

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **BEPREVE**<sup>TM</sup>

Bepotastine besilate ophthalmic solution 1.5% w/v

Selective Histamine H1 Receptor Antagonist

Bausch & Lomb Incorporated  
1400 North Goodman Street  
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# BEPREVE™

Bepotastine besilate ophthalmic solution 1.5% w/v

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Ophthalmic	Solution bepotastine besilate/ 1.5% w/v	Benzalkonium chloride 0.005% w/v as preservative <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v is indicated for the treatment of itching associated with allergic conjunctivitis.

#### **Geriatrics (> 65 years of age):**

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

#### **Pediatrics (<18 years of age):**

Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v have not been established in pediatric patients under 3 years of age. 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 from adults.

### CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

## WARNINGS AND PRECAUTIONS

### General

BEPREVE is for topical ophthalmic use only.

To minimize contamination of the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

### Carcinogenesis and Mutagenesis

Please refer to animal data in TOXICOLOGY section.

### Ophthalmologic

BEPREVE should not be used to treat contact lens-related irritation. BEPREVE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

### *Special Populations*

#### **Pregnant Women:**

Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats and rabbits at oral doses representing up to approximately 2,000 times and 5,000 times maximal recommended ophthalmic dose in humans, respectively (See TOXICOLOGY).

However, there are no adequate and well-controlled studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### **Nursing Women:**

Following oral administration, bepotastine besilate has been identified in the milk of nursing rats. It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v is administered to a nursing woman.

#### **Pediatrics (<18 years of age):**

Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v have not been established in pediatric patients under 3 years of age. 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 from adults.

**Geriatrics (> 65 years of age):**

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

**ADVERSE REACTIONS****Adverse Drug Reaction Overview**

Safety of bepotastine besilate 1.5% w/v ophthalmic solution was evaluated in 3 U.S. clinical trials (Phase 2/3 and 3, 653 subjects exposed to bepotastine besilate 1.5% w/v). The product was generally well tolerated. The most common reported adverse reaction occurring in approximately 13.5% of subjects treated with bepotastine besilate ophthalmic solution was mild and transient taste-perversion. Other adverse reactions associated with the disturbance of taste were bad taste and after taste which occurred in approximately 6.9% and 2.1%, respectively. Other adverse reactions occurring in 2-10% of subjects were eye irritation and headache. No subject experienced a serious adverse event during clinical trials.

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

A total of 653 subjects were exposed to bepotastine besilate ophthalmic solution 1.5% w/v in U.S. clinical studies.

Safety parameters monitored during bepotastine besilate ophthalmic solution clinical trials included: adverse events (reported, elicited, and observed); distance visual acuity; slit lamp biomicroscopy; intraocular pressure (IOP); dilated funduscopy; ocular comfort examination. Additionally, physical examination and pregnancy test were conducted in Phase 3 safety study (CL-SAF-0405071).

Adverse events occurred in >1% of subjects are provided in Table 1.

**Table 1. Incidence of treatment-related adverse events occurred in >1% of subjects receiving bepotastine besilate 1.5% w/v ophthalmic solution in U.S. clinical studies**

<b>System Organ Class Preferred Term<sup>1</sup></b>	<b>Bepotastine besilate ophthalmic solution 1.5% w/v (n=653)</b>	<b>Placebo (n=365)</b>
	n (%)	n (%)
<b>Eye disorders</b>		
Eye irritation	29 (4.4)	10 (2.7)
<b>Nervous system disorders</b>		
Taste perversion <sup>2</sup>	88 (13.5)	4 (1.1)
Bad taste <sup>2</sup>	45 ( 6.9)	1 (0.3)
Headache	18 (2.8)	6 (1.6)
After taste	14 (2.1)	2 (0.5)

1 - System Organ Class and Preferred Terms were coded according to MedDRA version 9.1 for ISTA-BEPO-CS01, and were coded according to MedDRA version 10.1 for CL-S&E-0409071-P and CL-SAF-0405071-P.

