Evaluating Clinical Perceptions of a New Medication for Ocular Itch Associated with Allergic Conjunctivitis— Results of the Bepreve® 1.5% First Experience Field Survey

Jai G Parekh, MD, MBA, FAAO

Managing Partner, Brar-Parekh Eye Associates, Woodland Park, New Jersey, Chief of Cornea and External Diseases, St Joseph's Regional Medical Center, Paterson, and Clinical Assistant Professor of Ophthalmology, The New York Eye and Ear Infirmary

Abstract

Allergic conjunctivitis associated with seasonal or perennial allergy is an increasingly prevalent complaint. Patients seeking professional evaluation for symptoms of ocular allergy usually have exhausted over-the-counter options and expect rapid, effective relief from the treatment prescribed. With the introduction of Bepreve® (bepotastine besilate ophthalmic solution) 1.5%, a survey of US doctors was conducted to evaluate their opinions and impressions of the medication following the initial patient trial. Responses from 427 practitioners, representing a total of 7,340 patient experiences, suggest that Bepreve is a rapidly effective and comfortable treatment. Nearly all respondents reported being satisfied or very satisfied with the performance of Bepreve. These survey data from the office setting are consistent with clinical trial results demonstrating that Bepreve provides rapid, durable, and comfortable relief of ocular itch.

Keywords

Bepotastine besilate, allergic conjunctivitis, ocular itching, antihistamine/mast cell stabilizer, Bepreve®

Disclosure: The author is a consultant to ISTA Pharmaceuticals.
Acknowledgment: Editorial assistance was provided by BioComm Network, Inc.
Received: December 15, 2010 **Accepted:** February 22, 2011 **Citation:** *US Ophthalmic Review*, 2011;4(1):69–72 *DOI: 10.17925/USOR.2011.04.01.69*
Correspondence: Jai G Parekh, MD, MBA, FAAO, Brar-Parekh Eye Associates, 1031 McBride Avenue, Ste D-106, Woodland Park, NJ 07. E:brarparekh3@optimum.net

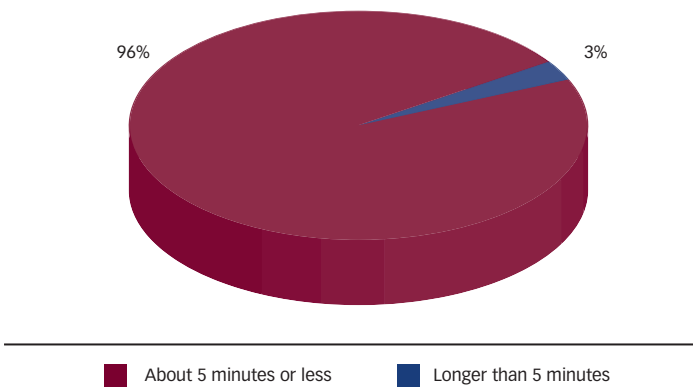
Support: The publication of this article was funded by ISTA Pharmaceuticals, Inc. The views and opinions expressed are those of the author and not necessarily those of ISTA Pharmaceuticals, Inc.

Estimates of the incidence of allergic conjunctivitis vary, but it is an increasingly common condition that may affect >20% of the general population.[1] Annually, at least 40 million Americans experience symptoms related to indoor or outdoor allergies,[2] with nearly 25 million adults and children receiving a diagnosis or reporting seasonal allergy (hayfever) in 2009.[3] One analysis of national health survey data found that ocular allergy symptoms may be four times more prevalent than nasal symptoms.[4] Symptoms associated with allergic conjunctivitis, including bilateral itching, redness, and tearing, are among the most common complaints resulting in referrals to eye care professionals. Approximately 35% of patients who are evaluated for these symptoms are diagnosed with allergic conjunctivitis.[5] Ocular allergy is treated with a variety of prescription and over-the-counter systemic and topical agents, principally antihistamine/mast cell stabilizers and corticosteroids. Many patients seen in a doctor's office have already failed to achieve adequate relief from prior treatments; therefore, identifying therapies that are rapidly effective is important to the clinical community.

