Insert to

Sponsored by ISTA Pharmaceuticals, Inc.

Cataract & Refractive Surgery TODAY

April 2011

# Treating Allergic Conjunctivitis in the Ophthalmic Practice

**Therapeutic strategies that provide patients with immediate relief from ocular itch.**

Featuring:

Elizabeth A. Davis, MD (Moderator)

Richard M. Awdeh, MD

Terry Kim, MD

Parag A. Majmudar, MD

# Treating Allergic Conjunctivitis in the Ophthalmic Practice

## Therapeutic strategies that provide patients with immediate relief from ocular itch.

Allergic conjunctivitis may affect patients differently depending on their location in the country, but we ophthalmologists can learn from one another about how to best treat allergic symptoms in the eye. In general, allergic conjunctivitis is the most common form of ocular allergy. It can affect up to 40% of the population, which translates to more than 100 million individuals in the United States.[1] This incidence may be increasing worldwide because of pollutants, technological factors, etc.[2] Ophthalmologists are usually the clinicians who first identify the conjunctivitis component of an allergic response. Patients may present while taking systemic allergy medications, but these agents often do not address the ocular component of allergy.

**—Elizabeth A. Davis, MD**

### PARTICIPANTS


**Elizabeth A. Davis, MD**, is a partner at Minnesota Eye Consultants and an adjunct clinical assistant professor at the University of Minnesota in Minneapolis. Dr. Davis may be reached at (952) 567-6067; eadavis@mneye.com.

**Richard M. Awdeh, MD**, is an assistant professor of ophthalmology at the Bascom Palmer Eye Institute in Miami. Dr. Awdeh may be reached at (305) 326-6000; rawdeh@med.miami.edu.

**Terry Kim, MD**, is a professor of ophthalmology at Duke University School of Medicine and the associate director of corneal and refractive surgery services at Duke University Eye Center in Durham, North Carolina. Dr. Kim may be reached at terry.kim@duke.edu.

**Parag A. Majmudar, MD**, is an associate professor, Cornea Service at the Rush University Medical Center, and he is in private practice at Chicago Cornea Consultants, Ltd. Dr. Majmudar may be reached at (847) 822-5900; pamajmudar@chicagocornea.com.


### CONTENTS



*The participants are paid consultants to ISTA Pharmaceuticals, Inc.*

## PRESENTATION AND DIAGNOSIS

**Dr. Davis:** I'd like to begin by asking the panel how you approach the initial examination of a patient who presents with symptoms of allergic conjunctivitis.

**Dr. Awdeh:** Sometimes it may be difficult to diagnose allergic conjunctivitis during the initial examination, because the presenting symptoms can suggest a multitude of ophthalmic diseases. The patient's medical history becomes very important in determining if he or she really has allergic conjunctivitis, such as a history of seasonal allergy and itching, for example. I may ask patients to show me how they rub their eye, because this can sometimes be a telling sign. Dr. Kim's partner, Alan Carlson, MD, has described the subtle differences in patterns of eye rubbing between patients with keratoconus and those with ocular allergy.[3] Keratoconus patients tend to rub centrally and deeply, whereas a person with allergies may rub more on their lid and lashes. Next, I try to find out if there is a seasonal component to the patient's symptoms.

**Dr. Davis:** That there may be distinctions between eye rubbing is an interesting idea. Are there any particular symptoms to which you pay more attention when trying to differentiate between allergies versus dry eye and other ocular conditions?

**Dr. Kim:** The hallmark of allergic conjunctivitis is ocular itching. Other symptoms may be present that can cloud the diagnosis, but an itchy eye can help us pinpoint ocular allergy. Of course, practitioners have to be aware not only of seasonal allergies, but of food and environmental allergies as well. Food allergies occur in approximately 3% to 4% of adults,[4] and sensitivity to pollution, dyes and perfumes, and myriad other chemicals is on the rise worldwide.[5]

Furthermore, I think we ophthalmologists need to pay better attention to the comfort of our patients' eyes, because chronic eye rubbing can increase the risk of developing ectatic corneal disorders such as keratoconus.[6] It is especially important to discourage eye rubbing in patients who have had LASIK or cataract surgery because of the risk of slipped or dislocated LASIK flaps or corneal wound dehiscence.

**Dr. Davis:** If a patient who has allergic conjunctivitis requests LASIK or cataract surgery, would you proceed?

> "[There are] subtle differences in patterns of eye rubbing between patients with keratoconus and those with ocular allergy."
>
> —Richard M. Awdeh, MD

Do you feel the allergic condition could potentially affect the surgical outcome? What would be your endpoints before performing the surgery?

