DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 60,116
NDA 20-688
NDA 21-545
NDA 21-861

Alcon Research, Ltd.
Mail Code R7-18
6201 South Freeway
Fort Worth, TX 76134-2099

Attn: Seane D. Jones, MS, RAC
Associate Director, Regulatory Affairs

Dear Ms. Jones:

Reference is made to your Proposed Pediatric Study Request submitted to IND 60,116 on March 22, 2007, for olopatadine.

To obtain needed pediatric information on olopatadine, 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), that you submit information from the following studies:

Type of Study to be Performed

Study 1: Safety and efficacy study in patients 6 years to <12 years of age
Study 2: Safety and PK study in patients 2 years to <6 years of age

Objective/Rationale

Study 1: To assess the efficacy and safety of olopatadine nasal spray in patients 6 years to <12 years of age when administered at an age- and/or weight-appropriate dose.

Study 2: To assess the safety of olopatadine nasal spray in patients 2 years to <6 years of age. To assess the pharmacokinetics (i.e., C_{max} and AUC) of olopatadine and its active metabolites in patients 2 years to <6 years of age and to compare to those seen in adolescents and adults given the dose of olopatadine proposed for use in adolescents and adults.

Indication to be Studied: Allergic rhinitis

Age Groups in Which Study Will Be Performed

Study 1: Patients from 6 years to <12 years of age. Enroll patients so that there will be approximately equal representation of the following two age groups at the time of randomization: 6 years to <9 years, 9 years to <12 years.

Study 2: Patients from 2 years to <6 years of age. Enroll patients so that there will be approximately equal representation of the following two age groups at the time of randomization: 2 years to <4 years and 4 years to <6 years.

Study Design

Study 1: Perform a randomized, placebo-controlled, parallel-group efficacy and safety study with a treatment duration of two weeks. Provide an assessment of compliance with study treatment.

Study 2: Perform a randomized, placebo-controlled, parallel-group safety study with a treatment duration of two weeks. Provide an assessment of compliance with study treatment. Assess the single- and multiple-dose pharmacokinetics of olopatadine and its active metabolites. For the PK assessments, obtain a minimal amount and limited number of blood samples at adequate sampling times to evaluate pharmacokinetics appropriately. Sampling times may be selected based on an optimum sampling strategy for the best estimation of the pharmacokinetics of olopatadine and its active metabolites.

Number of Patients to be Studied

Study 1: Enroll a sufficient number of patients to ensure a minimum of 250 patients per treatment arm (i.e., a total of at least 500 patients for the study) will complete at least 2 weeks of the study treatment, with at least 150 patients in each of the two following age groups: 6 years to <9 years and 9 years to <12 years.

Study 2: Enroll a sufficient number of patients to ensure that a minimum of 50 patients complete at least two weeks of study treatment, with at least 20 patients in each of the two following age groups: 2 years to <4 years and 4 years to <6 years.

Entry Criteria

Study 1: Patients 6 years to <12 years of age who have symptoms of allergic rhinitis.

Study 2: Patients 2 years to <6 years of age who have symptoms of allergic rhinitis or who have had such symptoms in the past.

Clinical Endpoints

Study 1: Include symptom scores that are recorded by parents or caregivers as efficacy endpoints. Assess efficacy at the start of the study and daily for the duration of

the study. Include percent change from baseline in Total Nasal Symptom Score (TNSS), based on parent or caregiver reflective symptom assessments as the primary efficacy endpoint. Include percent change from baseline in TNSS, based on parent or caregiver instantaneous assessments as a secondary efficacy endpoint. Include evaluations of parent or caregiver assessed individual symptom scores as secondary efficacy endpoints.

Include recordings of adverse events, vital signs, physical examinations, and nasal examinations as safety endpoints. Perform vital signs, physical examinations, and nasal examinations at screening or baseline and toward the end of the study while participants are still on study drug. Record adverse events in a diary record.

Study 2: Determine the plasma concentration of olopatadine and its active metabolites using the same validated assay method employed previously or using an adequately cross-validated assay method.

Include recordings of adverse events, vital signs, physical examinations, and nasal examinations as safety endpoints. Assess safety endpoints at screening or baseline and toward the end of the study while participants are still on study drug. Record adverse events in a diary record.

Study Evaluations

Study 1: Include assessment of reflective and instantaneous symptoms recorded by parents or caregivers as study evaluations. Assess efficacy at the start of the study and daily for the duration of the study. Conduct Study 1 before conducting Study 2.

Study 2: Report plasma concentrations and pharmacokinetic parameters such as C_{max}, T_{max}, AUC, CL/F, and $t_{1/2}$ for olopatadine and its active metabolites. Explore the effects of covariates, such as age, weight, height, and body surface area on the pharmacokinetics of olopatadine and its active metabolites. Utilize appropriate prior pharmacokinetic data available in children and adults. Provide a descriptive comparison of the pharmacokinetics of olopatadine and its active metabolites in children and adults.

Include descriptive analyses of adverse reactions, vital signs, physical examinations, and nasal examinations as study evaluations.

Drug Information

Dosage form: Nasal spray solution

Route of administration: Intranasal

Regimen:

Study 1: Administration of an age- and/or weight-appropriate dose or doses, with dosing and dosing intervals as determined by pharmacokinetic and/or clinical data.

Study 2: Administration of one or more dose levels with the total daily dose provided based on age- and/or weight considerations.

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

The bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the current proposed drug product to the age appropriate formulation may be conducted in adults.

Drug-specific Safety Concerns

Safety concerns include unanticipated adverse reactions, particularly paradoxical excitability, somnolence, fatigue, hyperkinesia, epistaxis, and/or nasal irritation.

Statistical Information

Study 1: Provide analyses of efficacy based on parent or caregiver-assessed symptom scores using an appropriate statistical test for the data.

Provide descriptive analyses of adverse events, vital signs, physical examinations, and nasal examinations, and provide pharmacokinetics parameters as noted above in ***Study Evaluations***.

Study 2: Provide descriptive analyses of the pharmacokinetics parameters, adverse events, vital signs, physical examinations, and nasal examinations.

Labeling That May Result from the Study

Appropriate sections of the label may be changed to incorporate the findings of the study.

Format of Reports to be Submitted

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) 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, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for Submitting Reports of the Study

Reports of the above study must be submitted to the Agency on or before July 1, 2009. Please keep in mind that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the study in response to this Written Request.

Response to Written Request

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric study will be initiated.

Please 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. Please notify us as soon as possible if you wish to enter into a Written Agreement by submitting a Proposed Written Agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study should be submitted as a New Drug Application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from the study. 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, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (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 and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, 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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Guidance for Industry, *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and*

Conditions, is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Anthony Zeccola, Regulatory Project Manager, at (301) 796-1318.

Sincerely yours,

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
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/

Robert Meyer

7/19/2007 11:26:07 AM