CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVAULATION AND MITIGATION STRATEGY REVIEW

Date:	September 19, 2014
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Doris Auth, Pharm.D., Team Leader, DRISK
Division Director:	Cynthia LaCivita, Pharm.D., Acting Director, DRISK
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Xtoro (finafloxacin)
Therapeutic class & dosage form:	Antibacterial agent; otic suspension
OND Review Division:	Division of Anti-infective Products
Application Type/Number:	NDA 206307
Application received:	April 25, 2014
PDUFA/Action Date:	December 24, 2014
Applicant/sponsor:	Alcon Research, Ltd
OSE RCM #:	2014-943

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the fluoroquinolone otic antibiotic, Xtoro (finafloxacin). The proposed indication for finafloxacin is treatment of acute otitis externa (AOE) with or without an otowick, in pediatric (age (b) (4) and older), adult, and elderly patients.

Alcon Research submitted the application April 25, 2014. Alcon Research did not submit a Risk Evaluation and Mitigation Strategy (REMS) or risk management plan. The application was granted priority review status[1], with action to be taken on the application by December 24, 2014.

2 REGULATORY HISTORY

The following are milestones important to this application:

- Pre-NDA meeting September 27, 2013
- Application submitted April 25, 2014
- Filing date June 24, 2014
- PDUFA goal date December 25, 2014

3 MATERIALS REVIEWED

We reviewed the following:

- Application submitted April 25, 2014.
- Discipline presentations at the mid-cycle meeting for NDA 206307, meeting held July 28, 2014.
- Draft clinical safety review by Rhea Lloyd, M.D., Medical Officer for the application.

4 RESULTS OF REVIEW

4.1 OVERVIEW OF CLINICAL PROGRAM[2]

The data submitted in support of efficacy in the application were derived from two randomized, multicenter, vehicle-controlled clinical trials enrolling 1234 patients, half of whom were randomized to receive finafloxacin. Patients receiving finafloxacin had better clinical and microbiological outcomes compared to patients receiving vehicle (placebo). Clinical cure on Day 11 occurred in 72% and 69% in the patients receiving finafloxacin in the two trials compared to 33% and 40% in the patients receiving only

[1] Priority status was granted under the Title VIII of FDASIA, through the Generating Antibiotic Incentives Now (GAIN) program. Under GAIN, a drug may be designated as a qualified infectious disease product (QIDP). A drug that receives QIDP designation is eligible for priority review.

[2] Efficacy and safety summaries presented here is adapted from the data submitted by the sponsor and the summary in the draft safety review by Dr. Lloyd.

vehicle.

4.2 SAFETY CONCERNS

The safety database for finafloxacin comprises exposure in 632 patients, including the patients in the Phase 3 trials and patients exposed in pharmacokinetic studies.

The most serious safety concerns with this product, as presented by the sponsor in the Warnings and Precautions section of the draft labeling, include (b) (4) the possibility of overgrowth of fungi.

No serious adverse events occurred in clinical testing in patients receiving finafloxacin. One patient receiving vehicle experienced two serious adverse events, anxiety and gastroenteritis. The most frequently reported adverse events in patients receiving finafloxacin in the clinical trials were ear pruritus, otitis externa, and nausea.

4.3 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not propose risk management measures beyond labeling.

5 DISCUSSION OF A REMS FOR FINAFLOXACIN

No serious safety signals have emerged to date for finafloxacin that would require a REMS to ensure that the benefit outweigh the risks.. The risks placed in the *Warnings and Precautions* section of the labeling are common to otic products (i.e., to (b) (4) and antibacterial products (fungal overgrowth), and do not warrant a REMS.

6 CONCLUSION/RECOMMENDATION

DRISK believes that the risks of finafloxacin that have emerged to date can be communicated through labeling. We do not recommend a REMS at this time. Should any additional important risk information emerge during the review of the application, we ask that you include us in the discussion of appropriate risk management.

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/s/

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09/19/2014

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