



WRITTEN REQUEST

IND 110576

Alcon Research, Ltd.
Attention: Mr. Richard Reese
Assistant Director
Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Reese:

Reference is made to your April 16, 2012, Proposed Pediatric Study Request for finafloxacin otic suspension.

To obtain needed pediatric information on finafloxacin in the treatment of acute otitis externa in pediatric patients from six months of age and older, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the trials described below.

Clinical Trials: The trials must be randomized, double-masked, parallel, superiority trials of patients with otitis externa. The trials must be of at least 1 week duration and must include a minimum of three evaluations on different days, for example, baseline, day 3±1 day, and end of treatment.

Objective: The primary objective of the trials should be to evaluate the safety and the clinical cure rate between treatment groups. Enrolled patients must include male and female patients with a clinical diagnosis of acute otitis externa.

Age Groups/Number of Patients: Patients must be at least 12 months old at the time of enrollment. At least 60 of the patients enrolled in the trials must be between the ages of 12 months and 13 years, treated with finafloxacin, and evaluated for safety and efficacy. Children under the age of 12 months should not be included in the trials because otitis externa does not occur in children under the age of 1 year.

Representation of Ethnic and Racial Minorities: The trials must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why you were unsuccessful.

Trial endpoints: The primary endpoint for each trial must be complete relief of otic tenderness and clearing of ear canal erythema. Additionally, otic cultures must be taken at baseline and between 2 and 10 days after the start of treatment.

Statistical: In each trial, with a two-sided alpha level of 0.05 and a presumptive clinical cure rate of 74% of treated patients, 140 bacterial culture positive patients per treatment group yields 90% power to detect a 20% lower clinical cure rate in the control group compared to the finafloxacin group.

Extraordinary results: In the course of conducting these trials, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug information: Finafloxacin, in an appropriate formulation, must be compared to a concurrent active, vehicle, or steroid control.

Labeling that may result from the trials: You must submit proposed pediatric labeling to incorporate the findings of the trials. Under section 505A(j) of the Act, regardless of whether the trials demonstrate that finafloxacin is safe and effective, or whether such trial results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the trials. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the trials.

Format and types of reports to be submitted: You must submit full trial reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the trials should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the trial reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that trial data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at <http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/Cder/guidance/7087rev.htm>.

Timeframe for submitting reports of the trials: Reports of the above trials must be submitted to the Agency on or before June 30, 2016. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the trials reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the trials at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric trials will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the trials. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the trials, but have not submitted the trial reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above trials to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the trials should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these trials. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric trials conducted in response to this Written Request within 210 days of submission of your trial reports. These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

EDWARD M COX
02/22/2013