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APPLICATION NUMBER:

22-228

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-288
Submission Date(s):	12NOV2008
Brand Name	Bepreve™
Generic Name	Bepotastine Besilate Ophthalmic Solution 1.5%
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	ISTA Pharmaceuticals®, Inc.
Relevant IND(s)	IND 66,864
Submission Type; Code	Original NDA; 505(b)(1) application; 1S (new molecular entity)
Formulation; Strength(s)	Bepotastine Besilate Ophthalmic Solution 1.5%
Indication	Treatment of ocular itching associated with allergic conjunctivitis in patients age 3 years or older

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1. EXECUTIVE SUMMARY

Bepotastine besilate is a selective histamine H_1-receptor antagonist. Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is a sterile ophthalmic solution of bepotastine besilate proposed for the treatment of itching associated with signs and symptoms of allergic conjunctivitis in patients aged 3 years or older. The proposed dosage and route of administration for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is as follows: instill one drop into the affected eye(s) twice a day (BID). Bepotastine besilate (also known as TAU-284 and SNJ-1773) was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. as a treatment for allergic rhinitis. An oral preparation of bepotastine besilate (Talion® tablets, Mitsubishi Tanabe Pharma Corporation [formerly Tanabe Seiyaku Company, Ltd.]) was approved in Japan in July 2000 and launched in October 2000. In January 2002, the additional indication of pruritus/itching accompanying urticaria and other skin diseases was approved in Japan.

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. To support the safety and efficacy of Bepreve™ (bepotastine besilate ophthalmic solution), 1.5%, the applicant conducted one Phase 2/3 (single site) and one Phase 3 (multisite), placebo-controlled, double-masked, randomized conjunctival allergen challenge (CAC) efficacy studies with bepotastine besilate ophthalmic solutions 1.0% and 1.5% in male and female subjects aged 10 years and older who have a positive history of allergic conjunctivitis (Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P). Both pivotal trials evaluated the clinical efficacy of two bepotastine besilate ophthalmic solutions (1.0% and 1.5%) at each of two durations of action (8 hours, considered acceptable for a drug intended for dosing BID, and 16 hours, considered acceptable for a drug intended for dosing QD) by having 5 subject visits over approximately 7 weeks. In addition, a Phase 3 multisite, double-masked, randomized, placebo-controlled, parallel-group study (CL-SAF-0405071-P) evaluated the safety of bepotastine besilate ophthalmic solution 1.5% administered 2 times per day (BID) for 6 weeks in healthy, normal volunteers 3 years of age and older.

1.1. Recommendation

The clinical pharmacology information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is a sterile ophthalmic solution of bepotastine besilate proposed for the treatment of itching associated with signs and symptoms of allergic conjunctivitis in patients aged 3 years or older. The proposed dosage and route of administration for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is as follows: instill one drop into the affected eye(s) twice a day (BID). The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1.0% and 1.5% ophthalmic solution was evaluated in a multiple-dose pharmacokinetic (PK) study in 12 healthy

adults (Study SNJ-TO-02). 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 the below 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.

Based on the assessment of systemic exposure information for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5%, the regulatory requirement for submission of in vivo bioavailability data has been adequately addressed.

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Concurrence:

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Charles R. Bonapace, Pharm.D.
Team Leader

cc:
Division File: NDA 22-288
HFD-520 (CSO/Rodriguez)
HFD-520 (MO/Wadhwa)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

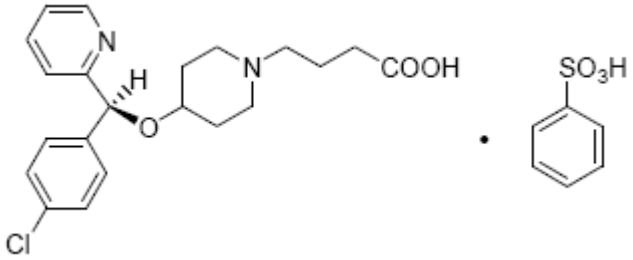
2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is a sterile, clear colorless to pale yellow aqueous solution containing bepotastine besilate as the active ingredient. Bepreve™ ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8 and an osmolality of approximately 290 mOsm/kg.

Structural Formula: $C_{21}H_{25}ClN_2O_3 \bullet C_6H_6O_3S$

Chemical Structure:



Chemical Name: (+)-(S)-4-{4-[(4-Chlorophenyl)(2-pyridyl)methoxy] piperidino} butyric acid monobenzenesulfonate

Compendial Name: Bepotastine Besilate

International Nonproprietary Name (INN): Bepotastine

Company Laboratory Code: TAU-284, SNJ-1773

Chemical Abstract Service (CAS) Registry Number: 190786-44-8

Molecular Weight: 547.06

The qualitative and quantitative composition of the proposed Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% drug product is shown in Table 2.2-1.

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