# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-285**

# SUMMARY REVIEW

**MEMORANDUM**

DATE: September 11, 2008

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-285

SUBJECT: Action Memo for NDA 22-285, for the use of Keppra XR (levetiracetam) Extended Release Tablets in the Treatment of Partial Onset Seizures

NDA 22-285, for the use of Keppra XR (levetiracetam) Extended Release Tablets in the Treatment of Partial Onset Seizures, was submitted by UCB, Inc., on 11/13/07. Keppra is currently approved in an immediate release oral formulation as well as in an intravenous formulation, and they are both approved for the treatment of several different seizure types. The application contains a report of a single, randomized controlled trial in patients with partial seizures, as well as the requisite chemistry and clinical pharmacology data. The application has been reviewed by Dr. David Claffey, chemist, Dr. Gilbert Burckart, clinical pharmacologist, Dr. Jingyu Luan, statistician, Dr. Martin Rusinowitz, medical reviewer, and Dr. Billy Dunn, neurology team leader. The review team recommends that the application be approved.

As the clinical team has described, the results of the single multi-center, randomized, placebo controlled trial, together with the previous controlled trial data obtained with the approved immediate release formulation, clearly establish the effectiveness of this once a day extended release formulation as a treatment for patients with partial seizures.

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Although this single controlled trial examined only a 1000 mg/day dose of Keppra XR, the linear kinetics of this formulation at higher doses, together with the observation that similar daily doses of both the XR and immediate release formulations result in similar Cmax's and AUCs, allow us to be able to offer dosing recommendations up to 3000 mg/day in labeling, based on the same maximum daily dosing recommendation for the immediate release formulation.

There are no safety issues that are unique to this formulation.

Dr. Burckart has recommended that the sponsor commit to performing a Phase 4 study of the kinetics of Keppra XR in geriatric patients, given that essentially no geriatric patients were studied with this formulation. Although it is true that the XR formulation was given to only one geriatric patient, we know that the drug is primarily excreted by the kidney, and clearance in the elderly will largely be determined by the status of the patient's renal function. This is well-described in current labeling, and, in my view, can be handled similarly in labeling for this product.

Although immediate release (and intravenous) Keppra is approved for several different seizure types, the trial submitted with the application for Keppra XR studied only those patients with partial seizures, and, therefore, Keppra XR will be approved only as treatment for this seizure type.

In summary, the sponsor has demonstrated substantial evidence of effectiveness for Keppra XR as an adjunctive treatment for partial seizures in patients 16 years of age and older. The sponsor has committed to performing a Phase 4 study examining the kinetics of Keppra XR in patients between the ages of 12-16 years old, in order to meet their PREA obligation. We have agreed with the sponsor on product labeling. For these reasons, then, I will issue an Approval letter for this NDA, to include that agreed-upon label.

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/s/
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Russell Katz
9/12/2008 03:27:35 PM
MEDICAL OFFICER