DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-035

UCB Pharma, Inc.
Attention: Patricia A. Fritz
Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Fritz:

Reference is made to your Proposed Pediatric Study Request submitted on February 21, 2001 for Keppra® (levetiracetam) 250 mg, 500 mg, and 750 mg Tablets to IND 45,151.

To obtain needed pediatric information on levetiracetam, 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:

Types of Studies

Study 1: Pharmacokinetic Study (1 month to 16 years)
Study 2: Pediatric Efficacy and Safety Study (1 month to 16 years)
Study 3: Pediatric Safety Study (1 month to 16 years)

Indications to be studied (i.e. objective of each study):

Study 1: To determine the steady-state pharmacokinetics and to support dose selection in pediatric patients with partial onset seizures ages 1 month to 16 years.

Study 2: To establish efficacy by a randomized, double-blind, placebo controlled design and short-term safety of levetiracetam as adjunctive therapy in the treatment of partial onset seizures in pediatric patients ages 1 month to 16 years.

Study 3: To determine the long-term safety of levetiracetam as adjunctive therapy in the treatment of partial onset seizures in pediatric patients enrolling enough patients to ensure that aprroximately 100 are exposed to levetiracetam for a minimum of 6 months.

Age group in which studies will be performed:

Study 1: 1 month to 16 years.
Study 2: 1 month to 16 years
Study 3: 1 month to 16 years

For studies 1 to 3: Patients should be approximately uniformly distributed throughout this age range.

For study 1, sufficient number of patients (a minimum of 6 patients in each of the age ranges of 1 month to 2 years, 2 to 6 years, 6 to 12 and 12 to 16 years for a traditional pharmacokinetic study) should be enrolled to sufficiently characterize the pharmacokinetics of levetiracetam. If a population pharmacokinetics approach is utilized an appropriate number of patients should be selected (at least 50 patients).

Study Endpoints:
Study 1: For all age groups of pediatric patients (ages 1 month to 16 years), the pharmacokinetic study design could be either a traditional pharmacokinetic design (frequent sampling) or a population pharmacokinetic design using sparse sampling approach. If a sparse sampling approach is followed, approximately 3 – 4 blood samples per patient in 3 – 4 time brackets should be collected instead of blood samples at 3 – 4 fixed time points after levetiracetam dose. Pharmacokinetic measurements as appropriate and assessment of blood levels of concomitant anti-epileptic medications and levetiracetam to determine potential drug interactions where feasible. Pharmacokinetic parameters such as AUC, Cmax, oral clearance, terminal half life etc. should be reported.

Study 2: A single standard measure of seizure frequency to be chosen as the primary outcome measure, and standard measures of safety (clinical-including signs and symptoms-and laboratory). Safety measures should include monitoring of the cognitive/neuropsychiatric effects of levetiracetam.

Study 3: Appropriately frequent standard measures of safety (clinical-including signs and symptoms-and laboratory). Safety measures should include long term monitoring of the cognitive/neuropsychiatric effects of levetiracetam.

Drug Information:

Dosage Form: Oral tablet or other formulations as appropriate for younger patients. If a formulation other than the approved tablet is to be studied, its relative bioavailability needs to be assessed. The full study reports of the relative bioavailability study(ies) should be submitted to the Agency. If age-appropriate formulation(s) can not be developed, you will need to provide complete documentation of your attempts along with justification as to why this was not possible as part of your letter requesting an amendment to this Written Request.
Route of Administration: Oral
Regimen: To be determined by the development plan

Drug specific safety concerns: Cognitive/neuropsychiatric effects of levetiracetam.

Statistical information, including power of study and statistical assessments:
Study 1: Assessment of the effect of age on pharmacokinetic parameters and comparison to historic data in adults (who received the same concomitant medications). In addition, effects of other covariates such as body weight, body surface area, gender and concomitant medications on

levetiracetam pharmacokinetic parameters should be assessed. Evaluation of effect of levetiracetam on other antiepileptics should be done where feasible.

Study 2: Assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and descriptive analysis of safety data. A sufficient number of pediatric patients to be able to detect a statistically significant difference between treatment and control should be included.

Study 3: Descriptive analysis of the safety.

Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 5, 2006. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please 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. 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 studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. 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.

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.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Melina Fanari, R.Ph., Senior Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
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 Temple
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