Bepotastine besilate is a highly selective histamine H1 receptor antagonist and an inhibitor of mast cell degranulation.[6,7] Studies in laboratory and animal models of systemic allergy and allergic conjunctivitis have suggested additional mechanisms of action, including the inhibition of interleukin-5 (IL-5) production and eosinophil migration to ocular inflammatory sites, leukotriene B4 and leukotriene D4 activity, and platelet-activating factor (PAF) activity.[8,9] These multiple mechanisms suggest that bepotastine has activity in both the early and the late phases of the allergic response.

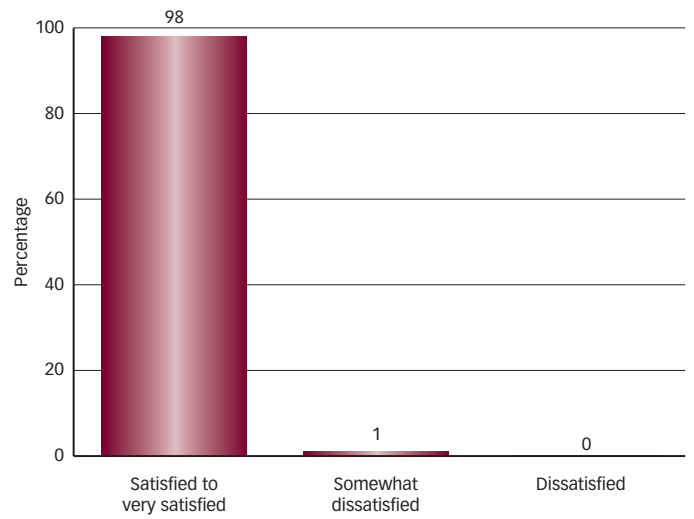
Bepostastine besilate has an extensive record of safety and efficacy as a systemic treatment for a variety of allergic conditions. It has been marketed in Japan (Talion®, Mitsubishi Tanabe Pharma Corporation) as an oral medication for allergic rhinitis since 2000 and for pruritis accompanying urticaria and skin diseases (eczema, dermatitis, prurigo, and dermal pruritis) since 2002. During this time, more than 850 million systemic doses have been administered with no drug-related serious adverse events reported.[10] In 2006, ISTA Pharmaceuticals licensed the exclusive North American rights to the ophthalmic formulation of bepotastine besilate, and in 2007 the exclusive North American rights to the nasal dosage form and the right to negotiate for an oral form.

Figure 1: 'How Quickly Did Your Patients Feel Relief from Ocular Itch with Bepreve?' Question Responses*



**≤1% responses incomplete.*

Figure 2: 'Overall, How Would You Rate Your Experience with Bepreve in Your Practice?' Question Responses*



**≤1% responses incomplete.*

ISTA's ophthalmic formulation, Bepreve® (bepotastine besilate ophthalmic solution) 1.5%, was approved by the US Food and Drug Administration (FDA) in September 2009 for the treatment of ocular itching associated with allergic conjunctivitis. The company announced in December 2010 the initiation of a phase II clinical study of the nasal spray formulation for the treatment of symptoms associated with seasonal allergic rhinitis.

The Bepreve First Experience Survey

In January 2010, ISTA Pharmaceuticals initiated a field survey to evaluate the opinions and impressions of Bepreve among practitioners following initial patient trial. Ophthalmologists, allergists, and optometrists were recruited to treat a minimum of 10 patients each with Bepreve and then complete a 13-item questionnaire to provide information on their current treatment of choice, their impressions of the efficacy and comfort of Bepreve in the patients they had treated, and their overall satisfaction with the medication. Doctors who completed and submitted the questionnaire received compensation for their professional time.

