CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

OTHER REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information *****

Date: August 14, 2009

To: Raphael Rodriguez
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Beth Carr, Pharm.D., Regulatory Review Officer
Lynn Panholzer, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Bepreve ™ (bepotastine besilate ophthalmic solution) 1.5%
NDA: 22-288

DDMAC has reviewed the proposed product labeling for Bepreve ™ (bepotastine besilate ophthalmic solution) 1.5% (Bepreve) submitted by Wiley Chambers via email on August 14, 2009 (attached); and we offer the following comments. Please feel free to contact me at (301) 796-3674 with any questions or clarifications.

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

- *"Remove contact lenses prior to instillation of Bepreve."*

For clarification purposes, we recommend adding the sentence, "Lenses may be reinserted after 10 minutes following administration of Bepreve," to the above Warning and Precaution.

FULL PRESCRIBING INFORMATION

6 ADVERSE REACTIONS

In accordance with the January 2006 Guidance for Industry: Adverse Reactions Section of the Label for Human Prescription Drugs and Biologics – Content and Format, please include the following:

- Please include an adequate description of the data sources for the adverse event data, as outlined in the guidance. For example, please include information on whether the trials were double blinded, randomized, and placebo controlled trials, if available. Also, please include the dosage, frequency, and duration of therapy that patients received.

- Identify adverse reactions, if any, that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.

14 CLINICAL STUDIES

The description of the clinical studies is vague and may be used by the sponsor to promote in a misleading manner. We suggest rewriting this section with the following information: number of patients studied in each arm of the trial, age ranges of the patients, major study endpoints, descriptions of the measurement tools used to evaluate the outcomes (the measurable signs of ocular itching), actual results (tabular format), and any appropriate accompanying statistics.

We recommend that specific efficacy data be included to qualify the superiority claims made in the label. Broad claims about the superiority of the drug versus vehicle without the context of the actual data may be used to misleadingly overstate the efficacy of the drug in promotional materials.

- *"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 CAC 15 minutes post-dosing and a CAC 8 hours post dosing of Bepreve."*

This claim is very vague and may be used promotionally to overstate the efficacy of Bepreve. Specifically, it does not identify the specific endpoint(s) that were measured. We recommend that the claim be revised to specify the measure of relief from ocular itching to which the claim refers.

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/s/

BETH M CARR
08/27/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 28, 2009
To:	Wiley Chambers, M.D., Acting Director Division of Anti-Infective & Ophthalmology Products
Through:	Laura Pincock, Pharm.D., Acting Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Raichell S. Brown, Pharm.D., J.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Bepreve (Bepotastine Besilate Ophthalmic Solution) 1.5%
Application Type/Number:	NDA # 22-288
Applicant/sponsor:	ISTA Pharmaceuticals
OSE RCM #:	2008-1998

1 INTRODUCTION

This review is in response to a request from the Division of Anti-Infective & Ophthalmology Products on December 15, 2008 to evaluate the labels and labeling of Bepreve (Bepotastine Besilate Ophthalmic Solution) 1.5% for the potential to contribute to medication errors. The Applicant submitted container labels, carton labeling, and insert labeling on February 16, 2009. The Division of Medication Error Prevention and Analysis also completed a Proprietary Name Review of Bepreve (See OSE Review #2008-1987 dated February 6, 2009).

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton labeling, and insert labeling submitted on February 6, 2009 (See Appendices A through H).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton labeling, and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We are willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis (DMEPA) on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, OSE Regulatory Project Manager, at 301-796-0558.

3.1 COMMENTS TO THE DIVISION

Based on our assessment of the insert labeling, we recommend that the Applicant implement the following revisions:

1. Remove the trailing zero after the decimal point in the net quantity statements in the insert labeling.

   1 mL (not 1.0 mL)

   5 mL (not 5.0 mL)

   10 mL (not 10.0 mL)

   DMEPA, consistent with recommendations from the Institute of Safe Medication Practices (ISMP) and National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), advises against the use of trailing zeros because they are error-prone and can result in ten-fold misinterpretation if the decimal is not seen.

2. Revise the statement in the DOSAGE AND ADMINISTRATION section that currently reads,

   (b) (4)

   to read

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

   Use of the phrases, 'For relief within 3 minutes' and 'for relief lasting up to 8 hours' may create the impression that this product should be used on an as needed basis. In addition, use of the phrase 'for relief lasting at least 8 hours' may lead to the inappropriate dosing of Bepreve every 8 hours.

3. Add or relocate the following statement, currently located in the WARNINGS AND PRECAUTIONS section, to the DOSAGE AND ADMINISTRATION section of the insert labeling because it is necessary for the proper administration of the product by patients who wear contact lenses.

   Remove contact lenses prior to installation of Bepreve. Lenses may be reinserted after 10 minutes following administration of Bepreve.

3.2 COMMENTS TO THE APPLICANT

We have evaluated your container labels and carton labeling for Bepreve (Bepotastine Besilate Ophthalmic Solution) 1.5%. Please revise your container labels and carton labeling as follows:

1. Container Labels and Carton Labeling:

   a. Remove the trailing zero located after the decimal point in the net quantity statements. For example,

      1 mL (not 1.0 mL)

      5 mL (not 5.0 mL)

      10 mL (not 10.0 mL)

      DMEPA, consistent with recommendations from the Institute of Safe Medication Practices (ISMP) and National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), advises against the use of trailing zeros because they are error-prone and can result in ten-fold misinterpretation if the decimal is not seen.

   b. Increase the prominence of the established name, while ensuring that the prominence of the dosage form remains commensurate to that of the established name.

      According to 21 C.F.R. §201.10(g)(2), required statement on a label can lack appropriate prominence by reason of the "style of type" in which the statement appears or "crowding" of the words within the statement. The statement "bepotastine besilate ophthalmic solution" lacks appropriate prominence because of one or both of these reasons.

   c. Relocate the route of administration statement to the principle display panel. Presentation of the route of administration on the principle display panels is customary and, thereby, fosters greater comprehension of the information by enhancing its clarity and ease of access. (See 21 C.F.R. 201.15(a)(1)).

2. Container Labels:

   a. Add the designation "Expiration Date," or a similarly appropriate designation, to the side or back panel of the container label.

   b. Add the designation "Lot number," or a similarly appropriate designation, to the side or back panel of the container label coupled with the expiration date designation as it appears on the carton labeling.

3. Carton Labeling:

Relocate the net quantity statement away from the statement of strength on the carton labeling to decrease the potential for confusion between the numerical statements. DMEPA notes that the Applicant has separated the net quantity and statement of strength on the container labels; similar positioning could be used on the carton labeling.

APPENDICES

Appendix A: Container Label for 1 mL (Professional Sample)

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/s/

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07/28/2009

LAURA L PINCOCK
07/28/2009

DENISE P TOYER
07/29/2009

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07/29/2009