	36
Safety Population	36	35	36
ITT Population with LOCF	36	35	36
PP Population	35	32	34

Study ISTA-BEPO-CSO1: Patient Withdrawals

Subject No.	Treatment Group	Reason For Withdrawal
1026-025	Vehicle	Subject decision/non-compliance-missed Visit 3B and Visit 4
1045-040	Bepotastine 1.5%	Subject decision/non-compliance-missed Visit 3B and Visit 4
1064-052	Bepotastine 1.5%	Unacceptable baseline itching and redness at Visit 5
1140-063	Bepotastine 1.5%	Subject decision/non-compliance-missed Visit 3B and Visit 4

Study CL-S&E-0409071: Patient Disposition

	Bepotastine 1%	Bepotastine besilate 1.5%	Vehicle
Randomized	44	43	43
Safety Population	44	43	43
ITT Population with LOCF	44	43	43
PP Population	43	38	36

Study CL-S&E-0409071: Patient Withdrawals

Subject No.	Treatment Group	Reason For Withdrawal
1003-050	Vehicle	Subject decision/non-compliance
2001-066	Vehicle	Subject decision/non-compliance
3016-010	Vehicle	Subject decision/non-compliance
3028-027	Bepotastine 1.5%	Subject decision/non-compliance
3057-002	Bepotastine 1.5%	Exclusion criteria*
4007-125	Bepotastine 1.5%	Subject decision/non-compliance
4045-128	Vehicle	Subject decision/non-compliance
5003-110	Vehicle	Subject decision/non-compliance
5005-111	Bepotastine 1.5%	Subject decision/non-compliance
5012-099	Bepotastine 1.5%	Exclusion criteria*
5016-098	Vehicle	Subject decision/non-compliance
5031 -097	Bepotastine 1%	Subject decision/non-compliance
5034-101	Vehicle	Subject decision/non-compliance

*Subjects manifested signs or symptoms of clinically active allergic conjunctivitis (defined as any ocular itching or an ocular redness score >1, for any vessel bed) at the start of the study visit.

Study CL-SAF-0405071: Subject Disposition

	Bepotastine besilate 1.5%	Vehicle
Number of Randomized subjects	575	286
Number of Subjects in Safety Population *	575	286
Number of Pediatric Subjects in Safety Population	87	40
Patients that Underwent ECC-Baseline	133	69
Patients that Underwent ECC- Day 84	125	68
Number of Subjects Completed Study**	532 (92.5%)	269 (94.1%)
Reason For Withdrawal		
AE	6	6
Protocol Violation	3	0
Subject Decision/Non-Compliance	32	10
Other	2	1

*Safety population defined as subjects who received at least 1 dose of investigational product.
**A completed subject is defined as one who has completed all study visits and received at least 75% of scheduled doses.

Twelve subjects withdrew from the study early with an AE being listed as the reason for study discontinuation (six in bepotastine group and six in the vehicle group).

Study CL-SAF-0405071: Patient Withdrawals Due to Adverse Events

Subject Number	Treatment Group	AE Leading to Discontinuation
3010-541	Bepotastine	Intermittent headaches associated with study drops
3018-549	Vehicle	Sinusitis and ear infection
3076-604	Vehicle	Neck and shoulder pain subsequent to car accident
3079-607	Bepotastine	Intermittent HTN worsening over 20 days of dosing and non-ocular allergies
3098-625	Bepotastine	Pneumonia
3102-629	Bepotastine	Intermittent headache and earache
5084-842	Vehicle	Sinusitis
6059-053	Vehicle	Eyelid pain and eyelid margin crusting
6110-093	Bepotastine	Bronchitis and ocular stinging and photophobia
6241-209	Vehicle	Eye irritation, redness, blurred vision, and burning upon instillation
6300-259	Vehicle	Three styes
6318-274	Bepotastine	Eye irritation

Study CL-SAF-0405071: Treatment Emergent Ocular Adverse Events (Safety Population)