2 - Lower-level term. MedDRA version 9.0 codes all taste-related adverse events to the preferred term 'dysgeusia'. Many medical dictionaries define dysgeusia as an impairment, distortion, dysfunction or alteration of taste. Thus, dysgeusia is an inaccurate term for the description of the taste of an investigational product, referring to subversion of taste sensations rather than the inherent quality of taste for the investigational product.

Most adverse events were mild and transient. No subject experienced a serious adverse event.

No clinically significant findings were observed during other safety measurements (visual acuity, IOP, slit lamp microscopy, dilated funduscopy, endothelial cell counts). There was no clinically significant difference in ocular comfort (measured on a 4 point grading scale, where 0 was comfortable, 3 – severely uncomfortable) upon instillation between study and control groups.

***Less Common Clinical Trial Treatment-Related Adverse Drug Reactions (<1%)***

**Eye disorders:** asthenopia, allergic conjunctivitis, dry eye, eyelid margin crusting, eyelid oedema, eyelid pain, eye pain, eye swelling, foreign body sensation in eyes, keratitis, lacrimation increased, ocular hyperaemia, photophobia, punctuate keratitis; **nervous system disorders:** parosmia; **infections and infestation:** herpes zoster, sinusitis; **respiratory, thoracic, and mediastinal disorders:** cough, pharyngolaryngeal pain, postnasal drip, rhinorrhea, sinus congestion, sneezing; **ear/nose/throat:** Pharyngolaryngeal pain; **gastrointestinal disorders:** lower abdominal pain, diarrhea, dry mouth, gastroesophageal reflux disease, nausea; **muskuloskeletal and connective tissue disorders:** ear and labyrinth disorder, ear pain,

eustachian tube obstruction, tinnitus; **skin and subcutaneous tissue disorders:** Photosensitivity reaction; **vascular disorders:** hyperaemia; **general disorders and administrative site conditions:** chest pain.

### **Post-Market Adverse Drug Reactions**

Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

## **DRUG INTERACTIONS**

### **Overview**

There have been no clinical trials on potential drug-drug interactions for bepotastine besilate.

Drug-drug, drug-food, drug-herb and drug-laboratory interactions have not been studied.

In vitro metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Clinically relevant systemic drug-drug interactions are not anticipated due to the topical route of ocular administration.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

There are no special dosage considerations necessary for BEPREVE (bepotastine besilate) ophthalmic solution 1.5% w/v.

### **Recommended Dose and Dosage Adjustment**

Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

## Missed Dose

If a dose is missed, a single drop should be instilled as soon as remembered before returning to the normal dosing schedule. Patients should not try to catch up on missed drops by applying more than one dose at a time.

## Administration

BEPREVE should not be instilled while wearing contact lenses. Contact lenses should be removed prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE (see WARNINGS and PRECAUTIONS, Ophthalmologic).

To minimize contamination of the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

## OVERDOSAGE

No data are available regarding overdose of BEPREVE (bepotastine besilate ophthalmic solution). No cases of overdose were reported in clinical trials of bepotastine besilate ophthalmic solutions.

A topical overdosage may be flushed from the eye(s) with warm tap water.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Bepotastine besilate is a second generation dual acting antihistamine with several described mechanisms of action that play role in allergic response. Primary mechanisms of action include non-sedating, selective antagonism of H<sub>1</sub>-histamine receptors, stabilization of mast cells, inhibitory action on eosinophilic migration to inflammatory sites, and suppression of vascular permeability. Bepotastine besilate exhibits strong affinity to H<sub>1</sub> receptors, and does not selectively bind to histamine H<sub>3</sub>, adrenergic ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ), muscarinic, serotonin (5-HT<sub>2</sub>), and benzodiazepine receptors. It inhibits production of interleukin-5 (IL-5), key factor in eosinophil activation, as well as other mediators of inflammatory and allergic reactions, such as leukotriene B<sub>4</sub> (LTB<sub>4</sub>), leukotriene D<sub>4</sub> (LTD<sub>4</sub>), platelet activating factor (PAF), substance P. Bepotastine demonstrates activity in both early and late phases of the allergic response.

