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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

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