	Bepotastine besilate 1.5% N=575	Vehicle N=286
Eye disorders		
Eye irritation	27	6
Dry eye	6	5
Ocular hyperemia	2	4
Asthenopia	1	3
Eye pain	2	2
Eye puritis	3	1
Lacrimation increased	3	0
Photophobia	2	1
Conjunctival cyst	1	1
Conjunctival hemorrhage	0	2
Eyelid margin crusting	1	1
Eyelid pain	1	1
FBS	2	0
Punctate keratitis	1	1
Abnormal sensation in eye	0	1
Eye discharge	0	1
Eye swelling	1	0
Eye edema	1	0
Eyelid pruritis	1	0
Glare	1	0
Keratitis	1	0
Vision blurred	0	1
Vitreous floaters	1	0
Vascular Disorders		
Hyperemia	2	0
General disorders		

	Bepotastine besilate 1.5% N=575	**Vehicle N=286**
Sensation of pressure	0	1
Infections		
Hordeolum	0	1
Injury		
Contusion	0	1
Skin disorders		
Photosenstivity reaction	1	0
Nervous system disorders		
Taste perversion	84	4
Bad taste	45	1
Headache	20	7
After taste	14	2
Nerve compression	0	1
Parosmia	1	0
Taste abnormality	1	0
Taste bitter	1	0
Taste metallic	1	0
Infections		
Nasophayngitis	12	5
Influenza	3	0
Sinusitis	1	2
Bronchitis	2	0
UTI	1	1
Ear infection	0	1
Folliculitis	1	0
Herpes zoster	1	0
Pharyngitis	0	1
Pneumonia	1	0
Tooth abscess	0	1
Vaginal infection	1	0
Viral pharyngitis	0	1
Respiratory disorders		
Nasal congestion	5	0
Rhinorrhea	3	2
Cough	2	2
Post-nasal drip	4	0
Pharngolaryngeal pain	1	1
Sneezing	2	0
Wheezing	2	0
Asthma	1	0
Sinus congestion	1	0
Musculoskeletal		
Back pain	1	1

	Bepotastine besilate 1.5% N=575	**Vehicle N=286**
Plantar fasciitis	1	1
Tendonitis	1	1
Arthralgia	1	0
Musculoskeletal pain	0	1
Neck pain	0	1
Osteoarthritis	1	0
Pain in extremity	1	0
GI disorders		
GERD	2	0
Tooth impacted	1	1
Abdominal pain	0	1
Dry mouth	1	0
Nausea	1	0
Paresthesia oral	0	1
Vomiting	0	1
Injury and poisoning		
Contusion	1	1
Accident	1	0
Animal bite	0	1
Fall	1	0
Joint sprain	1	0
Limb injury	0	1
Procedural pain	1	0
Road traffic accident	1	0
Tendon rupture	0	1
Skin disorders		
Drug eruption	1	0
Eczema	0	1
Rash	1	0
Urticaria	0	1
Ear disorders		
Ear pain	1	0
Eustachian tube obstruction	1	0
Tinnitus	1	0
Cardiac disorders		
Extrasystole	1	0
General disorders		
Chest pain	1	0
Immune system disorders		
Hypersensitivity	1	0
Metabolism disorder		
Hypercholesterolemia	0	1

	Bepotastine besilate 1.5% N=575	**Vehicle N=286**
Vascular disorders		
HTN	1	0

*Treatment-emergent adverse events were defined as those occurring during the 6-week dosing period.

The most commonly reported non-ocular AEs were in the taste-related category. The taste-related category includes specific AEs described by the subjects as taste perversion, bad taste, aftertaste, taste abnormality, bitter taste, or metallic taste. In the bepotastine 1.5% group, 25% of subjects reported at least 1 taste-related AE. This incidence had a statistical significance greater than the 2.4% incidence reported in the vehicle treatment group (P <0.0001).

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Bepreve, dosed twice a day, is safe for the treatment of itching associated with allergic conjunctivitis.

The most common adverse reaction occurring in approximately 25% of patients was a taste perversion following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

9. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on June 26, 2009 at the Hilton Hotel Washington/Silver Spring, 8727 Colesville Road, Silver Spring, Maryland. Michael X. Repka, M.D., chaired the meeting.

