CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D., M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	22-288
Applicant Name	ISTA Pharmaceuticals Inc.
Date of Submission	November 12, 2008
PDUFA Goal Date	September 12, 2009
Proprietary Name / Established (USAN) Name	Bepreve / bepotastine besilate ophthalmic solution 1.5%
Dosage Forms / Strength	Topical ophthalmic solution
Proposed Indication	Indicated for the treatment of itching associated with allergic conjunctivitis
Action:	Recommended for Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sonal D. Wadhwa, M.D.
Statistical Review	Mushfiqur Rashid, Ph.D.
Pharmacology Toxicology Review	Theresa Allio, Ph.D.
CMC Review/OBP Review	Shrikant Pagay/ Elaine Morefield, Ph.D.
Microbiology Review	John W. Metcalfe, Ph.D.
Clinical Pharmacology Review	Kimberly L. Bergman, Pharm.D.
DDMAC	Beth Carr, Pharm.D., Lynn Panholzer, Pharm.D.
DSI	Jean Mulinde, M.D.
CDTL Review	William M. Boyd, M.D.
OSE/DEpi	
OSE/DMEPA	Raichell S. Brown, Pharm.D., J.D.
OSE/DRISK	
Other – Div. Director Review	Wiley A. Chambers, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction

Bepotastine besilate is a relatively selective H_1 receptor antagonist and has an inhibitory action on eosinophilic infiltration to inflammatory sites.

Bepotastine besilate ophthalmic solution 1.5% is a sterile ophthalmic solution of bepotastine besilate. The solution also contains sodium chloride (b) (4), monobasic sodium phosphate dehydrate (b) (4), benzalkonium chloride as a preservative, sodium hydroxide for pH adjustment, and water for injection as a solvent.

The proposed indication is treatment of ocular itching associated with allergic conjunctivitis in patients age 3 years and older.

The proposed dosing regimen is instill one drop into the affected eye(s) twice a day.

The proposed proprietary name is Bepreve.

The support of clinical safety and efficacy for bepotastine besilate ophthalmic solution consisted of 3 clinical studies conducted in the US. One safety study (CL-SAF-0405071-P) and two efficacy studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) were performed.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of bepotastine besilate ophthalmic solution 1.5% for the indication proposed. For a detailed discussion of NDA 22-288, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Review.

2. Background/Regulatory

Bepotastine besilate was originally developed in Japan as a treatment for allergic rhinitis. An oral preparation (Talion tablets, Mitsubishi Tanabe Pharma Corporation) was approved in Japan in July 2000 as a treatment for allergic rhinitis. In January 2002, the additional indication of pruritis/itching accompanying urticaria and other skin diseases was approved in Japan. Bepotastine is not an approved product in the U.S.

A series of meetings were held between the applicant and the Agency regarding the development of Bepotastine besilate ophthalmic solution. Studies CL-S&E-0409071 (7/23/07-SPA response and 12/3/07 SPA final response) and CLSAF-0405071 (7/23/07 SPA response) were performed under SPA. There was an EOP 2 Meeting on 8/15/07, SPA Meeting on 9/17/08, and pre-NDA Meeting on 8/4/08.

NDA 22-288 is submitted as a "stand alone" NDA.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology

Reviewer Recommendations: *From the chemistry, manufacturing, and controls standpoint, the reviewer recommended the NDA for approval.*

I concur that there are no outstanding CMC issues precluding approval.

Drug substance impurities did not exceed acceptable concentrations. All excipients are of USP/NF grade. Release and stability testing included all standard tests for sterile ophthalmic solutions. The drug substance and drug product quality is reproducible based on the batch analysis data for release and stability. Manufacturing processes for the drug substance and drug product are well controlled. In the course of the review, queries were sent to the sponsor and all responses were deemed satisfactory by the reviewer.

Four facilities involved in the manufacturing, testing, or packaging of the product were inspected and all evaluated as satisfactory.

Stability testing supports an expiry of 12 months for the 1 mL fill and 18 months for the 2.5 mL, 5mL, and 10mL fill when stored at 25 degrees C.

4. Non-Clinical Pharmacology Toxicology

Reviewer Recommendations: *The reviewer had no objections to the approval of this NDA from a Pharmacology/Toxicology perspective. No additional non-clinical studies were recommended. Labeling as Pregnancy Category C is recommended. The Pharm/Tox Reviewer recommended that Bepreve should only be used during pregnancy and labor/delivery if the potential benefit justifies the potential risk to the fetus. The Pharm/Tox Reviewer recommended that caution should be exercised when Bepreve is administered to nursing women.*

I concur that there are no outstanding pharm tox issues that preclude approval. Appropriate information concerning use by pregnant and nursing women is included in Section 8 of the PI.

Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving systemic exposures approximating 350 times and rats receiving systemic exposures approximating 200 times that anticipated with human topical ocular use. There was no evidence of mutagenicity in *in-vitro* testing.

Evidence of infertility and conceptus loss was seen in rats given oral bepotastine besilate 1000 mg/kg/day. There was no evidence of infertility observed in rats given 200 mg/kg/day (representing approximately 3330 times the maximal systemic concentration anticipated for topical ocular use in humans). A rare skeletal malformation was observed in the fertility/early embryo development study in rats at the 1000 mg/kg dose. An increased rate of stillborns and decreased rate of pup development was observed in rats at high doses of bepotastine besilate, but not at doses resulting in concentrations well-exceeding that anticipated for topical ocular use in humans. There are no adequate and

well-controlled studies of bepotastine besilate in pregnant women. Thus, Pregnancy Category C was recommended.

In lactating rat studies, the milk concentration of bepotastine besilate was higher than the maternal blood plasma concentration. It is not known if the drug is excreted in human milk. Thus, the reviewer recommended a caution be included in the label.

There was evidence in animal studies that the drug may have an affinity for melanin binding based on the observation of presence in the iris in an ocular toxicity study and in the pigmented tissues in a radio-labeled study. The association with melanin appears reversible, reaching below the limit of detection 30 days post a single dose.

A 26 week study in dogs using the 4 and 8X per day dosing with the 1.5% solution. The 4X per day dosing was determined to be the NOAEL based on decreases in A and B wave amplitude in electroretinograms in the 8X per day group. The NOAEL provides a 15X safety factor over that of anticipated systemic exposures anticipated with topical use in humans.

5. Clinical Pharmacology/Biopharmaceutics

Reviewer Recommendations: *The reviewer stated that the clinical pharmacology information provided by the applicant is acceptable. The reviewer concluded that the proposed dosing regimen of one drop of the 1.5% solution into the affected eye(s) twice a day is supported by the data submitted.*

I concur that there are no outstanding clinical pharmacology issues that preclude approval.

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. Additional data from multiple Phase 1 studies from the Japanese oral development program were also submitted in this application. The clinical pharmacology findings from these studies are summarized as follows:
- Following ophthalmic administration of bepotastine besilate bilaterally four times daily for seven days in healthy male subjects, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentrations were suggestive of a dose dependent increase in exposure; Cmax values for 1.0% and 1.5% bepotastine besilate were 5.138 ± 2.503 ng/mL and 7.335 ± 1.876 ng/mL, respectively. Plasma concentrations at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.
- Following a single, oral 10 mg dose of bepotastine besilate in healthy subjects, the maximum plasma concentration of bepotastine was 101.3 ± 3.5 ng/mL. This is over 10 times that of the Cmax attained following one drop of 1.5% bepotastine besilate

ophthalmic solution instilled to both eyes four times daily. Thus, the potential for adverse effects resulting from systemic exposure following administration of bepotastine besilate ophthalmic solution, 1.5% is low.
- The plasma protein binding of bepotastine in humans was approximately 55% and independent of bepotastine concentration following oral administration.
- *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes and bepotastine does not inhibit the activity of CYP3A4, CYP2C9, and CYP2C19. Thus, bepotastine besilate has a low potential for drug interactions via inhibition of CYP3A4, CYP2C9, and CYP2C19.
- Following single oral doses ranging from 2.5 to 40 mg in healthy male volunteers, approximately 76 to 88% of the bepotastine besilate dose was excreted in urine by 24 hours.

The Reviewer also reviewed studies CL-SAF-0405071-P, ISTA-BEPO-CS01, and CL-S&E-0409071-P and concurred with findings regarding Efficacy and Safety detailed below in Sections 7 and 8 of this review. The Reviewer stated that the 1.5% solution is acceptable from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Reviewer Recommendation: *Approval*

I concur that there are no outstanding clinical microbiology or sterility issues that preclude approval.

Manufacturing processes, container closure and package integrity, preservative effectiveness to maintain sterility were reviewed and deemed satisfactory. No microbiology deficiencies were identified.