**Dr. Majmudar:** If the individual were in the middle of allergy season, I would tell him or her to wait for the symptoms to subside before undergoing LASIK or cataract surgery. We want surgical patients' eyes to have as little itching and inflammation as possible, both in terms of optimizing the outcome and so the patient is not tempted to rub his or her eyes after the surgery, which could cause a complication. For those who are already scheduled for surgery during allergy season and have symptoms, I will treat them for a couple weeks preoperatively.

**Dr. Kim:** I have seen a few slipped LASIK flaps in allergy sufferers that I presumed were due to eye rubbing. Also of interest, some studies in the peer-reviewed literature have suggested a potential relationship between diffuse lamellar keratitis (DLK) and allergy.[7,8] Hence, there may be some rationale to treating allergic conjunctivitis patients to ensure that their eyes are quiet and to reduce eye rubbing.

**Dr. Davis:** My staff and I have also noticed a correlation between cases of DLK and allergy season as well as environmental factors like building construction.

**Dr. Davis:** How do you distinguish dry eye syndrome from allergic conjunctivitis? These conditions can overlap and exacerbate one another.

**Dr. Kim:** Most ophthalmologists use some type of fluorescein stain to evaluate the corneal surface. When a cornea lacks punctate staining, I tend to lean toward allergy as opposed to dry eye as the etiology. I may even use lissamine green, rose bengal, or other ancillary

dyes to further distinguish between dry eye versus allergic eye disease.

**Dr. Davis:** Do you look at tear break-up time?

**Dr. Kim:** Definitely. Although this is an easy, 10-second test, it is an underutilized diagnostic modality. I prefer not to use fluorescein from a dropper bottle, because it tends to flood the tear film and interfere with the accurate reading of the tear break-up time, and it may also conceal subtle corneal epithelial abnormalities like anterior basement membrane dystrophy. I like to apply a drop or two of topical proparacaine onto a sterile fluorescein strip and then dab this strip onto the palpebral conjunctiva and have the patient blink a few times. Then, I ask the patient to refrain from blinking for 10 seconds while I observe the corneal surface to see if the tear film breaks up during this time. If the tear film breaks up before 10 seconds, it is considered abnormal and signifies the presence of evaporative dry eye disease/blepharitis. We also have to pay attention to the lid margin and check for abnormal meibomian gland secretions that may point toward a diagnosis of dry eye versus allergy.

**Dr. Majmudar:** Regarding a correlation between dry eye and allergies, many individuals who have allergies will start developing contact lens intolerance as a sign that their symptoms are starting.

**Dr. Davis:** Do you ask your allergy sufferers to refrain from wearing contact lenses while they are treating their allergies?

**Dr. Majmudar:** I think it depends on the patient's comfort level. I uniformly recommend that they not use anti-allergy eye drops while wearing their contacts. Some of them, however, put their contact lenses in after they have used the anti-allergy drop and see how comfortable their eyes feel. I find that most patients who have mild allergies still wear contact lenses, and I tell them to use anti-allergy drops in the morning before they insert the lenses as well as in the evening after they take them out, and I recommend that they wait 10 minutes between using each.

**Dr. Davis:** What is the most disturbing symptom of ocular allergy for patients? What is the primary complaint that brings them into the office?

> "When a cornea lacks punctate staining, I tend to lean toward allergy as opposed to dry eye as the etiology."
>
> —Terry Kim, MD

**Dr. Kim:** In my patient population, I would say that itching and rubbing are the primary complaints, followed by cosmesis issues such as periocular skin changes, including redness, swelling, and scaling. I think such symptoms bother patients and motivate them to see an eye care specialist.

**Dr. Awdeh:** I agree with Dr. Kim that ocular itching is the main complaint allergy patients have.

## THERAPEUTIC APPROACHES

**Dr. Davis:** When do you ask your established seasonal allergic conjunctivitis patients come in to initiate treatment for ocular itching?

**Dr. Kim:** Usually, seasonal allergy patients know when they start to have symptoms. In my experience, these patients start therapy about 1 month before the pollen gets really heavy, even if they are not strongly symptomatic. They may also continue to use medication for up to 1 month after the heaviest part of the allergy season ends if they are still symptomatic. People can now go online (for example, to www.pollen.com) and find out what the pollen count is for their area at any given time.

