CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-308

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	5/28/09
From	Edward M. Cox, MD, MPH
Subject	Office Director Decisional Memo
NDA #	22-308
Applicant Name	Bausch & Lomb, Inc.
Date of Submission	6/02/2008
PDUFA Goal Date	4/02/2009
Proposed Proprietary Name / Established (USAN) Name	Besivance / besifloxacin ophthalmic suspension
Dosage Forms / Strength	Ophthalmic suspension, 0.6% as base
Proposed Indication	Treatment of bacterial conjunctivitis
Action:	**Approval**

Besivance (besifloxacin ophthalmic suspension) 0.6%, is a sterile ophthalmic suspension of besifloxacin, a fluoroquinolone antibacterial agent developed for treatment of bacterial conjunctivitis.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of besifloxacin for treatment of bacterial conjunctivitis. For a detailed discussion of NDA 22-308, the reader is referred to the individual discipline specific reviews. In addition, the Team Leader and Acting Division Director's reviews summarize key issues in the NDA submission. This memorandum will focus on selected issues from the application.

Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls Reviewer recommends approval. The Office of Compliance recommendation regarding manufacturing facilities is an overall recommendation of acceptable. The Product Quality Microbiology Review also recommends approval.

Pharmacology / Toxicology

The recommendation from the Pharmacology/Toxicology discipline is for approval. Besifloxacin is labeled as a Pregnancy Category C agent.

Microbiology

The recommendation from the Microbiology Reviewer is for approval. Besifloxacin, similar to other fluoroquinolones, acts by inhibiting bacterial DNA gyrase and topoisomerase IV. Besifloxacin is active against a number of gram-positive and gram-negative bacteria. Data support chromosomal mutations in the *gyrA* gene as a mechanism for development of resistance to besifloxacin. Mutations in *gyrB*, *ParC*, and *parE* could potentially also contribute to development of resistance.

Clinical Pharmacology

The Clinical Pharmacology Reviewer for besifloxacin notes that systemic levels of besifloxacin after ocular administration are less than 0.7 ng/mL. The concentration and dosing interval (three times a day) were found to be acceptable based upon the observed microbial eradication rates and the low incidence of adverse events.

Clinical and Statistical

The efficacy of besifloxacin in the treatment of bacterial conjunctivitis was demonstrated in two vehicle controlled trials (studies # 373 and #433) that studied besifloxacin 0.6%, one drop TID, for 5 days for the treatment of bacterial conjunctivitis. Both studies were multi-center, double-blind, randomized, vehicle controlled studies. The primary analysis timepoint was Visit 3 (Day 8 +1day) for study 373 and Visit 2 (Day 4 +/-1day) for study 433. In both studies #373 and #433, besifloxacin was superior to its vehicle in the primary efficacy analyses of clinical resolution in patients with a positive culture and bacterial eradication. The results for clinical resolution in the ITT population are also consistent with the results for clinical cure in patients with a positive baseline culture and the results for bacterial eradication.

Study #434 was an active controlled trial of besifloxacin 0.6%, one drop TID for 5 days compared to moxifloxacin 0.5% for 5-days for the treatment of bacterial conjunctivitis. The numerical results for besifloxacin and moxifloxacin were similar for the primary efficacy endpoint, but a justification for a noninferiority margin has not been provided for this study; additional work would be needed to justify the findings observed in study #434.

There are safety data from approximately 1100 patients treated with besifloxacin 0.6%, most of whom received 5 days of treatment. In patients with bacterial conjunctivitis, ocular adverse events were often reported more frequently in the vehicle group, as many events appear to be consistent with the symptoms of bacterial conjunctivitis. In the pooled adverse event data from the three phase 3 clinical trials, 12% of subjects in the besifloxacin arms, 16% of subjects in the vehicle arms, and 9% of subjects in the moxifloxacin arm reported at least one adverse event. In subjects who received besifloxacin, the most frequently reported adverse events were blurred vision reported by 2.1% of besifloxacin subjects (reported by 3.9% of vehicle subjects); eye pain reported by 1.8% of besifloxacin subjects (reported by 1.8% of vehicle subjects); eye irritation reported by 1.4% of besifloxacin subjects (reported by 2.9% of vehicle subjects); eye pruritis reported by 1.1% of besifloxacin subjects (reported by 1.6% of vehicle subjects). The safety data for patients who received more than 5 days of therapy were also reviewed. The adverse event profile within the limited number of patients that received more than 5 days of therapy did not demonstrate difference from those who received 5 days of therapy. A postmarketing requirement will be included in the approval letter to further evaluate for serious unexpected adverse events with therapy of 7 days duration.

As noted in the statistical review, the data from studies #373 and #433 support the efficacy of besifloxacin for the treatment of bacterial conjunctivitis. The Clinical Reviewer, Medical Team Leader, and Acting Division Director also recommend approval of besifloxacin and note

that the data support either approval for a duration of either 7 days or 5 days and express a preference for a treatment duration of 7 days.

