

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-505

PHARMACOLOGY REVIEW

April 14, 2003

Review and Evaluation of Pharmacology and Toxicology
Original NDA Review

NDA: 21-505
Sponsor: UCB Pharma
Smyrna, GA
Received: June 21, 2002
Drug: Levetiracetam (Keppra) oral solution
Indication: Epilepsy

Recommendations:

This 505(b)(2) application for an oral solution of levetiracetam relies on preclinical toxicology data submitted to the original tablet NDA (21-035) for supporting safety information. This is considered adequate for the drug substance; and since no unusual excipients are used in the new formulation, there are no Pharm/Tox objections to approval. However, the following recommendations are made regarding the sponsor's proposed changes to the clinical pharmacology section of the label:

CLINICAL PHARMACOLOGY

Mechanism Of Action

The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam at concentrations up to 10 μ M did not demonstrate binding affinity for benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites or second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents. Levetiracetam does not appear to directly facilitate GABAergic neurotransmission, but has been shown

to oppose the activity of negative modulators of GABA- and glycine-gated currents in neuronal cell culture. A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam; however, the identification and function of this binding site is currently unknown.

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cc:
NDA (21-505)
Div File
HFD-120/BRosloff/MGriffis/EFisher

JS
J.E. Fisher, Ph.D.