**Dr. Davis:** Should we have allergic conjunctivitis patients discontinue oral allergy medications? Should we worry about oral allergy medications exacerbating dry eye? I have seen this problem in a few patients.

**Dr. Majmudar:** It is important for us to ask what over-the-counter medications our allergic conjunctivitis patients have already tried, and we may even need to contact their primary care physician or pediatrician for this information. I let my patients continue oral medications, although I prefer to treat ocular symptoms with a topical treatment.

**Dr. Kim:** I also let my patients stay on oral allergy medications unless they are scheduled for corneal laser surgery. I ask these patients to discontinue these drugs temporarily because I want to minimize dryness on the corneal surface. However, we have to remember to ask our surgical patients to list all medications they are taking, because they tend not to think of over-the-counter drugs as medications. They often forget to mention that they are on an antihistamine, for example.

**Dr. Davis:** How do we use steroids to treat ocular allergy? Should we reserve these drugs for severe cases?

**Dr. Awdeh:** I think steroids work well as an initial short-pulse therapy for controlling acute presentations of severe allergic conjunctivitis.

**Dr. Majmudar:** I use topical steroids in the more severe presentations of allergic conjunctivitis with acute inflammation, so approximately 50% of my cases. I do not prescribe steroids for typical seasonal allergies that will last a week or two. I do feel that 1 week of pulsed doses of a steroid are helpful, however, in patients with perennial allergies who experience flare-ups. As long as we monitor these eyes, I do not think steroids cause much trouble. I then prescribe an antihistamine/mast-cell stabilizer to keep ocular itching under control.

**Dr. Davis:** Let's discuss antihistamine/mast-cell stabilizers. Are there agents that allow us to give certain patients less dosing for just a short period of time versus symptomatic individuals who need long-term interruption of the inflammatory cascade? For example, I base my choice for treating ocular itch associated with allergic conjunctivitis on efficacy and comfort. I look for an agent that provides a rapid onset of action and duration of effect, and a b.i.d. or q.d. dosing regimen is an added bonus.

**Dr. Majmudar:** I stratify patients based on what I know about them and their history. For patients who experience documented, chronic seasonal allergies the same time every year, I instruct them to start dosing the drop as soon as they feel the symptoms and use it every day b.i.d. for 2 to 3 weeks until they feel their symptoms have subsided.

For individuals with less-defined symptoms, I may tell them to use the drops twice per day for 1 week and then evaluate their symptoms. If they are experiencing a transient allergy, they may feel better in that short amount of time and can stop taking the drug.

> "I base my choice for treating ocular itch associated with allergic conjunctivitis on efficacy and comfort."
>
> —Elizabeth A. Davis, MD

**Dr. Kim:** I tell seasonal allergy sufferers to start therapy early in the allergy season, while their symptoms are still mild. Missing even one dose of medication opens the window to allergens entering the receptor sites, and then the patient may experience a cascade effect. I think it makes sense for the people who know they have allergies to continue on b.i.d. dosing throughout the allergy season as long as they are symptomatic.

**Dr. Awdeh:** I think patients with allergic conjunctivitis experience what I call an *itch-rub cycle*. Their eyes start itching, and then they rub, and their rubbing causes mechanical damage to the cell walls. This in turn worsens the itching, and the two problems exacerbate one another. I agree that reminding patients who suffer from ocular itching to maintain consistent dosing while they are symptomatic during allergy season helps them break this cycle.

## USE OF BEPREVE TO TREAT OCULAR ITCH ASSOCIATED WITH ALLERGIC CONJUNCTIVITIS

**Dr. Davis:** I want to discuss BEPREVE (bepotastine besilate ophthalmic solution) 1.5% (ISTA Pharmaceuticals, Inc., Irvine, CA), because it is one of the newer treatments on the market. BEPREVE is indicated for the treatment of itch associated with allergic conjunctivitis, and I have found it be very effective in this application. BEPREVE is a nonsedating drop that is both a highly specific H1 antihistamine receptor antagonist and a mast-cell stabilizer.[9-11] In clinical studies, this drop was found to be comfortable, work rapidly, and provide a long duration of effect (Figures 1 and 2). It is prescribed b.i.d., so patients get effective relief for the entire day. BEPREVE was evaluated in two clinical trials

(one single-center and one multicenter) utilizing the validated conjunctival allergen challenge (CAC) model.[12,13] Integrated results from these studies showed that BEPREVE had a fast onset of action, reducing ocular itching by 82% from baseline at 3 minutes.[14] Fully 95% of the eyes treated with BEPREVE had a clinically significant reduction of ocular itch—meaning at least one unit of improvement compared to baseline—at onset of action (an average of 3, 5, and 7 minutes).[15] My clinical experience has been consistent with these data; BEPREVE has worked well in a high percentage of my patients and is very comfortable.