Results

Of 800 questionnaires distributed, 427 responses were received, representing a total of 7,340 patient experiences.[11] Each respondent treated an average of 17 patients with Bepreve. Almost three-quarters of respondents (74%) reported that Patanol® (olopatadine hydrochloride ophthalmic solution [OHOS]) 0.1% or Pataday™ (OHOS) 0.2% was their treatment of choice at the time they initiated the Bepreve trial. One-quarter (25%) preferred Elestat® (epinastine HCl ophthalmic solution) 0.05%, with the remainder identifying a variety of prescription and over-the-counter eye drops, including Alrex® (loteprednol etabonate ophthalmic suspension) 0.2%, Zaditor® (ketotifen fumarate ophthalmic solution) 0.035%, and Optivar® (azelastine hydrochloride ophthalmic solution) 0.05%.

From a list of nine attributes, survey participants selected 'works effectively' (92%), 'convenient dosing regimen' (58%), and 'comfortable drop' (54%) as the top three attributes of their preferred therapy. When asked about a further trial of Bepreve, 96% of respondents stated they were likely or very likely to continue their evaluation if Bepreve demonstrated attributes similar to or beyond those demonstrated by their therapy of choice.

Asked to rate the observed efficacy of Bepreve in their patients, 99% of respondents agreed or strongly agreed that Bepreve was effective at treating ocular itch associated with allergic conjunctivitis. When asked how quickly their patients reported feeling relief from ocular itch with Bepreve, 96% of respondents said response time was either within one minute, within a couple of minutes, or within about five minutes (see *Figure 1*). Doctors also rated the comfort of Bepreve very favorably, with 97% reporting that their patients found the drop comfortable or very comfortable.

Describing their overall impression of the medication's performance, 98% of these clinicians said they were satisfied to very satisfied with their first use of Bepreve in their ocular allergy patients (see *Figure 2*). Nearly all (99%) reported that they would be likely to prescribe Bepreve.

Discussion

The Bepreve First Experience program incorporated a brief, simple survey instrument to provide some structure to the nationwide in-office evaluation of a new prescription ocular allergy product, outside of a formal study protocol, while collecting qualitative data on professional perceptions of the agent's efficacy and comfort.

Although this survey did not employ scientific sampling methods and therefore did not produce results that are statistically representative or projectable, it provided a snapshot of current clinical practice, representing the combined experience of hundreds of doctors across thousands of patient treatments, and a gauge of Bepreve's actual performance relative to the expectations of these clinicians, the attributes of other ocular allergy medications, and the findings of formal clinical trials.

Overwhelmingly positive ratings in questions related to Bepreve's efficacy and comfort suggest that for the majority of participants, the new agent met or exceeded established expectations about a treatment for ocular itch associated with allergic conjunctivitis. These results may also imply that respondents believe Bepreve shares the top-ranked

attributes—specifically efficacy, convenience, and comfort—of other leading ocular allergy medications.

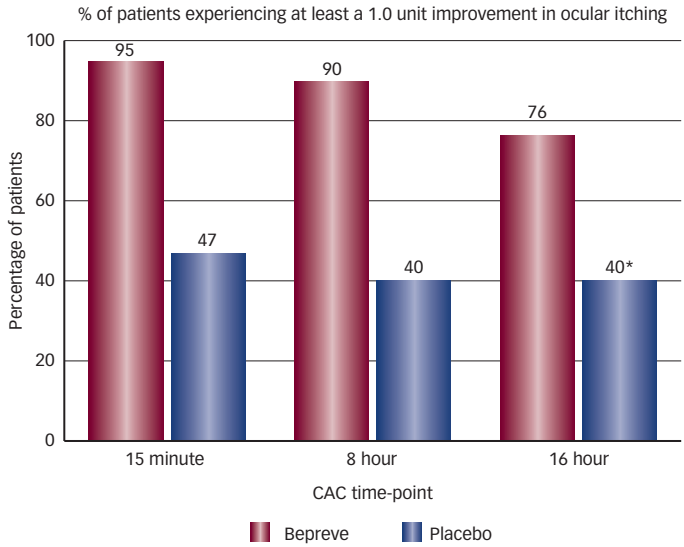
Furthermore, as a reflection of actual experience in the office, these findings are consistent with the clinical evidence available from pivotal trials of Bepreve. Two prospective, randomized, double-masked, placebo-controlled phase III trials (one single-center and one multicenter) were conducted in the US, both utilizing the validated conjunctival allergen challenge (CAC) model.[12,13] Both studies demonstrated that Bepreve has a rapid onset of action and provides durable relief of ocular itching. Patients treated with Bepreve had statistically ($p \leq 0.001$) and clinically (greater than one-unit difference) significant improvement in itching at three minutes.[14] An integrated analysis of these two studies revealed that 95% of Bepreve-treated eyes experienced a clinically significant reduction of ocular itch at onset of action (average of three, five, and seven minutes) compared with only 47% of placebo-treated eyes (see *Figure 3*).[15]

