CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-308

OTHER REVIEW(S)

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:	March 10, 2009
To:	Wiley Chambers, MD, Director Division of Anti-Infective and Ophthalmology Products
Through:	Kristina Arnwine, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Division Director Division of Medication Error Prevention and Analysis, HFD 420
From:	Lori Cantin, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Label and Labeling Review
Drug Name(s):	Besivance (Besifloxacin Ophthalmic Suspension) 0.6%
ApplicationType/Number:	NDA 22-308
Applicant:	Bausch and Lomb, Inc.
OSE RCM #:	2009-110

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton labeling for product, Besivance, needs improvement. The Medication Error Prevention and Analysis staff believes the areas of needed improvement we have identified can be addressed prior to approval and provide recommendations in Section 5.2.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Products to evaluate the product design, container label, carton and insert labeling to identify areas that could lead to medication errors. A review of the proposed proprietary name, Besivance, is forthcoming under separate cover in OSE review #2009-107.

1.2 REGULATORY HISTORY

The labels and labeling for this product were originally reviewed by DMEPA as part of the review for the for the proposed proprietary name, Optura, in OSE Review # 2008-415, dated September 23, 2008. In this review, the name 'Optura' was found to be unacceptable and changes to the labels and labeling that were aimed at reducing the risk of medication errors were recommended. The Applicant submitted a request for a proprietary name review for 'Besivance' on January 8, 2009, which included revised labels and labeling. The labels and labeling contained in this submission incorporated the new proposed proprietary name 'Besivance', as well as the changes recommended by DMEPA in OSE Review # 2008-415.

1.3 PRODUCT INFORMATION

Besivance (Besifloxacin) is an 8-chloro fluoroquinolone anti-infective ophthalmic suspension indicated for the treatment of bacterial conjunctivitis. The recommended dose is one drop in the affected eye(s) three times a day for 7 days. It is available as a sterile ophthalmic suspension at a concentration of 0.6% base (6 mg/mL), in 2 mL and 5 mL bottles.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on January 8, 2009, the following labels and insert labeling for the Division of Medication Error Prevention and Analysis review (see Appendices A, B, C, and D for images):

- Sample Container Label (5 mL)
- Trade Container Label (2 mL)
- Sample Carton Labeling (5 mL)
- Trade Carton Labeling (2 mL)
- Prescribing Information (no image)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

The areas of needed improvement identified in OSE review # 2008-415 were addressed by the Applicant. However, this review of the container labels, carton labeling, and package insert labeling identified additional areas of needed improvement, specifically regarding the prominence and presentation of information on the carton labeling.

3.1.1 Carton Labeling

The route of administration statement "For Ophthalmic Use Only" is not prominently displayed on the sample and trade carton labels.

The more important information regarding the route of administration "For Ophthalmic Use Only" follows the information "Rx only, Sterile" on the trade and sample carton labeling.

The statement "SAMPLE-NOT FOR RESALE" on the sample carton labeling lacks prominence.

4 DISCUSSION

4.1 LABEL AND LABELING RISK ASSESSMENT

Our analysis of the labels and labeling notes a lack of prominence of the route of administration statement "For Ophthalmic Use Only" on the 2 mL sample and 5 mL trade carton labeling. This important information should be more prominently displayed. The more important information regarding the route of administration "For Ophthalmic Use Only" follows the information "Rx only, Sterile" on the 2 mL sample and 5 mL trade carton labeling. Reversal of the presentation of this information will allow for increased prominence of information regarding the route of administration. For example:

For Ophthalmic Use Only

Rx only
Sterile

Additionally, we note that the size of the graphic is quite large and precludes the use of this space for the presentation of this more relevant information. The size of the graphic should be reduced, if necessary.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

The statement "SAMPLE-NOT FOR RESALE" on the 2 mL sample carton labeling lacks prominence. The sample and trade packaging should be readily distinguishable from each other. We recommend that the Applicant increase the size of the font for this statement. The size of the graphic should be reduced if it interferes with the more prominent presentation of this information.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and the design of the proposed carton labeling are areas that need improvement. The Medication Error Prevention and Analysis staff believes the areas of needed improvement we have identified can be addressed prior to approval and provide recommendations in Section 5.2.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Marlene Hammer, OSE project manager, at 301-796-0757.

5.2 COMMENTS TO THE APPLICANT

1. Increase the prominence of the route of administration statement "For Ophthalmic Use Only" on the 2 mL sample and 5 mL trade carton labeling, as this important information should be more prominently displayed.

2. Reversal of the order of presentation of information regarding the route of administration "For Ophthalmic Use Only" and "Rx only, Sterile" on the 2 mL sample and 5 mL trade carton labeling to allow for increased prominence of information regarding the route of administration. For example:

   For Ophthalmic Use Only

   Rx only
   Sterile

   Note: The size of the graphic is quite large and may preclude the use of this space for the presentation of a more prominent route of administration statement. The size of the graphic should be reduced if necessary.

3. Increase the prominence of the statement "SAMPLE-NOT FOR RESALE" on the 2 mL sample carton. The sample and trade packaging should be readily distinguishable from each other. We recommend that you increase the size of the font for this statement. If the size of the graphic interferes with increasing the prominence of this information it should be reduced.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

Memorandum

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

Date: January 26, 2009

To: Alison K. Rodgers
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Beth Carr, Pharm.D., Regulatory Review Officer
Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Tradename™ (besifloxacin ophthalmic suspension) 0.6%
NDA: 22-308

DDMAC has reviewed the proposed product labeling, including the package insert (PI), draft carton label, and draft container label for Tradename™ (besifloxacin ophthalmic suspension) submitted by the applicant on January 8, 2009; and we offer the following comments. We have also taken into consideration the labeling for Zymar® (gatifloxacin ophthalmic solution) 0.3% and Vigamox® (moxifloxacin hydrochloride ophthalmic solution) 0.5%. Please feel free to contact me at (301) 796-3674 with any questions or clarifications.