DSI recommendations

Inspections of five clinical sites and the company (Bausch & Lomb) were performed and are summarized in the Division of Scientific Investigation's Clinical Inspection Summary. DSI recommends that data from site #691449 (Zosa) not be used in support of the NDA because of serious concerns regarding data reliability and integrity at the site. Inspections were also performed of Bausch & Lomb and the DSI assessment is as follows:

> *While the FDA sponsor inspection revealed a regulatory violation of sponsor obligations in the conduct of Study #434 (selection of an investigator without substantiating their prior research experience in accordance with Bausch & Lomb, Inc Standard Operating Procedures), overall data submitted by the Applicant in the NDA appear reliable, with the exception of data from Dr. Zosa and perhaps Dr. Asbell. In their letter date September 17, 2008, the Sponsor has provided adequate assurance that their method for clinical site selection is being revised and improved.*

The applicant has also identified problems at another site (site #748395, Asbell). The DSI evaluation of this site is still pending at this time. The data from Zosa's and Asbell's sites are not relied upon to support the approval. I have discussed the issue of the outstanding inspection of site #748395 and the implications for the NDA with DSI. The recommendation from DSI is that the action on NDA 22-308 does not need to be held until after the inspection of site #748395. The inspection of other sites and of Bausch and Lomb provided adequate assurances on the quality and reliability of the data in the NDA.

DMEPA

DMEPA has reviewed the trade name Besivance and found the trade name to be acceptable. DDMAC does not object to the proposed trade name from a promotional perspective. DDMAC has also provided comments on the proposed label that have been incorporated in the label, when appropriate.

Pediatrics and Geriatrics

The clinical trials included patients between 1 and 98 years old. The pediatric study requirement for ages less than one year is waived because the necessary studies are impossible or highly impracticable. This is because ophthalmia neonatorum, a related but different condition, affects children under 1 month of age. There are too few children with bacterial conjunctivitis between 1 month and 1 year of age to study. The applicant has fulfilled the pediatric study requirement for ages one year and older for this application. Therefore, no additional pediatric studies are needed at this time.

Advisory Committee

Besifloxacin was presented to the FDA's Dermatologic and Ophthalmic Advisory Committee on December 5, 2008. The Committee voted unanimously (Yes 9; No 0) in favor of approval of besifloxacin for the treatment of bacterial conjunctivitis. The committee agreed that safety and efficacy were demonstrated by the data presented. The committee made suggestions to add language for use in patients with pre-existing dry eye and other corneal surface conditions in the labeling.

Duration of Therapy

At the time of the PDUFA goal date the issue of duration of therapy had not been fully resolved. As noted in the Medical Officer, Team Leader, and Acting Division Director's reviews, I had proposed that the appropriate duration of therapy was the duration studied in the clinical trials of 5 days. Given the differences in opinion on the issue, I requested a meeting to further discuss the issue with OND management and the Office of Medical Policy. The focus of the discussion was on the data from the trials that had been conducted, the findings from these studies, and convention in approaching duration of therapy for topical ophthalmic antibacterial drugs for treatment of bacterial conjunctivitis. Several previously approved topical ophthalmic antibacterial drugs were studied for durations less than 7 days and approved for a duration of 7 days. It was noted that the clinical trials for antibacterial drugs for treatment of bacterial conjunctivitis are not designed to specifically investigate duration of therapy and that convention in the field has been that the labeled duration for ophthalmic topical antibacterial is 7 days. The points from the meeting were that it would not be appropriate to approve this drug for a duration of therapy of less than 7 days duration given the nature of the clinical trials conducted (that they did not include a comparison of 5 days of therapy to 7 days of therapy) and the convention in the field. In addition, there was insufficient information to make assessments regarding the development of resistance or the rates of relapse with 7 vs. 5 days of therapy. In order to obtain additional safety data to look for unexpected serious adverse events at a duration of 7 days, a postmarketing requirement will be included in the approval to gather additional safety data in patients who receive 7 days of therapy. This safety study will provide additional data to further bound risk of adverse events for patients who receive 7 days of therapy. In addition, the applicant should be encouraged to perform additional studies to further evaluate duration of therapy for treatment of bacterial conjunctivitis with besifloxacin.

Summary

The safety and efficacy data evaluating Besivance (besifloxacin ophthalmic suspension) 0.6%, support an acceptable risk benefit profile for Besivance for the treatment of bacterial conjunctivitis. The labeling provides information on conditions of use and adverse events. The approval letter includes a postmarketing requirement to perform a safety trial to gather additional data to further characterize evaluate for serious unexpected adverse events with the 7 day regimen. This trial should be a randomized, parallel arm, vehicle-controlled, clinical trial to evaluate the safety of Besivance (besifloxacin ophthalmic suspension) 0.6% when administered three times a day, four to twelve hours apart, for 7 days. The clinical trial must enroll at least 300 patients with signs and symptoms of bacterial conjunctivitis (ocular redness and discharge) and may include patients randomized in a 2:1 ratio (Besivance: control). The study's objective is to collect safety information. Clinical outcomes should be collected in this study as this information can also be important in the assessment of the safety data. Microbial cultures are required at baseline to document the appropriate enrollment of patients. The applicant has agreed to conduct this study under the following timeframe: Final Protocol Submission: October 2009, Trial Completion Date: April 2012 and Final Report Submission: October 2012.

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/s/

Edward Cox
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MEDICAL OFFICER