## Pharmacodynamics

Primary effects of bepotastine besilate ophthalmic solution were studied in U.S. clinical trials. Bepotastine was found to improve signs and symptoms of allergic conjunctivitis, such as itching and tearing. In animal studies, bepotastine besilate was also found to inhibit conjunctival edema in guinea pigs.

### *Penetration of blood-brain barrier.*

Bepotastine besilate had little effect on displacement of the tricyclic antidepressant doxepin from brain histamine H1 receptors (a measure of the ability to cross the blood-brain barrier), thus confirming its low sedating propensity

### *Cardiac effects.*

Effects of bepotastine besilate ophthalmic solution (0.5% w/v, 1.0% w/v, or 1.5% w/v) on 12-lead ECGs of healthy individuals was compiled from 2 clinical studies in healthy male volunteers. No drug-related QTc prolongation or drug-related abnormal ECG was observed with any concentration of bepotastine besilate ophthalmic solution (0.5% w/v, 1.0% w/v, or 1.5% w/v) for 25 repeated doses given QID over a 7 day period.

## Pharmacokinetics

**Absorption:** Non clinical experiments suggested that bepotastine besilate ophthalmic solution 1.5% w/v has very little systemic exposure.

**Distribution:** Ophthalmic dosing of bepotastine besilate ophthalmic solution 1.5% w/v in rabbits led to the highest drug levels (>20X levels seen in plasma) in cornea, conjunctiva, and iris ciliary body

**Metabolism:** In vitro metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes. In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

**Excretion:** The half-life of bepotastine in human plasma from normal human volunteers after oral administration was 2.3-3.3 hours and was consistent regardless of dose or of frequency of dosing. The terminal half-life of bepotastine after ophthalmic administration can be estimated from pre-clinical studies to be 7-8 hours. The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

### *Special Populations and Conditions*

**Pediatrics:** There have been no clinical studies on the effects of dosing with bepotastine besilate ophthalmic solution in pediatric patients.

**Geriatrics:** The effects of age on the plasma concentrations of bepotastine besilate ophthalmic solution has not been evaluated.

**Gender:** The effects of gender on the plasma concentrations of bepotastine besilate ophthalmic solution has not been evaluated.

**Race:** The effects of race on the plasma concentrations of bepotastine besilate ophthalmic solution has not been evaluated.

**Hepatic Insufficiency:** There is no clinical information on the potential effects of hepatic impairment on the pharmacokinetics of bepotastine.

**Renal Insufficiency:** There have been no clinical studies on the effects of dosing with bepotastine besilate ophthalmic solution in patients with renal impairment.

## **STORAGE AND STABILITY**

Store at controlled room temperature, 15°C – 25°C.

## **SPECIAL HANDLING INSTRUCTIONS**

None.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following sizes: 7.5 mL (with 1 mL (sample) or 5 mL fill volumes), and 10 mL (with 10 mL fill volume).

Each mL of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v contains:

**Active:** Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine).

**Preservative:** benzalkonium chloride 0.005%

**Inactive ingredients:** monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

**Additional Information:** BEPREVE (bepotastine besilate ophthalmic solution) is supplied as a sterile, aqueous 1.5% w/v solution, with a pH of 6.8 and an osmolality of approximately 290 mOsm/kg.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

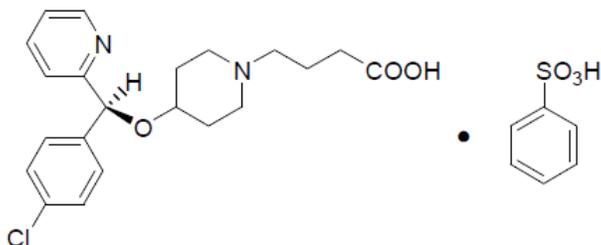
#### Drug Substance

Proper name: Bepotastine (INN)

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

Molecular formula and molecular mass:  $C_{21}H_{25}ClN_2O_3 \cdot C_6H_5O_3S$  and 547.06

Structural formula:



Physicochemical properties: White or pale yellowish white crystalline powder with a melting point of approximately 162 °C; very soluble in acetic acid (100); freely soluble in N, N-dimethyl formamide and methanol; sparingly soluble in water and ethanol (99.5); slightly soluble in acetonitrile; practically insoluble in 2-propanol and ethyl acetate.