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

- To ensure consistency among ophthalmic fluoroquinolones, please consider modifying the "Indications and Usage" sentence to the following:
    - Tradename™ (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by **susceptible strains of** the following organisms. (emphasis added)

- We note that there is a disclaimer in the "Indications and Usage" section that states, "Efficacy for this organism was studied in fewer than 10 infections." Is efficacy demonstrated in fewer than 10 infections considered substantial evidence to support the use of this product in infections caused by these organisms?

- Please clarify here and in the Full Prescribing Information if *S. aureus* includes infections caused by both MRSA and MSSA, as this has been an issue in promotional materials for similar products.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Please see the above comments made in the HIGHLIGHTS section

5 WARNINGS AND PRECAUTIONS

5.3 Growth of Resistant Organisms with Prolonged Use

- ***"As with other anti-infectives**, prolonged use may result in overgrowth of non-susceptible organisms, including fungi."* (emphasis added)

  The bolded pharase minimizes the risk associated with the use of Tradename™ (besifloxacin ophthalmic suspension). To ensure that the warning and precaution is appropriately portrayed, please consider modifying the sentence to the following:
  - "Prolonged use of Tradename™ (besifloxacin ophthalmic suspension) may result in overgrowth of non-susceptible organisms, including fungi."

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

- In accordance with the January 2006 Guidance for Industry: Averse 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.
  - Is it necessary to include the number of adverse events per the total of patients or would it be sufficient to just include the rate of the adverse

events? For example, presenting blurred vision as occurring in only 38 out 1810 patients could minimize the risk of this adverse event.

- Is information known on which adverse events were proven to be caused by the drug? If so, please include this information here.

- [redacted] b(4)

Please consider deleting the above statement unless there is substantial evidence to support that Tradename could not cause any of the adverse events listed. The claim may be used promotionally to minimize potential adverse events caused by Tradename™ (besifloxacin ophthalmic suspension).

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- *"There is no evidence that the ophthalmic administration of Tradename™ has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals."*

Is this statement necessary in this section? It implies that the drug has been studied in humans and is proven to not cause any issues with weight bearing joints. Is this supported by substantial evidence? Please consider deleting the first portion of this statement and moving the latter portion to the "Animal Toxicology And/Or Pharmacology" section.

12 CLINCIAL PHARMCOLOGY

12.4 Microbiology

- *"The compound has broad-spectrum activity against* [redacted] *Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV."* b(4)

This statement could be used promotionally to broaden the indication for this product. Please consider modifying the above sentence to the following:

- "The antibacterial action of besifloxacin results from inhibition of both bacterial DNA gyrase and topoisomerase IV."

- *"The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminogylcoside, macro lie, tetracycline, β-lactam, sulfonamide, and cyclic peptide antibiotics."*

  This statement is promotional in tone and could be used to support superiority claims over other antibiotic agents. Please delete.

- *"Therefore, besifloxacin may be active against pathogens resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin."*

  This statement appears speculative and to not be supported by substantial evidence. It could be used promotionally to broaden the indication for the product and promote the product as having less resistance than other antibiotics. Please delete.

- [redacted] b(4)

  It appears this statement is implying that besifloxacin will not develop resistance to either of these organisms. Is this supported by substantial evidence? Please consider deleting this statement and only including a quantifying amount for the concentration achieved in the tear fluid by besifloxacin.

13 NONCLINCIAL TOXICOLOGY

13.2 Animal Toxicology And/Or Pharmacology

- [redacted] b(4)

  Please consider qualifying the term, [redacted] As it stands, the term is vague and may be used promotionally to minimize the potential risks associated with besifloxacin. b(4)

14 CLINICAL STUDIES

- [redacted] b(4)

  Please consider deleting this statement as it is promotional in tone. Please only include quantifying measures of the outcomes of the clinical study.

- Please delete the term "superior" each time it is used in this section. This term is promotional in tone. Please consider replacing with "statistically significant" where applicable.

- We note that this section states patients were only dosed for 5 days in the clinical study, but that the recommended dosage for the product is 7 days. Please clarify this in the label. If this is correct, please add a statement that the full course of therapy is 7 days. Otherwise, the sponsor could use this to promote the drug for a shorter duration of treatment than is recommended.

- How was "clinical resolution" defined? Please include this information in this section.

- We note that p-values are not included for either the clinical resolution rate or the eradication rate. If these are available, please include them along with the appropriate endpoint of the study.

- Was "eradication rate for causative pathogens" a pre-specified endpoint of the clinical study? If not, please delete. We note that the result for this endpoint is significantly higher than for the clinical resolution rate and it could be used promotionally to overstate the clinical efficacy of besifloxacin.

- Please include the number of patients included in each arm of the clinical trial.

17 PATIENT COUNSELING

- *"Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction."*

  Please consider adding examples of signs and symptoms of an allergic reaction (in consumer friendly language) for clarity.

MEDICATION PACKAGING

Draft Carton and Container Label

DDMAC has no comments on the proposed labels at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Beth M Carr
1/26/2009 09:34:20 AM
DDMAC PROFESSIONAL REVIEWER