NDA 21-035

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

Dear Ms. Fritz:

Please refer to your new drug application (NDA) dated February 1, 1999, received February 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Keppra (levetiracetam) 250 mg, 500 mg, and 750 mg Tablets.

We acknowledge receipt of your submissions dated:

March 1, 1999
April 20, 1999
April 26, 1999
April 27, 1999
May 12, 1999
May 13, 1999
June 1, 1999
June 2, 1999
June 11, 1999
June 14, 1999
June 15, 1999
July 6, 1999
July 13, 1999
July 16, 1999
July 26, 1999
July 29, 1999
August 16, 1999
August 27, 1999
August 30, 1999
August 31, 1999
September 24, 1999
September 30, 1999
October 5, 1999
November 15, 1999
November 17, 1999
November 22, 1999

The primary user fee goal date is December 1, 1999 and the secondary user fee goal date is February 1, 2000.

This new drug application provides for the use of Keppra as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

Biopharmaceutics

1. We remind you of your commitment, specified in your submission dated November 22, 1999, to adopt the following dissolution methodology and specification for all three strengths of levetiracetam tablets:

   Apparatus: USP Apparatus 2 (Paddle) rotated at 50 rpm
   Medium: 900 ml of water at 37.0±0.5°C
   Specification: Not less than […] % in 15 minutes

2. We encourage you to consider attempting PK/PD correlation in the course of the continued development of Keppra ™.

The final printed labeling (FPL) must be identical to the attached labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-035." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated November 17, 1999. These commitments are listed below.

1) Submit the detailed pathology peer review of the rat carcinogenicity study which is ongoing, and also the statistical evaluation of the peer reviewed pathology data. This review is due for completion in November, and we request that the report be submitted as soon as possible.

2) Conduct a two year mouse carcinogenicity study using appropriately high doses. A gavage study would be preferable, since the effect of palatability of the drug-diet admixture on decreased weight gain has not been carefully examined in mice. If you

choose to repeat a dietary study your three month dose ranging study must be designed not only to select doses for the definitive study but also to examine the effect of palatability on decreases in body weight.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you are currently developing protocols for our review which propose the use of Keppra in pediatric patients and therefore, we are deferring submission of your pediatric studies.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Melina Malandrucco, R.Ph., Regulatory Management Officer, (301) 594-5526.

Sincerely,

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