CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

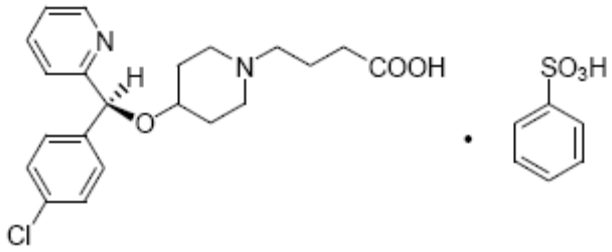
CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 25, 2009
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	22-288
Applicant	ISTA Pharmaceuticals, Inc.
Date of Submission	November 12, 2008
PDUFA Goal Date	September 12, 2009
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 and has an inhibitory action on eosinophilic infiltration to inflammatory sites.

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

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 is a new molecular entity in the United States.

Studies CL-S&E-0409071 and CL-SAF-0405071 (7/23/07 SPA response) were performed after submission of a Special Protocol Assessment (SPA). There was an EOP 2 Meeting held on 8/15/07, a SPA Meeting held on 9/17/08, and a pre-NDA Meeting on 8/4/08.

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. 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.

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

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.

3. CMC

From the two CMC Reviews finalized 7/27/09 and 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 (b) (4). 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 was originally developed as an oral tablet dosage form and received approval in Japan in 2000 for allergic rhinitis. Bepotastine besilate ophthalmic solution 1.5% is an aqueous solution to be administered as drops at or near physiological pH range of tears. The formulation contains sodium chloride, monobasic sodium phosphate as dihydrate, benzalkonium chloride, sodium hydroxide and purified water; typically these components are used for adjusting tonicity, preservative action, pH adjustment, buffering capacity and a vehicle for administration. It was demonstrated during the formulation development that sodium chloride, in addition to its use to (b) (4) All excipients are of USP/NF grade. It is manufactured as a (b) (4) solution.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Table of Composition of Bepotastine Besilate Ophthalmic Solution

Components	Function	Amount/mL	(b) (4) Batch Composition	(b) (4) Batch Composition	% w/v
Bepotastine besilate	Active pharmaceutical ingredient	15 mg[1] (b) (4)	(b) (4)		
Sodium chloride			(b) (4)		
Monobasic Sodium Phosphate, Dihydrate					
Benzalkonium chloride	Preservative	0.05 mg	(b) (4)		
Sodium hydroxide	pH adjuster	qs to pH 6.8	(b) (4)		
Water for Injection	Solvent	qs			

[1] For Bepreve™ 1.5% drug product
[2] For Bepreve™ 1.0% drug product

PROPOSED REGULATORY SPECIFICATIONS:

(b) (4)

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