### CLINICAL TRIALS

#### Study demographics and trial design

The clinical program included one Phase 2/3 and one Phase 3, placebo-controlled, double-masked, randomized clinical efficacy trial with bepotastine besilate ophthalmic solution 1.0% w/v and bepotastine besilate ophthalmic solution 1.5% w/v in male and female subjects aged 10 years and older who had a positive history of allergic conjunctivitis (study ISTA-BEPO-CS01 and study CL-S&E-0409071-P).

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% w/v also was evaluated in a randomized clinical safety study of 861 healthy subjects over a period of 6 weeks.

**Table 2. Summary of patient demographics for clinical trials in conjunctival allergen challenge (CAC) studies**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender
ISTA-BEPO-CS01	Single center, double-masked, randomized, placebo-controlled, CAC study	Bepotastine besilate ophthalmic solution 1.0% w/v, 1.5% w/v, or Placebo Dose: One drop at Visit 3A, Visit 4, and Visit 5 Route: ophthalmic Duration: 7 weeks	107	41.7 years (11.0 - 73.0)	Female: 58 (54.2%) Male: 49 (45.8%);
CL-S&E-0409071-P	Multi-center, double-masked, randomized, placebo-controlled, CAC study	Bepotastine besilate ophthalmic solution 1.0% w/v, 1.5% w/v, or Placebo Dose: One drop at Visit 3A, Visit 4, and Visit 5 Route: ophthalmic Duration: 7 weeks	130	33.8 years (11.0 - 63.0)	Female: 75 (57.7%) Male: 55 (42.3%)
CL-SAF-0405071-P	Multi-center, randomized, double-masked, placebo-controlled, parallel-group safety study	Bepotastine besilate Opth. Sol. 1.5% w/v or placebo, one drop in each eye BID	861	34.4 years (3.0 to 84.0) years	Female: 367 (63.8%) Male: 208 (36.2%)

## Study results

### *Efficacy*

Efficacy of bepotastine besilate ophthalmic solution was evaluated in two conjunctival allergen challenge (CAC) studies, ISTA-BEPO-CS01 and CL-S&E-0409071-P, using multiple allergens, both seasonal and perennial. Primary endpoints included ocular itching (measured on a 5-point scale, from 0 (none) to 4 (incapacitating itch with an irresistible urge to rub)) and conjunctival hyperemia (measured on a 5-point scale, from 0 (none) to 4 (extremely severe)). Both primary endpoints were evaluated at 3 visits assessing onset of action (Visit 5), 8-hour duration of action (Visit 4), and 16-hour duration of action (Visit 3B). Ocular itching was evaluated at 3, 5, and 7 minutes following a CAC, while conjunctival hyperemia was evaluated at 7, 15, and 20 minutes following a CAC in both pivotal efficacy CAC trials.

Results for bepotastine besilate 1.5% w/v (intention-to-treat (ITT) population with last observation carried forward (LOCF) analysis) are provided in Table 3 and

Table 4 for ocular itching and conjunctival hyperemia, respectively.

Table 3. Mean differences in itching grades after instillation of bepotastine besilate 1.5% w/v, compared to placebo

	Onset of action (Visit 5)			8-hour duration of action (Visit 4)			16-hour duration of action (Visit 3B)		
	time post CAC test			time post CAC test			time post CAC test		
	3 min	5 min	7 min	3 min	5 min	7 min	3 min	5 min	7 min
ISTA- BEPO- CS01	1.4	1.4	1.3	1.3	1.5	1.4	0.9	1.0	1.0
<i>p-value</i>	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
CL- S&E- 0409071 -P	1.5	1.6	1.4	1.3	1.3	1.2	0.6	0.7	0.8
<i>p-value</i>	<0.000 1	<0.000 1	<0.000 1	<0.000 1	<0.000 1	<0.000 1	0.005 1	0.002 1	0.000 3

