CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

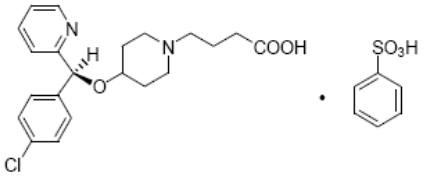
SUMMARY REVIEW

Division Director Review

Date	August 19, 2009
From	Wiley A. Chambers, M.D.
NDA #	NDA 22-288
Applicant	ISTA Pharmaceuticals, Inc.
Date of Submission	November 12, 2008
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.

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

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 besilate (in any dosage form) has not previously been approved in the United States for any indication.

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.

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.

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

3. CMC

The CMC Reviewer recommends approval in his review dated 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 no odor and a bitter taste. 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 ophthalmic solution 1.5% is an aqueous solution. The formulation contains sodium chloride, monobasic sodium phosphate as dihydrate, benzalkonium chloride, sodium hydroxide and purified water. It was demonstrated during the formulation development that sodium chloride, in addition to its use to (b) (4) also helps in (b) (4) All excipients are of USP/NF grade. It is manufactured as a (b) (4) solution.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Bepotastine besilate	Active	(b) (4)
Sodium chloride		(b) (4)
Monobasic Sodium Phosphate, Dihydrate		
Benzalkonium chloride	Preservative	(b) (4)
Sodium hydroxide	pH adjuster	qs to pH 6.8

Water for Injection qs to 1 mL

PROPOSED REGULATORY SPECIFICATIONS:

(b) (4)

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

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer has no objection to the approval of this NDA as noted in the review dated 7/21/09.

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 radio-labeled 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 radio-labeled compound, bepotastine besilate was no longer detected in pigmented tissues).

A 26 week study in dogs using 4 and 8X per day dosing with the 1.5% 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.

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 radio-labeled 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 bepotastine 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

The clinical pharmacology information provided by the Applicant is acceptable in a review dated 5/22/09.

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.

6. Sterility Assurance

The application was recommended for approval from a Product Quality Microbiology prospective in the Review dated 6/17/09.

(b) (4)

7. Clinical/Statistical - Efficacy

Medical Officer Review dated 8/13/2009 recommends approval of the application.

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

- 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).

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

Efficacy Summary Statement
Relief of ocular itching was demonstrated in replicated trials at the initial and 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%. The data support bepotastine 1.5% with bid dosing for the treatment of itching associated with allergic conjunctivitis.

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

8. Safety

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

All Patients

	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

**A completed subject is defined as one who has completed all study visits and received at least 75% of scheduled doses.

Pediatrics

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.

Patient Withdrawals – All studies

Study	Subject No.	Treatment Group	Reason For Withdrawal
CL-S&E-040901	5031 -097	Bepotastine 1%	Subject decision/non-compliance
CL-SAF-0405071	6110-093	Bepotastine 1.5%	Bronchitis and ocular stinging and photophobia
CL-S&E-040901	3057-002	Bepotastine 1.5%	Exclusion criteria – Ocular redness or itching prior to challenge
CL-S&E-040901	5012-099	Bepotastine 1.5%	Exclusion criteria – Ocular redness or itching prior to challenge
CL-SAF-0405071	6318-274	Bepotastine 1.5%	Eye irritation
CL-SAF-0405071	3102-629	Bepotastine 1.5%	Intermittent headache and earache
CL-SAF-0405071	3010-541	Bepotastine 1.5%	Intermittent headaches associated with study drops
CL-SAF-0405071	3079-607	Bepotastine 1.5%	Intermittent HTN worsening over 20 days of dosing and non-ocular allergies
CL-SAF-0405071	3098-625	Bepotastine 1.5%	Pneumonia
CL-S&E-040901	3028-027	Bepotastine 1.5%	Subject decision/non-compliance
CL-S&E-040901	4007-125	Bepotastine 1.5%	Subject decision/non-compliance
CL-S&E-040901	5005-111	Bepotastine 1.5%	Subject decision/non-compliance
ISTA-BEOP-CS01	1045-040	Bepotastine 1.5%	Subject decision/non-compliance-missed Visit 3B and Visit 4
ISTA-BEOP-CS01	1140-063	Bepotastine 1.5%	Subject decision/non-compliance-missed Visit 3B and Visit 4
ISTA-BEOP-CS01	1064-052	Bepotastine 1.5%	Unacceptable baseline itching and redness at Visit 5
CL-SAF-0405071	6241-209	Vehicle	Eye irritation, redness, blurred vision, and burning upon instillation
CL-SAF-0405071	6059-053	Vehicle	Eyelid pain and eyelid margin crusting
CL-SAF-0405071	3076-604	Vehicle	Neck and shoulder pain subsequent to car accident
CL-SAF-0405071	5084-842	Vehicle	Sinusitis
CL-SAF-0405071	3018-549	Vehicle	Sinusitis and ear infection
CL-S&E-040901	1003-050	Vehicle	Subject decision/non-compliance
CL-S&E-040901	2001-066	Vehicle	Subject decision/non-compliance
CL-S&E-040901	3016-010	Vehicle	Subject decision/non-compliance
CL-S&E-040901	4045-128	Vehicle	Subject decision/non-compliance
CL-S&E-040901	5003-110	Vehicle	Subject decision/non-compliance
CL-S&E-040901	5016-098	Vehicle	Subject decision/non-compliance
CL-S&E-040901	5034-101	Vehicle	Subject decision/non-compliance
ISTA-BEOP-CS01	1026-025	Vehicle	Subject decision/non-compliance-missed Visit 3B and Visit 4
CL-SAF-0405071	6300-259	Vehicle	Three styes