Overall, Bepreve produced an 82% reduction in itching at three minutes.[16] Rapid clearance of ocular itch was even more dramatic in patients with itch graded as severe (three or higher on a four-point scale). In integrated results, 68% of Bepreve-treated eyes had complete clearing of itch at three minutes compared with only 3% of placebo-treated eyes (see *Figure 4*).[17] These data appear to be borne out in the Bepreve First Experience survey finding that 96% of respondents reported patient relief from ocular itching in five minutes or less.

The differences in efficacy between Bepreve and placebo remained clinically and statistically significant at eight hours. Following a single dose, 90% of Bepreve-treated eyes continued to have clinically significant reduction of ocular itch at this time-point compared with only 40% of those treated with placebo (see *Figure 3*).[7] This established eight-hour duration of action was the basis for the twice-daily dosing schedule for Bepreve. However, Bepreve also produced clinically significant improvement in 76% of patients, compared with 40% of placebo-treated patients, at 16 hours in the integrated analysis of both pivotal trials (see *Figure 3*).[18]

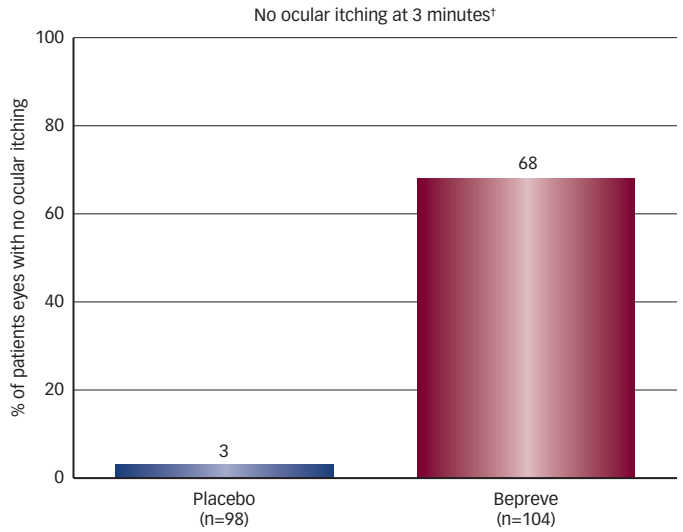
In addition to data from the two pivotal trials, the safety and comfort of Bepreve were evaluated in a six-week safety trial of more than 1,500 healthy eyes (no symptoms of allergy) in subjects as young as three years of age. Across all of these studies, Bepreve was shown to be safe and well tolerated, with ocular adverse events similar to placebo. The most common adverse reaction, occurring in approximately 25% of patients in the six-week safety study and in less than 7% of patients in the two pivotal trials, was mild taste following instillation. Other adverse reactions occurring in 2–5% of patients were eye irritation, headache, and nasopharyngitis. Only taste and eye irritation were considered likely to be related to the study medication. Adverse events were mild and transient and none resulted in study discontinuations. There were no serious ocular or systemic reported adverse events, including drowsiness or dry mouth.[6,14] In the six-week safety study in normal eyes, Bepreve demonstrated comfort equal to placebo,[19] a finding mirrored in the very high proportion of 'comfortable' to 'very comfortable' ratings of the medication in the Bepreve First Experience survey.

Figure 3: Percentage of Patients Demonstrating a Clinically Significant Effect at Each Time-point



**Estimated. CAC = conjunctival allergen challenge.*

Figure 4: Complete Relief of Ocular Itch in Patients with Severe Response (Screen Grade ≥3)*



**Analysis in patients with more severe response in ocular itching at screening (grade ≥3).*
†Dose applied 15 minutes prior to conjunctival allergen challenge (CAC).