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Members present (voting):
Michael X. Repka, M.D. (Acting Chair), Allan R. Rutzen, M.D.
Temporary Voting Members:
Michael W. Belin, M.D.; Lynn K. Gordon, M.D., Ph.D.; Susan M. MacDonald, M.D.; Philip Lavin, Ph.D.; Paula Cofer (Patient Representative)
Industry Representative (non-voting):
Ellen Strahlman, M.D., M.H.Sc
FDA Participants (non-voting):
Edward M. Cox, M.D., MPH; Wiley Chambers, M.D.; Rhea Lloyd, M.D.; Sonal Wadhwa, M.D.,; Yan Wang, Ph.D.
Open Public Hearing Speaker:
None

The following questions were posed to the Committee:

1. Do you think adequate safety and efficacy for bepotastine ophthalmic solution has been demonstrated for the treatment of itching due to allergic conjunctivitis?

The committee voted 7-Yes and 0-No.

2. If yes, on which study(ies) are you basing your decision?

All committee members stated they based their decision on Studies ISTA-BEPO-CS01 CL-S&E-0409071, and CL-SAF-0405071.

3. If no, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

Not applicable.

4. Do you have any suggestions concerning the proposed draft labeling of the product?

There were no suggestions regarding the proposed draft labeling.

10. Pediatrics

This drug was tested in a pediatric population. Safety and efficacy of Bepreve (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested.

Per the DSI review finalized 6/29/09:

The clinical safety and efficacy evaluation plan for bepotastine besilate ophthalmic solution in the U.S. has consisted of 3 clinical studies conducted in the U.S., a large 6-week multisite randomized, placebo-controlled safety study and two randomized, placebo-controlled, double-masked efficacy conjunctival allergen challenge (CAC) trials (one Phase 2/3 single site study and one Phase 3 multisite study). The Phase 3 multisite, double-masked, randomized, placebo-controlled, parallel group safety study (CL-SAF-0405071-P) evaluated the safety of bepotastine besilate ophthalmic solution 1.5% administered two times per day (BID) for 6 weeks in healthy, normal volunteers ages 3 years and older. In addition, the two U.S. efficacy CAC trials (ISTA-BEPO-CS01 and CL-S&E-0409071-P) evaluated the safety and efficacy of bepotastine besilate ophthalmic solution (1.0% and 1.5%) in the same clinical trial design using the conjunctival allergen challenge (CAC) model in male and female subjects aged 10 years and older with allergic conjunctivitis.

Four domestic sites were selected for inspection. This is a re-inspection of Dr. Torkildsen who was previously inspected 10/05/2006 and received a final classification of NAI.

The clinical investigator (CI) sites requested for inspections for CL-S&E-0409071-P were those with the highest enrollment numbers (approximately one half of subjects enrolled in the study). For CL-SAF-040571-P the CI site requested for inspection enrolled greater that one third of all subjects enrolled in the study. For ISTA-BEPO-CS01, the single CI site requested for inspection has previously been inspected by the FDA (inspected 10/05/2006 and received a final classification of NAI), as this site was responsible for all enrolled subjects in this pivotal study a re-inspection of the CI was considered necessary.

In general, Protocols CL-S&E-0409071, ISTA-BEPO-CS01, and CL-SAF-0405071-P appear to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the inspection of ISTA Pharmaceuticals Inc. is NAI.

The final classifications of the Clinical Investigator inspections of Dr. Torkildsen and Dr. Michaelson are Voluntary Action Indicated (VAI). While regulatory violations occurred at these sites, the safety and efficacy data from these sites are considered reliable.

The preliminary classifications of the Clinical Investigator inspections of Dr. Bergmann and Dr. Macejko are 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

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment considered the potential similarity of 39 names to the proposed name, Bepreve. However, DEMEPA concluded that these names would not render the proposed name, Bepreve, vulnerable to name confusion that could lead to medication errors. Thus, DMEPA has no objection to the use of the proprietary name Bepreve for this product. The Division of Anti-Infective & Ophthalmology Products concurred with this assessment.

DMEPA also provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate.

DDMAC

DDMAC reviewed the proposed product labeling for Bepreve (bepotastine besilate ophthalmic solution) 1.5% submitted by the applicant on August 12, 2009, and offered the following comments.