Panelists, what is your first-line medication for itching associated with allergic conjunctivitis?

**Dr. Awdeh:** Because Bascom Palmer is a tertiary referral ophthalmic center for the entire country, my colleagues and I often see patients who have severe ocular itching. These are patients who have graded their itching and symptomatic complaints as at least level three on a scale of one to four. I have successfully treated such eyes using BEPREVE, and this personal experience supports the drug's phase 3 clinical data that showed an effective response to severe allergy. Nearly 70% of the patients with severe itch in those studies had complete relief of ocular itch at 3 minutes with BEPREVE (Figure 3).[16]

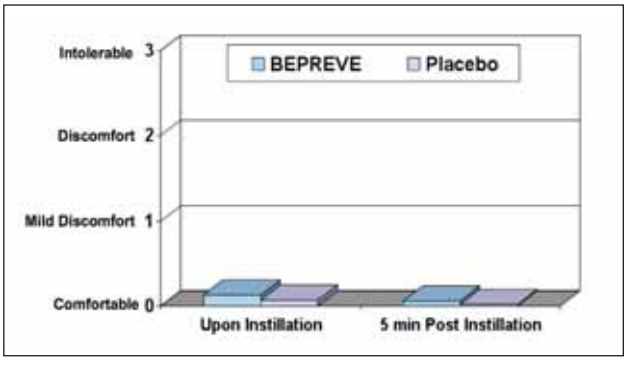



**Figure 1. In a 6-week safety trial (n=1,534 eyes), subjects demonstrated equal comfort with BEPREVE and placebo at instillation and 5 minutes after.**

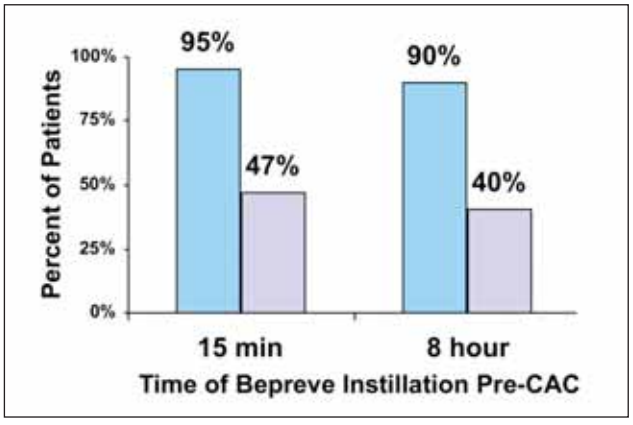



**Figure 2. Percentage of patients demonstrating a 1.0-unit improvement in ocular symptoms after instillation of BEPREVE.**

**Dr. Davis:** As we've already discussed, because ocular allergy does overlap with dry eye syndrome (which can be exacerbated by systemic antihistamines), I like the

## BEPREVE LABEL SUMMARY

INDICATIONS AND USAGE

BEPREVE is a histamine H1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

DOSAGE AND ADMINISTRATION

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

WARNINGS AND PRECAUTIONS

To minimize contaminating 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.

Patients should be advised not to wear a contact lens if their eye is red. 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.

BEPREVE is for topical ophthalmic use only.

ADVERSE REACTIONS

The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2% to 5% of subjects were eye irritation, headache, and nasopharyngitis.

*Please see full prescribing information for BEPREVE on the last page.*

> "BEPREVE comes in a 10-mL bottle, so we can tell patients that it should last for 2 months if used correctly."
>
> —Parag A. Majmudar, MD

fact that in clinical trials, BEPREVE was associated with less dry eye than placebo (1.0% vs 1.7%).[17]

**Dr. Kim:** The absence of a drying effect may be due to the high specificity of bepotastine for the H1 receptor. Because it has little or no specificity for other receptors (ie, adrenergic, muscarinic, dopamine, serotonin, etc.), it is less likely to cause such side effects.

I also like the fast action of BEPREVE. It is very helpful when treating patients for ocular itch. Furthermore, in my experience, the drop's b.i.d. dosing lasts throughout the cycle of itching and provides 24-hour relief.