7. Clinical/Statistical Efficacy

Clinical Reviewer Recommendations: *Approval. The reviewer stated that the clinical studies contained in the submission support the use of bepotastine besilate ophthalmic solution 1.5% for the treatment of itching associated with allergic conjunctivitis.*

Statistical Reviewer Recommendations: *Approval of Bepreve 1.5% for the treatment of ocular itching associated with allergic conjunctivitis.*

I concur that the efficacy of bepotastine besilate ophthalmic solution 1.5% for the treatment of ocular itching associated with allergic conjunctivitis has been demonstrated.

The support of efficacy for bepotastine besilate ophthalmic solution consisted of 2 clinical studies conducted in the U.S. (ISTA-BEPO-CS01 and CL-S&E-0409071-P). Both of these were conjunctival antigen challenge (CAC) studies. For the demonstration of efficacy in the treatment of allergic conjunctivitis, the Agency has recommended that evidence include demonstration of both statistical significance and clinical relevance in

the resolution of ocular itching and redness. In the case of antigen challenge studies or controlled environmental studies, the point estimate of the difference between groups is recommended to be at least one unit on a scale from zero to four as demonstration of clinical relevance.

Study ISTA-BEPO-CS01: A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Two Concentrations (1% and 1.5%) Bepotastine Besilate Ophthalmic Solution in the CAC Model of Acute Allergic Conjunctivitis

The primary objective of this study was to establish the efficacy of bepotastine besilate ophthalmic solution 1% and 1.5% compared to vehicle in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis at 15 minutes, 8 hours, and 16 hours following investigational product instillation. This was a single-center, double-masked, randomized, vehicle-controlled, CAC study planned for patients with a demonstrated history of allergic conjunctivitis who were ≥ 10 years of age. This study consisted of a total of 5 visits, conducted over approximately 7 weeks. The primary efficacy variables were subject-evaluated ocular itching at 3, 5, and 7 minutes post CAC and investigator-evaluated conjunctival redness at 7, 15, and 20 minutes post CAC. Itching and redness scales were based on a 5-unit (9 steps) grading scale with half unit (one step) increments allowed.

Subjects were evaluated during screening for a consistent allergic response to a defined allergen as judged by grades of 2.0 units or greater for ocular itching and hyperemia in at least 2 out of the 3 vessel beds examined during two screening visits. At Visit 1, allergen instilled in each eye of subjects was titrated for the induction of an ocular allergic response to obtain the lowest concentration of allergen that produced an allergic response. Any subject who met the criteria for an allergic response continued to Visit 2 at which time the allergen of the same identity and dose used in the previous visit was instilled in each subject eye and an ocular allergic response was confirmed. Only subjects who met the study criteria for a positive CAC reaction at Visits 1 and 2 continued to Visit 3A. At Visit 3A, a computer-generated randomization list was used to assign the subjects (in 1:1:1 proportions) to one of three treatment groups (bepotastine 1%, bepotastine 1.5%, or vehicle). Subjects in each treatment group received 3 doses of investigational product during the course of participation in this study. At Visits 3A, 4 (14 +/- 3 days post Visit 3A), and 5 (28 +/- 3 days post Visit 3A), a trained technician instilled 1 drop of the assigned investigational product into both eyes of each subject. CAC was performed, using the previously validated allergen dose for each subject at: 16 hours (duration-of-action acceptable for drugs intended to be dosed QD), 8 hours (duration-of-action acceptable for drugs intended to be dosed BID), or 15 minutes (onset of action) post investigational product instillation during Visit 3A, 4, and 5, respectively. Signs and symptoms of allergic conjunctivitis were then graded over a 20-minute period following the CAC.

A total of 107 subjects were randomized in study ISTA-BEPO-CS01. For ITT population, there was no difference among arms for age, gender, ethnicity, race, or eye

color. Six patients were excluded from the PP population (one for I/E protocol violation, one for missed visit protocol violation, and four early discontinuations). Thus, the PP population consisted of 101 subjects. Note that this is a single site trial.

Study C-S&E-0409071-P: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Two Concentrations of Bepotastine Besilate Ophthalmic Solution (1% and 1.5%) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis

The primary objective of this study was to establish the safety and efficacy of bepotastine besilate ophthalmic solution 1% and 1.5% compared to vehicle in alleviating the signs and symptoms of allergic conjunctivitis at 15 minutes, 8 hours, and 16 hours following investigational product instillation using the CAC model of allergic conjunctivitis in subjects with a history of allergic conjunctivitis. This was a multi-center, double-masked, randomized, vehicle-controlled, CAC study planned for approximately 130 subjects with a demonstrated history of allergic conjunctivitis who were ≥10 years of age. This study was conducted at 5 sites and consisted of 5 visits, completed over approximately 7 weeks. The primary efficacy measures, secondary efficacy measures, and study procedures were the same as for Study ISTA-BEPO-CS01. The only additional measure performed was patient ocular comfort scores.