= Statistical significance for difference in median values (placebo – active), Wilcoxon Rank Sum test

\*\* = Visit 3B required 16 hours between investigational product dosing and CAC test

\*\*\* = Visit 4 required 8 hours between investigational product dosing and CAC test

\*\*\*\* = Visit 5 required 15 minutes between investigational product dosing and CAC test

Table 4. Mean Difference in Conjunctival Hyperemia Grades after instillation of bepotastine besilate 1.5% w/v, compared to placebo

	Onset of action (Visit 5)			8-hour duration of action (Visit 4)			16-hour duration of action (Visit 3B)		
	time post CAC test			time post CAC test			time post CAC test		
	7 min	15 min	20 min	7 min	15 min	20 min	7 min	15 min	20 min
ISTA- BEPO- CS01	0.6	0.4	0.3	0.4	0.4	0.3	0.2	0.0	-0.1
<i>p-value</i>	0.004	0.039	0.151	0.029	0.062	0.137	0.208	0.755	0.711
CL- S&E- 0409071- P	0.4	0.4	0.2	0.2	0.1	0.1	0.1	0.1	0.1
<i>p-value</i>	0.0031	0.0114	0.2251	0.1067	0.3598	0.5909	0.5472	0.3882	0.5000

\* = Statistical significance for difference in median values (placebo – active), Wilcoxon Rank Sum test

\*\* = Visit 3B required 16 hours between investigational product dosing and CAC test

\*\*\* = Visit 4 required 8 hours between investigational product dosing and CAC test

\*\*\*\* = Visit 5 required 15 minutes between investigational product dosing and CAC test

Clinical significance was defined as change of more than one unit on the grading scale at a majority of time points evaluated.

Bepotastine besilate 1.5% w/v demonstrated both clinical and statistical significance for the reduction of ocular itching in the onset of action CAC test starting at 3 minutes, and 8-hour duration of action CAC test.

Bepotastine besilate 1.5% w/v showed both clinical and statistical significance in the onset of action CAC test starting at 3 minutes, and 8-hour duration of action CAC tests for the secondary endpoint: tearing.

## **DETAILED PHARMACOLOGY**

Bepotastine is topically active anti-allergic medication. It acts as a highly selective direct H<sub>1</sub>-receptor antagonist and mast cell stabilizer. Additionally, bepotastine reduces vascular permeability and down regulates migration of eosinophils to sites of inflammation. Bepotastine exhibits activity on H<sub>1</sub> receptors, interleukin-5 (IL-5), leukotriene B<sub>4</sub> (LTB<sub>4</sub>), leukotriene D<sub>4</sub> (LTD<sub>4</sub>), platelet activating factor (PAF), substance P, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ); and does not selectively bind to histamine H<sub>3</sub>, adrenergic ( $\alpha$ <sub>1</sub>, $\alpha$ <sub>2</sub>, $\beta$ ), muscarinic (M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>), serotonin (5-HT<sub>2</sub>), and benzodiazepine receptors.

In various allergic reaction models, bepotastine besilate showed an inhibitory effect comparable or superior to that of other antihistamines in Type-I allergic reaction models, in mediator-induced and antigen-induced eosinophilic infiltration models. Bepotastine besilate showed a statistically significant inflammation inhibitory effect in both immediate phase and late phase antigen-induced allergic rhinitis and asthma models, and suggested more potency than other antihistamines.

### ***Animal Pharmacology***

#### ***In vitro Pharmacology***

Several *in vitro* studies with animal or human biomaterials have been conducted with bepotastine besilate that have emphasized the selectivity of bepotastine for binding to the histamine H<sub>1</sub> receptor to a degree comparable or superior to that of several other antihistamine drugs. The pharmacological properties of the activity of bepotastine besilate was evaluated in a study performed on the binding inhibition activity of this drug in 30 types of receptors and in ion channels. Bepotastine showed binding inhibition activity of 50% or more at 3  $\mu$ g/mL only for the sigma receptor and no significant activity for Na channel, muscarinic M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub> receptors, the serotonin 5HT<sub>1A</sub> and 5HT<sub>3</sub> receptors, and NMDA receptor.