Study CL-SAF-0405071:
Treatment Emergent Ocular Adverse Events reported in greater than 1 patient

	Bepotastine besilate 1.5% N=575	**Vehicle N=286**
Taste perversion	84	4
Bad taste	45	1
Eye irritation	27	6
Headache	20	7
After taste	14	2
Nasophayngitis	12	5
Dry eye	6	5
Nasal congestion	5	0
Post-nasal drip	4	0
Rhinorrhea	3	2
Eye puritis	3	1
Lacrimation increased	3	0
Influenza	3	0
Ocular hyperemia	2	4
Eye pain	2	2
Cough	2	2
Photophobia	2	1
FBS	2	0
Hyperemia	2	0
Bronchitis	2	0
Sneezing	2	0
Wheezing	2	0
GERD	2	0
Asthenopia	1	3
Sinusitis	1	2
Conjunctival cyst	1	1
Eyelid margin crusting	1	1
Eyelid pain	1	1
Punctate keratitis	1	1
UTI	1	1
Pharngolaryngeal pain	1	1
Back pain	1	1
Plantar fasciitis	1	1
Tendonitis	1	1
Tooth impacted	1	1
Contusion	1	1

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.

The committee unanimously concluded that adequate safety and efficacy for bepotastine ophthalmic solution had been demonstrated for the treatment of itching due to allergic conjunctivitis. All committee members stated they based their decision on Studies ISTA-BEPO-CS01, CL-S&E-0409071, and CL-SAF-0405071.

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 because the disease is not considered to be reliably diagnoses below the age of 2 years. 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. Although there is no recognized differences in the disease in pediatric patients below the age of 10 and adults, patients under 10 years of age are not considered reliable historians for reported ocular itching scores.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was conducted as reported in the review dated 6/29/09. Four domestic sites were selected for inspection. This was 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 although it

had previously been inspected by the FDA (Torkildsen; 10/05/2006; NAI), was responsible for all enrolled subjects in this study.

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 had 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 their comments were considered as described in the CDTL review.

BIOSTATISTICS

The application is recommended for approval from the Biostatistics prospective as noted in the review dated 7/31/09. The studies 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 to be approved for the treatment of itching associated with allergic conjunctivitis with the labeling submitted on August 12 and 13, 2009 and found below.

The following package insert submitted by ISTA, Inc. on 8/12/2009 and carton and container labeling submitted on 8/13/09 are acceptable:

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

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-288, Bepreve (bepotastine besilate ophthalmic solution) 1.5% is recommended to be approved 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.

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. A subset of these events was observed with this product.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology reviews concur with the recommendation to approve 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.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs

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/s/

WILEY A CHAMBERS
08/25/2009