A total of 130 subjects were randomized in study C-S&E-0409071-P. For ITT population, there was no difference among arms for age, gender, ethnicity, race, or eye color. Thirteen patients were excluded from the PP population (all classified as discontinued/withdrawn, most no-shows based on CRF review). Thus, the PP population consisted of 117 subjects.

Efficacy Analyses for Both Studies: The primary efficacy analyses in the two phase 3 studies were based on the ITT population with LOCF method for imputing missing data. Sensitivity analyses using PP population and ITT population with observed data only were carried out and results consistent with those of the primary analyses. More conservative multiplicity adjustments were made by the Statistical Reviewer with no change in the conclusions of the analyses. The average score of each subject's eyes was the unit used for comparison between bepotastine and vehicle for all analyses. Clinical significance required at least a 1 unit difference in the point estimate between arms for the majority of time points at a study visit during the treatment period. Clinical success at a study visit required achievement of both statistical and clinical significance for a majority of time points. Clinical efficacy for ocular itching and conjunctival redness was considered to have been achieved by showing clinical success at Visit 5 (CAC at 15 min post dosing) as well as at Visit 3B (CAC 16 hours post dosing) and/or Visit 4 (CAC 8 hours post dosing).

In both studies, a robust statistically significant difference in mean itching grades vs. vehicle was noted for both the 1% and 1.5% bepotastine solutions for Visits 3A, 4, and 5 at 3, 5, and 7 minutes post CAC for both the ITT and PP populations. However, to demonstrate clinical significance, a difference between groups of at least one unit on the

ocular itching scale of 0-4 at a majority of time points evaluated was required. This difference of at least one unit was duplicated in the two trials only at the 8 hours post dosing CAC (Visit 4) with both the 1% and 1.5% concentrations of the drug. The 1.5% solution produced a greater difference in point estimate for the mean itching grades vs. vehicle than the 1% solution at both the 8 hours post dosing (Visit 4) and 16 hours post dosing (Visit 3A) CAC visits. Thus, the Clinical, Statistical, and CDTL Reviewers felt that the data supports a preferred dosing using the 1.5% solution bid for the treatment of itching associated with allergic conjunctivitis. The percentage of eyes with no itching at various post-CAC times was evaluated in a post-hoc analysis using the ITT population with LOCF. This post-hoc analysis supported the conclusion that the 1.5% solution had a clinical response of greater magnitude than the 1% solution. With respect to conjunctival redness, neither concentration of bepotastine was found to produce a clinically significant reduction (difference of at least one unit in the point estimate for mean conjunctival hyperemia scores) compared to vehicle at any study visit in either study. The Clinical and Statistical reviewer concurred that both the 1.0% and 1.5% solutions failed in the primary endpoint of conjunctival redness. Long-term effectiveness was not evaluated in these studies as the duration of treatment for the subjects in these trials was three single doses at three separate visits.

8. Safety

Recommendations: *The Clinical Reviewer and CDTL recommended that the benefits of using this drug outweigh the risks for the above indication. No proposed risk management action except standard post-marketing collection and reporting of adverse experiences and no Phase 4 clinical study commitments were recommended.*

I concur with these recommendations. The common adverse effects described in labeling include mild taste disturbance as well as eye irritation, headache, and nasopharyngitis.

Study CL-SAF-0405071: The main support of safety for bepotastine 1.5% came from study CL-SAF-0405071 "A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Bepotastine Besilate Ophthalmic Solution 1.5% Used Twice Daily in Healthy, Normal Volunteers". This trial was conducted at 6 sites in the U.S. The dosing regimen for all subjects was 1 drop administered bilaterally, twice daily, for 6 continuous weeks. The target study population was subjects 3 years of age and older with normal ocular health. Randomization was at a ratio of 2:1 (active: vehicle) and subjects were not stratified by age group. This study consisted of 4 visits conducted over approximately 43 days for all study participants except for a subset of subjects who underwent ocular endothelial cell counts (ECC). At 1 of the 6 study sites, a sub-population of subjects ≥10 years of age who agreed to undergo specular microscopy at Visit 1 (baseline) and again at Visit 5 (Day 84 + 7) was identified. To be enrolled, a baseline ECC of ≥2200 cells/mm2 was necessary. All subjects who did not undergo endothelial cell counts at Visit 1 completed the clinical trial at Visit 4.

