

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-505**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-505

UCB Pharma  
Attention: Patty Fritz  
Vice President, Regulatory Affairs  
1950 Lake Park Drive  
Smyrna, GA 30008

Dear Ms. Fritz:

Please refer to your new drug application (NDA) dated June 19, 2002, received June 20, 2002, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Keppra® (levetiracetam) Oral Solution 100mg/mL.

Your May 21, 2003 submission constituted a complete response to our April 17, 2003 action letter.

This new drug application provides for the use of Keppra® (levetiracetam) Oral Solution 100mg/mL as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

We completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the attached agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert) and submitted labeling (immediate container and carton labels submitted May 21, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the products misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission as "**FPL for approved NDA 21-505.**" Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we

hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising,  
and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Russell Katz

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*APPLICATION NUMBER:*

**21-505**

**APPROVABLE LETTERS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-505

UCB Pharma  
Attention: Patty Fritz  
Vice President, Regulatory Affairs  
1950 Lake Park Drive  
Smyrna, GA 30008

Dear Ms. Fritz:

Please refer to your new drug application (NDA) dated June 19, 2002, received June 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Keppra® (levetiracetam) Oral Solution 100mg/mL.

We acknowledge receipt of your submissions dated August 19, 2002, September 13, 2002, October 23, 2002, and April 9, 2003.

We have completed our review of this application, as amended, and have determined that it is approvable. Before the application may be approved, however, it will be necessary for you to address the following comments.

**Concern regarding Medication Dispensing Errors**

We are currently aware of several dispensing errors involving confusion between Keppra and Kaletra. Fortunately, these errors were noted before patients took the wrong medication. We anticipate that the likelihood for dispensing errors between Keppra and Kaletra will increase with the addition of the Keppra oral solution formulation. This increase is likely because orders such as "Keppra 5mL PO BID" and "Kaletra 5mL PO BID" are both within the usual dosing for each product. Therefore, we ask that you develop a plan to minimize this risk. As a starting point, we and our Division of Medication Errors and Technical Support (DMETS) propose several possible steps for your consideration, to include:

- Consider using a highlighted area or font style to emphasize the letters in the middle of the name that differ from Kaletra.
- Consider a "Dear Healthcare Practitioner" letter to alert practitioners to the potential for errors between Keppra and Kaletra.
- Alert patients to the potential confusion by directly addressing the problem in the Patient Package Insert (PPI).

**Labeling**

Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of Keppra® (levetiracetam) Oral Solution 100mg/mL. Please note that the PPI has been extensively revised and includes a "NOTE TO SPONSOR" that you should address.

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You must submit revised, draft labeling for Keppra® (levetiracetam) Oral Solution as part of your response to this letter. In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes and identify which version of Keppra® (levetiracetam) Oral Solution labeling was used as the base document.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

**Clinical**

In your submission, we noted a rather high incidence of urinalysis abnormalities among the cohort of patients treated for 6 months or longer (n=1036). Respectively, 24.5%, 25.7% and 8.3% of these patients experienced the presence of RBCs, WBCs, and protein in their urine. We ask you to investigate the cause of these abnormalities.

**Chemistry, Manufacturing, and Controls (CMC)**

We also remind you of your previous agreement to provide the following CMC information:

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\_\_\_\_\_

\_\_\_\_\_

Lastly, we have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

**Promotional Material**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Melina Griffis, R.Ph, Senior Regulatory Management Officer, at (301) 594-5526.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosure

21 Draft Labeling Page(s) Withheld

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Russell Katz  
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