DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064
NDA 22-157

WRITTEN REQUEST

UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

Attention: Susan Tegtmeyer, M.S.
Senior Manager, Regulatory Affairs

Dear Ms. Tegtmeyer:

Reference is made to your March 11, 2008, Proposed Pediatric Study Request for levocetirizine submitted to IND 72,233.

To obtain needed pediatric information on levocetirizine, 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 following studies:

Type of Studies:

Study 1: Pharmacokinetic (PK) and safety study in pediatric patients ≥ 6 months to < 6 years of age.

Study 2: Double-blind, randomized, placebo-controlled 2-week safety study in pediatric patients ≥ 6 months to < 12 months of age

Study 3: Double-blind, randomized, placebo-controlled 2-week safety study in pediatric patients 1 to < 6 years of age

Objective of Each Study:

Study 1: To assess the pharmacokinetics of levocetirizine in order to determine the dose for patients ≥ 6 months to < 6 years of age that result in comparable systemic exposures (i.e., C_{max} and AUC) of levocetirizine to those seen in adolescents and adults given labeled doses of levocetirizine. These data should be used to determine the appropriate dosage by age and/or by weight for studies 2 and 3.

Study 2: To assess the safety of levocetirizine in patients ≥ 6 months to < 12 months of age with symptoms of allergic rhinitis or chronic idiopathic urticaria.

Study 3: To assess the safety of levocetirizine in patients 1 to < 6 years of age with symptoms of allergic rhinitis or chronic idiopathic urticaria.

Indications to be Studied:

Studies 1, 2, and 3: Allergic rhinitis, urticaria

Age Group in Which Studies Will be Performed:

Study 1: Patients ≥ 6 months to < 6 years of age
Study 2: Patients ≥ 6 months to < 12 months of age
Study 3: Patients 1 year to < 6 years of age

Number of Patients to be Studied:

Study 1: A sufficient number of patients from each age group (≥ 6 months to < 2 years and ≥2 years to < 6 years) in order to achieve a standard error of 20% or less around the mean estimate for oral clearance and volume of distribution, and to detect any subgroup differences. The number of patients should be approximately evenly distributed in each of the following subgroups: ≥ 6 months to < 1 year, ≥ 1 year to < 2 years, ≥ 2 year to < 4 years, and ≥ 4 years to < 6 years. A minimum of three patients should be enrolled for each numerical age. The sample size for ensuring parameter estimation with such precision should be derived using prior knowledge, such as adult and/or pediatric PK data from older children. If a population pharmacokinetic approach is used, the number of patients should be increased as appropriate. Approximately four samples per pediatric patient are generally required for a population pharmacokinetic approach. Samples should be collected at various times following single-dose and multiple-dose drug administration to cover the entire concentration-time profile.

Study 2: Approximately 80 patients with a minimum of 60 completed patients and with at least 40 completed patients to receive active treatment.

Study 3: Approximately 150 patients with a minimum of 120 completed patients and with at least 80 completed patients to receive active treatment.

Study Endpoints:

Study 1: For a conventional pharmacokinetic study, determine the plasma concentration of levocetirizine and estimate the pharmacokinetic parameters of levocetirizine such as $C_{max,}$ $T_{max,}$ AUC, apparent oral clearance, apparent volume of distribution, and $T_{1/2}$. For a population pharmacokinetic study, both population and individual means and variability for appropriate pharmacokinetic parameters should be determined to predict the exposure in the pediatric patient population. Effects of covariates (i.e., age, weight, height, body surface area etc.) should be studied. To study the effects of these covariates, utilize all available data

including prior pharmacokinetic data available in children and adults. Safety endpoints must include adverse events, vital signs, and physical examinations. Clinical chemistries and hematology profiles should be included if a multiple-dose study is performed.

Studies 2 and 3: Safety variables to include adverse events, physical examination, vital signs, ECGs, and clinical chemistries and hematology profiles.

Drug Information:

Studies 1, 2, and 3

Dosage form: Age-appropriate dosage form (for which relative bioavailability has been established)

Route of administration: Oral

Regimen:

Studies 1, 2, and 3*:* Single- and/or multiple-dose administration of one or more dose levels at age- and/or weight-appropriate doses.

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

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. Under these circumstances, 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 labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

Drug-Specific Safety Concerns:

Unanticipated adverse reactions, particularly paradoxical excitability, somnolence, fatigue, tremor, and other CNS manifestations

Statistical Information, including Power of Studies and Statistical Assessments:

Study 1: Provide pharmacokinetic parameters and descriptive analyses of vital signs, physical examinations, and adverse events. Include descriptive analyses of laboratory studies if a multiple-dose study is performed.

Studies 2 and 3: Provide descriptive analyses of adverse events, vital signs, physical examinations, ECGs and laboratory studies.

Labeling that May Result from the Studies:

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that levocetirizine is safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies. 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 studies.

Format and Types of Reports to be Submitted:

You must submit full study 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 studies 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 reports, 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 studies:

Reports of the above studies must be submitted to the Agency on or before May 30, 2010. 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 studies. 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 studies 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 studies 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 studies 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 reports, 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 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 http://www.ClinicalTrials.gov.

If you have any questions, call Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

Sincerely,

{See appended electronic signature page}

Curt Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name / Subject
IND 72233	UCB PHARMA	LEVOCETIRIZINE

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/s/

CURTIS J ROSEBRAUGH
02/03/2009