575 subjects were randomized to bepotastine besilate 1.5% and 286 to vehicle. Of the 861 total subjects enrolled, 127 were pediatric subjects. Of the pediatric subjects, 72 were 3-9

years of age and 55 were 10-17 years of age. Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of bepotastine given by the topical route of administration. No deaths occurred during study CL-SAF-0405071. No serious adverse events were reported during study CL-SAF-0405071. 801 subjects completed the study and this was proportionate between arms. Twelve subjects withdrew from the study early with an AE being listed as the reason for study discontinuation (6 in the bepotastine group and 6 in the vehicle group).

Four adverse events occurred in ≥2% of subjects in the bepotastine besilate ophthalmic solution 1.5% treatment group: taste disturbance upon instillation, eye irritation, headache, and naso-pharyngitis. 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, 25.2% 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). There was a considerable variation in the frequency of taste-related issues reported as AEs between sites: the percentage of subjects in the bepotastine besilate ophthalmic solution 1.5% treatment group reporting a taste-related AE varied from 0% (investigative site 5) to 42% (investigative site 6). In addition, subjects receiving bepotastine 1.5% did not experience any clinically significant changes from baseline or compared to subjects receiving vehicle in any of the other safety measurements (visual acuity, intraocular pressure, dilated fundoscopy, slit-lamp biomicroscopy, ocular endothelial cell counts, and ocular comfort evaluations). The type and pattern of occurrence of treatment-emergent AEs related to the investigational product in the 2 pediatric age subgroups were similar to those observed in the overall safety population. There were no clinically significant differences in endothelial cell density between the bepotastine 1.5% and the vehicle arms. The data did not show evidence of a delayed toxicity or increased safety risks associated with duration of exposure.

Studies ISTA-BEPO-CS01 and C-S&E-0409071-P: The safety population was defined as all subjects in these studies who received at least one dose of test agent. There were 107 subjects in the safety population for ISTA-BEPO-CS01 and 130 subjects in the safety population for CL-S&E-0409071-P. In both studies, the following safety measures were evaluated: visual acuity, slit lamp biomicroscopy, IOP measurement, dilated fundoscopy, adverse event reporting. There were no SAEs or deaths reported. Adverse ocular events were infrequent and more common in the vehicle group. Non-ocular adverse events (none severe) occurred with greater frequency in the bepotastine arms in study ISTA-BEPO-CS01, and this was due to the greater incidence of dysgeusia in these groups. Ocular comfort was evaluated in study C-S&E-0409071-P on each occasion that subjects received investigational product. There were no differences in ocular comfort scores between the two concentrations of bepotastine and vehicle at any time point.

Other: Electrocardiograms were not obtained in any of the reviewed studies. Drug-drug interaction studies were not performed. The drug has not been tested in pregnant women.

Post-Marketing Reporting: Post-marketing reporting in Japan of Talion tablets was summarized for approximately 6 years of marketing experience. The most common adverse events were drowsiness (1.32%) and upper abdominal pain (0.13%). In addition, long term use of Talion tablets was investigated as part of another post-marketing study conducted in Japan. The most common adverse events were drowsiness and dry mouth (0.26%), and upper abdominal pain, facial edema, and pharyngeal edema (each 0.09%). Adverse events in the geriatric population were not different than that in the general population. A retrospective analysis of the safety of Talion tablets in pediatric patients ages 5-14 years was completed in Japan. The incidence of side effects was not different than that in the adult reports.

9. Advisory Committee Meeting

Since this is a NME (new molecular entity) advisory committee was convened on June 26, 2009.
The following questions were presented 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

A partial waiver of the 0 months -2 years and 11 months age group was requested by the sponsor with the rationale that study of this age group was not feasible as there were too few children in this age group with the condition to study. This partial waiver was approved as the disease is not considered to be reliably diagnosed below the age of 2 years.

Children 10 years of age and above were included in the CAC efficacy studies. There are no recognized differences in the disease in pediatric patients below the age of 10 years and older children or adults. However, children under 10 years of age are not considered reliable historians for the reporting of ocular itching scores. Thus, 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 adults.

