DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 60991

WRITTEN REQUEST

Alcon Research, Ltd.
Attention: Richard Reese
Global Project Regulatory Manager
6201 South Freeway
Mail Code: R3-50
Fort Worth, TX 76134-2099

Dear Mr. Reese:

Reference is made to NDA 20-688, the discussions at the July 30, 2012, Pre-NDA meeting of a Proposed Pediatric Study Request for olopatadine hydrochloride ophthalmic solution, 0.77%. Reference is also made to the Agency's written request dated July 19, 2007, and to your submission to NDA 21-861, adequately addressing the Agency's written request.

The clinical features, responses and treatments of allergic conjunctivitis are similar in adults, older children and younger children. Olopatadine hydrochloride ophthalmic solution, 0.1%, is approved for use in pediatric patients with allergic conjunctivitis. While the efficacy of olopatadine hydrochloride ophthalmic solution for the treatment of allergic conjunctivitis can be extrapolated from study(ies) of older children and adults to younger children with the same condition, the safety must be studied in younger children. To obtain needed pediatric information on a higher strength olopatadine hydrochloride ophthalmic solution (i.e., 0.77%), for the treatment of allergic conjunctivitis, 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, that you submit information from the following study.

- *Type of study*: Double masked, randomized, parallel group, controlled study of at least six weeks duration. This study must take into account adequate (e.g., proportionate to study 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 they were unsuccessful.

- *Indication to be studied:* Treatment of allergic conjunctivitis.

- *Age group in which study will be performed*: Pediatric patients aged ≥ 2 to ≤ 10 years of age at risk of having an episode of allergic conjunctivitis. Neonates and patients ≤ age 2 are not included in this study because allergic conjunctivitis cannot be accurately diagnosed in these patients.

- *Number of patients to be studied:* At least 30 pediatric patients treated with olopatadine hydrochloride ophthalmic solution, 0.77% and followed for at least 6 weeks.

- *Study endpoints:* While efficacy of the drug product can be extrapolated from studies in older children and adults, the primary endpoint of this trial must be safety examination of these children by slit lamp biomicroscopy along with the solicitation and recording of any adverse events associated with the use fo the product.

- *Drug information:* Olopatadine hydrochloride ophthalmic solution, 0.77% administered topically to the eye.

- *Drug specific safety concerns*: None

- *Statistical information, including power of study and statistical assessments:* Subjects should be randomized between active treatment and vehicle. Safety assessments in addition to the collection of any adverse experiences should include visual acuity and biomicroscopy assessments. Demographic characteristics, visual acuity, and adverse experiences should be summarized descriptively and compared for each treatment group. The minimum of 30 pediatric patients is expected to be sufficient to detect adverse events which have a true incidence of 10% or greater.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that olopatadine hydrochloride ophthalmic solution 0.77% is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. 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 study.

  Format and types of reports to be submitted: You must submit a full study reports (which has not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the report must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study 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 study report, you must submit all postmarketing adverse event reports regarding this drug that are available to

you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study 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 study:* A report of the above study must be submitted to the Agency on or before October 1, 2015. 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 study 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 studies 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 studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. 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 study, but have not submitted the study 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 study 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.

A report of the study 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 studies. When submitting the report, 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 II, 7500 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 301-827-5911.

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 studies conducted in response to this Written Request within 210 days of submission of your study report(s). 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, approvable, not approvable); 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/cder/pediatric/index.htm

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 Christina Marshall, Regulatory Health Project Manager, at 301-796-3099.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD
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
10/03/2013