CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

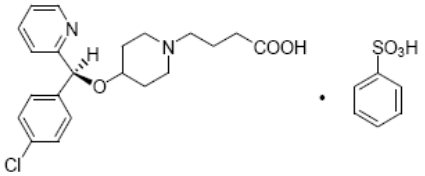
SUMMARY REVIEW

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.

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