#### ***In vivo Pharmacology***

Bepotastine besilate was found to inhibit the conjunctival edema provoked by the histamine solution injection to the upper palpebra. The inhibitory action became stronger in 0.01 to 1.0 %

concentration dose-dependently, and the action was almost the same in 1.0 and 1.5% w/v concentrations.

The anti-allergic activity of bepotastine besilate was investigated in various models using rats. Bepotastine dose-dependently inhibited the acceleration of histamine-induced vascular permeability in rat skin when orally administered ( $ID_{30}$  value: 0.10 mg/kg), and the inhibitory activity lasted for more than 4 hours. This activity was significant at 0.1 and 1 mg/kg and was more potent than those of ketotifen, terfenadine, cetirizine and epinastine at both of these concentrations. Bepotastine inhibited histamine release from rat peritoneal mast cells at a high concentration.

In mice, bepotastine inhibited the scratching induced by histamine but not serotonin. Bepotastine also dose-dependently suppressed scratching induced by substance P and LTB<sub>4</sub>. Bepotastine did not suppress the production of LTB<sub>4</sub> induced by intradermal injection of substance P, but rather suppressed the LTB<sub>4</sub>-induced increase in Ca<sup>++</sup>, as demonstrated in both cultured neutrophils and cultured dorsal root ganglion neurons. Bepotastine also inhibited both eosinophil number increase in bronchoalveolar lavage fluid and in peripheral blood. Study investigating effects of bepotastine on circulatory system showed that it exhibited very little effect of circulatory activity, and it is unlikely to show any arrhythmogenic activity. Bepotastine did not exhibit any effects on the central nervous system, digestive system, or blood metabolism at doses much higher than its effective dose.

#### *Metabolism and Pharmacokinetics*

Topical absorption, distribution, and excretion of bepotastine were investigated in pigmented rabbits. The tissue radioactivity level reached C<sub>max</sub> at 0.25-4 hr after administration. Radioactivity was highest in the cornea followed by the conjunctiva, iris/ciliary body, sclera, retina/choroid, aqueous humor, extraocular muscles, plasma, blood, lens and vitreous body, in this order. The radioactivity level in conjunctiva, one of the target tissues, reached 13075.9 ng-eq./g at 0.25 hr after administration, and decreased biphasically with a t<sub>1/2α</sub> of 1.89 hr and t<sub>1/2β</sub> of 13.32 hr. Bepotastine was eliminated from the iris/ciliary body and retina/choroid, both containing melanin, with a t<sub>1/2α</sub> of 5.22 hr and t<sub>1/2β</sub> of 47.35 hr, and t<sub>1/2α</sub> of 20.13 hr, respectively, which did not differ from the elimination profile from other tissues. The radioactivity level in each ocular tissue at 72 hr after administration was 0.4%-40.2% of the respective C<sub>max</sub> (cornea: 0.4%, conjunctiva: 1.6%, extraocular muscles: 3.0%, iris/ciliary body: 17.2%, lens: 40.2%, vitreous body: 1.9%, retina/ choroid: 5.3%, and sclera: 2.4%). The plasma radioactivity level reached the C<sub>max</sub> (214.8 ng-eq./mL) at 0.5 hr after administration followed by biphasic decrease with a t<sub>1/2α</sub> of 0.99 hr and t<sub>1/2β</sub> of 22.43 hr. The AUC<sub>0-∞</sub> was 668.56 ng-eq.·h/mL.

In a Phase 1 repeated dose safety and pharmacokinetic study, plasma C<sub>max</sub> values after 6-7 days of dosing were only about 1/10th the values seen with therapeutic doses of the oral bepotastine besilate formulation and plasma levels decreased to the limit of quantitation within 8-12 hours. This information, combined with the safety profile for oral bepotastine besilate and the pharmacokinetics of <sup>14</sup>C-labeled bepotastine in rabbit eye tissues following ophthalmic dosing, focuses attention for safety and efficacy purposes on local ocular tissue concentrations of bepotastine rather than systemic distribution.