Regarding the Highlights Section:

- For clarification purposes, DDMAC recommends adding the sentence, "Lenses may be reinserted after 10 minutes following administration of Bepreve," to the Warning and Precaution Highlights Section.

The addition of this statement to the Highlights Section is not recommended. It promotes the use of contact lenses when eyes are red and diminishes the relevance of Section 5.2 of the label which details proper use of contacts with this product, i.e., Patients should be advised not to wear a contact lens if their eye is red.

Regarding the Adverse Events Section:

- Please include an adequate description of the data sources for the adverse event data, as outlined in the guidance. For example, please include information on whether the trials were double blinded,

randomized, and placebo controlled trials, if available. Also, please include the dosage, frequency, and duration of therapy that patients received.

- Identify adverse reactions, if any, that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.

The addition of these statements to the Adverse Events Section is not recommended. The adverse events noted in Section 6 of the labeling were seen in all phases of development, including the conjunctival allergen challenge studies and the six week safety study. There were no adverse reactions resulting in a significant rate of discontinuation.

Regarding the Clinical Trials Section:

- We suggest rewriting this section with the following information: number of patients studied in each arm of the trial, age ranges of the patients, major study endpoints, descriptions of the measurement tools used to evaluate the outcomes (the measurable signs of ocular itching), actual results (tabular format), and any appropriate accompanying statistics.

- We recommend that specific efficacy data be included to qualify the superiority claims made in the label. Broad claims about the superiority of the drug versus vehicle without the context of the actual data may be used to misleadingly overstate the efficacy of the drug in promotional materials.

The addition of these statements to the Clinical Trials Section is not recommended. The trials failed on one of their primary endpoints, ocular redness. The efficacy information provided on itching was obtained from the conjunctival antigen challenge model using a placebo control. Supplying statistics for itching in tabular format would likely overstate the efficacy of the drug in promotional materials.

BIOSTATISTICS
Per the Biostatistics consultative review finalized 7/31/09:

The applicant has submitted two phase 3 conjunctival allergen challenge (CAC) studies: ISTA-BEPO-CS01 (single centered) and CL-S&E-0409071-P (multi-centered). In addition, the applicant has submitted a safety study (CL-SAF-0405071-P).

These studies have demonstrated that: (1) Both Bepreve 1.5% and Bepreve 1.0% achieved the pre-defined clinical and statistical significance in the primary endpoint of ocular itching; (2) Bepreve 1.5% had numerical advantage (in terms of the point estimate) over Bepreve 1.0% in the primary endpoint of ocular itching; (3) Both Bepreve 1.5% and Bepreve 1.0% failed in the primary endpoint of conjunctival redness.

12. Labeling

NDA 22-288, Bepreve (bepotastine besilate ophthalmic solution) 1.5% is recommended for approval for the treatment of itching associated with allergic conjunctivitis with the labeling found in the Appendix at the end of this CDTL review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-288, Bepreve (bepotastine besilate ophthalmic solution) 1.5% is recommended for approval for the treatment of itching associated with allergic conjunctivitis. There is substantial evidence of safety and effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Bepreve (bepotastine besilate ophthalmic solution) 1.5% experienced a statistically and clinically significant response in the reduction of ocular itching. The data support Bepreve (bepotastine besilate ophthalmic solution) 1.5% administered twice a day for the treatment of itching associated with allergic conjunctivitis.

The most common adverse reaction occurring in approximately 25% of patients was a taste perversion following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

RISK BENEFIT ASSESSMENT:
Bepotastine besilate ophthalmic solution 1.5% produced greater clinical response than bepotastine besilate ophthalmic solution 1% in reducing ocular itching at both 8-hour and 16- hour duration-of-action time points versus vehicle n studies ISTA-BEPO-CS01 and CL-S&E-0409071-P. The efficacy endpoints chosen for the phase 3 studies have been widely used in clinical studies of ophthalmic solutions and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, 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.

7 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS))

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22288	ORIG 1	ISTA PHARMACEUTICALS	BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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
08/25/2009

WILEY A CHAMBERS
08/25/2009