## THE VALUE OF BEPREVE

**Dr. Davis:** The cost of medications is becoming increasingly important to patients. How should we address this issue?

**Dr. Majmudar:** I agree that cost is a bigger issue now than it has been in the past. A lot of patients are taking multiple medications, and the cost adds up. I think we can help our patients understand this expenditure by pointing out the value of the medication. BEPREVE comes in a 10-mL bottle, so we can tell patients that it should last for 2 months if used correctly. In the long run, this may be more cost effective than their having to buy a smaller bottle every couple of weeks.

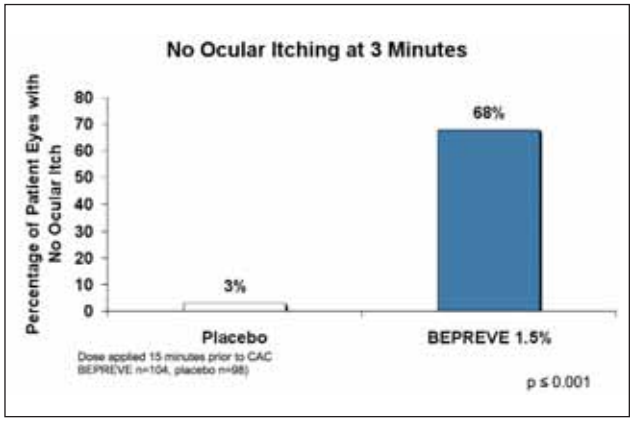



**Figure 3. Of the patients who had an extremely high itching score (grade 3) at screening, 68% achieved an ocular itching score of zero at the earliest time point of 3 minutes.**

**Dr. Kim:** I agree that we must consider the value of the medications as one factor in our treatment decision. If we can explain this effectively to our patients, they will adhere to the prescription. This conversation does not take much chair time. Again, BEPREVE's fast action against ocular itch helps demonstrate the effectiveness of the medication to patients.

**Dr. Davis:** To summarize, allergic conjunctivitis affects a large number of patients in the United States. BEPREVE dosed b.i.d. is a very effective and comfortable topical medication that quickly relieves ocular itch associated with allergic conjunctivitis for an extended duration of time. I believe BEPREVE plays a role in first-line therapy for this common condition. ■

1. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. *J Allergy Clin Immunol*. 2010;126(4):778-783.e6.
2. Segundo GR, Sopelete MC, Terra SA, et al. Diversity of allergen exposure: implications for the efficacy of environmental control. *Braz J Otorhinolaryngol*. 2009;75(2):311-316.
3. Carlson AN. Expanding our understanding of eye rubbing and keratoconus. *Cornea*. 2010;29(2):245.
4. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S116-125.
5. Genuis SJ. Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. *Sci Total Environ*. 2010;408(24):6047-6061.
6. Yeniad B, Alparslan N, Akarcay K. Eye rubbing as an apparent cause of recurrent keratoconus. *Cornea*. 2009;28(4):477-479.
7. MacRae SM, Rich LF, Macaluso DC. Treatment of interface keratitis with oral corticosteroids. *J Cataract Refract Surg*. 2002;28(3):454-461.
8. Boorstein SM, Henk HJ, Elner VM. Atopy: a patient-specific risk factor for diffuse lamellar keratitis. *Ophthalmology*. 2003;110(1):131-137.
9. Kato M, Nishida A, Aga Y, et al. Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. *Arzneimittelforschung*. 1997;47(10):1116-1124.
10. Yato N, Murata T, Saito N, et al. Anti-allergic activity of bepotastine besilate (TAU-284), a new anti-allergic drug. *Nippon Yakurigaku Zasshi*. 1997;110(1):19-29.
11. Nakahara T, Urabe K, Moroi Y, et al. Bepotastine besilate rapidly inhibits mite-antigen induced immediate reactions in atopic dermatitis. *J Dermatol Sci*. 2003;32(3):237-238.
12. Macejko TT, Bergmann MT, Williams JI, et al; Bepotastine Besilate Ophthalmic Solutions Clinical Study Group. Multicenter clinical evaluation of bepotastine besilate ophthalmic solutions 1.0% and 1.5% to treat allergic conjunctivitis. *Am J Ophthalmol*. 2010;150(1):122-127.e5.
13. Abelson MB, Torkildsen GL, Williams JI, et al; Bepotastine Besilate Ophthalmic Solutions Clinical Study Group. Time to onset and duration of action of the antihistamine bepotastine besilate ophthalmic solutions 1.0% and 1.5% in allergic conjunctivitis: a phase III, single-center, prospective, randomized, double-masked, placebo-controlled, conjunctival allergen challenge assessment in adults and children. *Clin Ther*. 2009;31(9):1908-1921.
14. Data on file. ISTA Pharmaceuticals®, Inc.
15. Data on file. ISTA Pharmaceuticals®, Inc.
16. Clark JC, Williams JI, Gow JA, et al. Bepotastine besilate ophthalmic solution 1.5% rapidly eliminates ocular itching in more severely allergic subjects in the conjunctival allergen challenge model of allergic conjunctivitis. Presented at: The Eastern Allergy Conference. May 6-9, 2010; Palm Beach, FL.
17. Data on file. ISTA Pharmaceuticals®, Inc.