## ***Human pharmacology***

### *Human pharmacodynamics*

The effect of bepotastine besilate on induction of interleukin-5 (IL-5), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interferon gamma (IFN- $\gamma$ ) cytokine production by human peripheral blood mononuclear cells (PBMCs) has been evaluated for patients sensitive to dust mite or Japanese cedar pollen allergens. Co-incubation of PBMCs with allergen and bepotastine besilate effectively suppressed allergen stimulation of IL-5 and TNF- $\alpha$  production, but not of IFN- $\gamma$ , at bepotastine besilate concentrations as low as 0.1  $\mu$ M.

Bepotastine has been shown to inhibit the production of IL-5 in human peripheral blood mononuclear cells (PMBC) and to inhibit antigenic stimulated proliferation of PMBCs as well. Bepotastine significantly blocked the increase in nasal mucosal permeability caused by histamine administration as measured by reduction in epithelial potential difference in human volunteers.

No drug-related QTc prolongation or drug-related abnormal ECG was observed with oral or ophthalmic bepotastine besilate at therapeutic doses. Positron emission tomography (PET) was used to determine the degree of histamine H1 receptor occupancy in the brain of healthy male volunteers for oral bepotastine besilate and demonstrated that ingestion of bepotastine besilate had little effect on displacement of the tricyclic antidepressant doxepin from brain histamine H1 receptors (a measure of the ability to cross the blood-brain barrier).

### *Human pharmacokinetics*

A clinical pharmacokinetic study of bepotastine besilate ophthalmic solution (1.0% w/v and 1.5% w/v) similarly suggested that systemic absorption of an ocular dose of bepotastine besilate was low, perhaps as little as 1/10<sup>th</sup> the amount absorbed following an equivalent oral dose.

The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% w/v and 1.5% w/v ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% w/v or 1.5% w/v bepotastine besilate ophthalmic solution to both eyes four times daily (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% w/v and 1.5% w/v strengths were  $5.1 \pm 2.5$  ng/mL and  $7.3 \pm 1.9$  ng/mL, respectively. Plasma concentration at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.

## **TOXICOLOGY**

The 1.0% w/v and 1.5% w/v bepotastine besilate topical solutions were tested in both rabbits (up to 4 weeks) and dogs (up the 26 weeks) at up to 8 treatments per day and were found to be nontoxic to the eye and adnexa, and to have no systemic effects.

In dogs treated orally with bepotastine besilate for 26 weeks, vomiting was observed in the administration groups treated with 100 mg/kg and above of bepotastine besilate. It was concluded that the bepotastine besilate toxic dose is 100 mg/kg and that the NOAEL is 30

mg/kg.

In rats treated orally for 4 or 26 weeks, the findings show that the increase in liver weight and the hypertrophy of the hepatocytes are associated with the inductions in the activity of the hepatic metabolizing drug enzyme and are an adaptive response of the body. A separate study showed that doses of 100 and 300 mg/kg of bepotastine besilate were clearly found to have inducibility of CYP2B1/2, CYP3A1/2, and CYP2A1, similar to positive control. Toxicological clinical examination showed weight gain inhibition as well as changes in general conditions and values whilst histopathological examination values indicated fatty changes in hepatocytes and hyperplasia of epithelium of urinary bladder. Symptoms observed during the dosing period and changes recorded throughout the study disappeared with the interruption of the treatment and all changes found to be reversible. These results establish the toxic dose at 600 mg/kg. However, there was no evidence of toxicity in the 20-mg/kg groups and it was concluded that the NOEL for repeated dose toxicity was 20 mg/kg.

There was no evidence of mutagenicity in the Ames test, in Chinese hamster cells, in mouse hepatocytes, or in the mouse micronucleus test.

In mouse and rat carcinogenicity studies, there was no evidence of carcinogenicity with the exception of a slightly higher incidence of hepatocellular tumors in female mice given the high dose (200mg/kg/day). This was attributed to the drug metabolizing activity of rats, with no significance when extrapolating to humans.

Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day, but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day (>27,000 times the anticipated human dose of bepotastine besilate ophthalmic solution 1.5% w/v). There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day.

The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborn and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**BEPREVE™**

**Bepotastine besilate ophthalmic solution 1.5% w/v**

Read this carefully before you start taking BEPREVE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BEPREVE.

**What is BEPREVE used for?**

BEPREVE is used for the treatment of itching associated with allergic conjunctivitis. Allergic conjunctivitis is eye inflammation caused by an allergic reaction to allergens like pollen, house dust, or animal dander.

**How does BEPREVE work?**

BEPREVE makes allergic reactions less intense by:

- (1) blocking the effects of histamine (a chemical that plays an important role in allergic reactions), and
- (2) stabilizing mast cells (cells that contain histamine and other chemicals involved in allergic reactions).

**What are the ingredients in BEPREVE?**

Medicinal ingredients: Bepotastine besilate.

Non-medicinal ingredients: benzalkonium chloride (as preservative), monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide and water.

**BEPREVE comes in the following dosage forms:**

Ophthalmic solution (eye drops), 1.5% w/v.

**Do not use BEPREVE if:**

You are hypersensitive to bepotastine besilate or to any ingredient in the formulation or component of the container.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BEPREVE. Talk about any health conditions or problems you may have, including if you:**

- **Wear contact lenses**

BEPREVE should not be used to treat contact lens-related irritation. BEPREVE should not be used while wearing contact lenses. Remove contact lenses prior to using BEPREVE. The

preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

- **Are pregnant or breastfeeding**

If you are pregnant, or might get pregnant, talk to your healthcare professional before you use BEPREVE. If you are breastfeeding, do not use BEPREVE as it may pass into your breast milk.

**Other warnings you should know about:**

BEPREVE is for use in the eyes only.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**How to take BEPREVE:**

When using BEPREVE, be careful not to touch your eye or surrounding areas with the dropper tip of the bottle to minimize possible contamination of the dropper tip and medicine.

Keep the bottle tightly closed when not in use.

If you wear contact lenses, remove them before using BEPREVE and do not put them back in for 10 minutes after using BEPREVE.

**Usual dose:**

The recommended dose of BEPREVE is one drop into the affected eye(s) twice a day.

**Overdose:**

If you think you have taken too much BEPREVE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you forget to use BEPREVE, use a single drop as soon as you remember, and then go back to your normal dosing schedule. Do not try to catch up on missed drops by applying more than one dose at a time.

**What are possible side effects from using BEPREVE?**

These are not all the possible side effects you may feel when taking BEPREVE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Headache
- Eye irritation
- Inflammation of the nose or throat
- Change in your sense of taste

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b><u>RARE</u></b> <b>Allergic Reaction:</b> itching, body rash, swelling of the lips, tongue and/or throat			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p><b>Reporting Side Effects</b></p> <p>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</p> <p><b>3 ways to report:</b></p> <ul style="list-style-type: none"> <li>• Online at MedEffect (<a href="http://www.healthcanada.gc.ca/medeffect">www.healthcanada.gc.ca/medeffect</a>);</li> <li>• By calling 1-866-234-2345 (toll-free);</li> <li>• By completing a Consumer Side Effect Reporting Form and sending it by: <ul style="list-style-type: none"> <li>- Fax to 1-866-678-6789 (toll-free), or</li> <li>- Mail to: Canada Vigilance Program Health Canada, Postal Locator 0701E Ottawa, ON K1A 0K9</li> </ul> </li> </ul> <p>Postage paid labels and the Consumer Side Effect Reporting Form are available on the MedEffect Canada Web site.</p> <p><i>NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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**Storage:**

Store at room temperature, 15°C -25°C

Keep out of reach and sight of children.

**If you want more information about BEPREVE:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website ([www.healthcanada.gc.ca](http://www.healthcanada.gc.ca)); the manufacturer's website ([www.bausch.ca](http://www.bausch.ca)) or by calling 1-888-459-5000.

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