Conclusion

Results from the Bepreve First Experience survey, reflecting the experience of 7,340 patients reported by 427 US ophthalmologists, allergists, and optometrists, included highly positive ratings for efficacy and comfort, suggesting that the new agent met or exceeded established expectations about prescription ocular allergy medications. Nearly all respondents reported being satisfied to very satisfied with Bepreve and likely to continue prescribing it for their patients. These subjective rankings from the office setting are generally consistent with the findings of well-controlled clinical trials demonstrating that Bepreve is a rapid, long-lasting, and comfortable treatment for itching associated with allergic conjunctivitis. ■

1. Abelson MB, Smith L, Chapin M, Ocular allergic disease: mechanisms, disease sub-types, treatment, *Ocul Surf*, 2003;1:127–49.
2. Asthma and Allergy Foundation of America, Allergy facts and figures. Available at: www.aafa.org/display.cfm?id=9&sub=30#prev (accessed December 2010).
3. Centers for Disease Control and Prevention, FASTSTATS – allergies and hay fever. Available at: www.cdc.gov/nchs/fastats/allergies.htm (accessed December 2010).
4. Singh K, Bielory L, Ocular allergy: a national epidemiologic study, *J Allergy Clin Immunol*, 2007;119:S154.
5. Granet D, Allergic rhinoconjunctivitis and differential diagnoses of the red eye, *Allergy Asthma Proc*, 2008;29:565–74.
6. Bepreve (bepotastine besilate ophthalmic solution) 1.5% prescribing information, ISTA Pharmaceuticals, Inc., CA, USA, 2009.
7. Kato M, Nishida A, Aga Y, et al., Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent bepotastine besilate, *Arzneimittelforschung*, 1997;47:1116–24.
8. Williams JI, Gow JA, Klier SM, et al., Nonclinical pharmacology, pharmacokinetics, and safety findings for the antihistamine bepotastine besilate, *Curr Med Res Opin*, 2010;26:2329–38.
9. Kida T, Fujii A, Sakai O, et al., Bepotastine besilate, a highly selective histamine H(1) receptor antagonist, suppresses vascular hyperpermeability and eosinophil recruitment *in vitro* and in vivo experimental allergic conjunctivitis models, *Exp Eye Res*, 2010;91(1):85–91.
10. Data on file. Osaka, Japan: Tanabe Seiyaku Co; June 2009. ISTA Pharmaceuticals®, Inc.
11. Data on file. Bepreve® 1st Experience survey results (March – August 2010). ISTA Pharmaceuticals®, Inc.
12. Abelson MB, Torkildsen GL, Williams JI, et al., 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;31:1908–21.
13. Macejko TT, Bergmann MT, Williams JI, et al., Multicenter clinical evaluation of bepotastine besilate ophthalmic solutions 1.0% and 1.5% to treat allergic conjunctivitis, *Am J Ophthalmol*, 2010;150:122–7.e5.
14. Berdy GJ, Oliff HS, Clinical safety and efficacy of bepotastine besilate ophthalmic solution to treat allergic conjunctivitis, *Expert Rev Ophthalmol*, 2010;5:595–602.
15. Data on file. CL-EFF-0910091-R. ISTA Pharmaceuticals®, Inc.
16. Data on file. NDA 22-288 (ISE). ISTA Pharmaceuticals®, Inc.
17. 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 azallergen challenge model of allergic conjunctivitis. Presented at Eastern Allergy Conference, Palm Beach, FL, May 6–9, 2010.
18. Williams JI, Schooley GL, Gow JA, et al., Bepreve™ 1.5% provides clinically meaningful reduction in allergen-induced ocular itching for subjects in an analysis of two phase 3 conjunctival allergen challenge (CAC) clinical trials, *J Allergy Clin Immunol*, 2010;125:AB38.
19. Data on file. CL-SAF-0405071-R. ISTA Pharmaceuticals®, Inc.