BRV890-1/11

# BEPREVE®
(bepotastine besilate ophthalmic solution) 1.5%

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use BEPREVE (bepotastine besilate ophthalmic solution) 1.5% safely and effectively.**

**See full prescribing information for BEPREVE.**

**BEPREVE**
**(bepotastine besilate ophthalmic solution) 1.5%**

**Initial U.S. Approval: 2009**

### INDICATIONS AND USAGE

BEPREVE is a histamine $H_1$ receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

### DOSAGE AND ADMINISTRATION

Instill one drop into the affected eye(s) twice a day (BID). (2)

### DOSAGE FORMS AND STRENGTHS

Solution containing bepotastine besilate, 1.5%. (3)

### WARNINGS AND PRECAUTIONS

- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE. (5.2)

### ADVERSE REACTIONS

The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 01/2010**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a histamine $H_1$ receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

### 2 DOSAGE AND ADMINISTRATION

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

### 3 DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution containing bepotastine besilate 1.5%.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

**5.1 Contamination of Tip and Solution**

To minimize contaminating 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.

**5.2 Contact Lens Use**

Patients should be advised not to wear a contact lens if their eye is red. 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.

**5.3 Topical Ophthalmic Use Only**

BEPREVE is for topical ophthalmic use only.

### 6 ADVERSE REACTIONS

The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

### 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy**

Pregnancy Category C. Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. 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 (approximately 3,300 times the topical ocular use in humans). The concentration of radiolabeled 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 stillborns 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.

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% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**8.3 Nursing Mothers**

Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 µg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

**8.4 Pediatric Use**

Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 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.

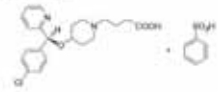
**8.5 Geriatric Use**

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

### 11 DESCRIPTION

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE contains 15 mg bepotastine besilate.

Bepotastine besilate is designated chemically as (+) -4-[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.

The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.

**Each mL of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% contains:**

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

**Preservative:** benzalkonium chloride 0.005%

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

### 12 CLINICAL PHARMACOLOGY

**12.1 Mechanism of Action**

Bepotastine is a topically active, direct $H_1$-receptor antagonist and an inhibitor of the release of histamine from mast cells.

**12.3 Pharmacokinetics**

**Absorption:** The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% 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% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 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.

**Distribution:** The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

**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, CYP2C8, and CYP2C19.

**Excretion:** The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

### 13 NONCLINICAL TOXICOLOGY

**13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility**

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 a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use.

No observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

### 14 CLINICAL STUDIES

Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 hours post dosing of BEPREVE.

The safety of BEPREVE was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

BEPREVE (bepotastine besilate ophthalmic solution) 1.5% 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 size:

5 mL (NDC 67425-007-50)
10 mL (NDC 67425-007-75)

**STORAGE**

Store at 15° – 25°C (59° – 77°F).

### 17 PATIENT COUNSELING INFORMATION

**17.1 Topical Ophthalmic Use Only**

For topical ophthalmic administration only.

**17.2 Sterility of Dropper Tip**

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

**17.3 Concomitant Use of Contact Lenses**

Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to 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.

**Rx only**


Manufactured for: ISTA Pharmaceuticals®, Inc.
Irvine, CA 92618

By: Bausch & Lomb Incorporated
Tampa, FL 33637

Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-004



® and ™ marks owned by ISTA Pharmaceuticals, Inc.
U.S. Patents: 6,307,052; 6,780,877

**© 2010 ISTA Pharmaceuticals, Inc.**


BRV859-7/10


Cataract & Refractive Surgery TODAY