Bepreve was tested for 6 weeks in 87 subjects ranging in age between 3 and 17 years of age in ISTA safety study CL-SAF-0405071-P. The safety profile did not differ in this group from the patient population 18 years and older.

The PeRC reviewed this NDA on 5/27/09.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

DSI inspections of selected sites for studies ISTA-BEPO-CS01, CL-S&E-0409071, and L-SAF-0405071 were conducted. In addition, inspection of the sponsor, ISTA Pharmaceuticals, was conducted. DSI concluded that, in general, the protocols appear to have conducted adequately and the data in support of the NDA appear reliable. There were regulatory violations noted at two investigator sites, but the safety and efficacy data from these sites was considered reliable.

Financial Disclosure: There were no investigators with proprietary interest or with any significant interest in the drug product in ISTA-BEPO-CS01, CL-S&E-0409071, or CL-SAF-0405071.

12. Labeling

DMEPA proprietary name risk assessment review was conducted and it was determined that the proposed name, Bepreve, would be unlikely to be vulnerable to name confusion that could lead to medication errors. DDMAC had no concerns regarding the proposed name from a promotional perspective.

DMEPA also provided recommendations on the packaging configuration and the package insert. These were incorporated in the labeling where appropriate. The DMEPA reviewer subsequently reviewed the final packaging configuration and package insert and indicated concurrence.

DDMAC recommended changes to the Warnings and Precautions section of the Highlights of Prescribing Information to add, “Lenses may be reinserted after 10 minutes following administration of Bepreve” to the sentence “Remove contact lenses prior to installation of Bepreve”. The CDTL disagreed with this recommendation due to concern that this may be misunderstood and promote the use of contact lenses when the eyes are red. I concur with the CDTL recommendation. More detailed information for contact lens use is included in the Warnings and Precautions section of the Full Prescribing information.

DDMAC recommended changes to the Adverse Reactions of the Full Prescribing Information to include additional detail concerning the data sources for the adverse event

data as well as identify adverse events that resulted in a significant rate of discontinuation or other clinical intervention. The CDTL recommended against additions to the Adverse Event section of the PI and I concur with this recommendation. The number of subjects enrolled and the duration of exposure for Study CL-SAF-0405071 as well as the two CAC studies are described in the Clinical Studies section of the PI. Adverse reactions which occurred in $\geq$ 2% of subjects have been included in the Adverse Reactions section of the PI. No adverse reactions occurred which resulted in a significant rate of discontinuation or other clinical intervention.

DDMAC recommended that specific efficacy data be included to qualify the superiority claims made in the label, "Bepreve …was more effective than its vehicle for relieving ocular itching induced by on ocular allergen challenge, both at CAC 15 minutes post-dosing and at CAC 8 hours post dosing of Bepreve." The CDTL recommended against additions to the Clinical Studies section of the PI and I concur with this recommendation. It would be challenging to communicate more detailed information concerning the efficacy standard of statistical and clinical significance for a CAC study in a cogent manner. Presentation of actual results in tabular format may lead a reader to conclude that a statistical difference in the point estimate met the efficacy standard, when in fact a clinically significant difference had not been observed.

Division concerns regarding the DDMAC recommendations were discussed with the DDMAC reviewer by Dr. Chambers. I discussed the DDMAC recommendations with the reviewer seeking additional clarity regarding the recommendations. My concurrence with the CDTL concerning these recommendations is discussed above.

13. Decision/Action/Risk Benefit Assessment

I concur with the recommendations of all reviewers for a regulatory action of approval.

Based upon the findings of adequate and well-controlled clinical trials, there is substantial evidence of efficacy and safety. Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P demonstrated that patients with allergic conjunctivitis receiving Bepreve (bepotastine besilate ophthalmic solution, 1.5%) experienced a clinically and significant response in the reduction of ocular itching during CAC. These studies provide evidence supportive of the recommended twice a day dosing. Study CL-SAF-0405071 characterized adverse events in health volunteers receiving Bepreve (bepotastine besilate ophthalmic solution, 1.5%) twice a day for six weeks. The most common adverse reaction was taste perversion following installation occurring in 25% of subjects. Adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nosopharyngitis. No adverse reactions occurred which resulted in a significant rate of discontinuation or other clinical intervention.

There are no recommendations for Post-marketing Risk Evaluation and Mitigation Strategies. There are no recommendation for Postmarketing Requirements and Commitments.

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

/s/

JOHN J FARLEY
09/08/2009

EDWARD M COX
09/08/2009