Clinical Pharmacology and Biopharmaceutics Review
BPCA Summary Review

Product (Generic Name):	Levetiracetam
Product (Brand Name) ;	Keppra™
Dosage Forms:	Oral Tablets and Solution
Dosage Strengths:	250, 500, 750 mg tablets 100 mg/mL Oral Solution
NDA:	21-035 SE5-040 21-505 SE5-007
NDA Type:	Supplement for Adjunctive Therapy in the Treatment of Partial Onset Seizures in Children from 4 to less than 16 years old in response to FDA Pediatric Written Request Letter.
Submission Date:	12/20/04
Sponsor:	UCB Pharma
OND Division:	HFD-120

Executive Summary

Keppra oral tablets and solution have been approved as adjunctive therapy in the treatment of partial onset seizures in adults. This sNDA provides support to change the current Keppra prescription labeling to include indication for adjunctive therapy in the treatment of partial onset seizures in children from 4 to less than 16 years old. It is proposed that dosing in children should be initiated with a daily dose of 20 mg/kg/day given in 2 divided doses. The daily dose may be increased after 2 weeks of therapy, and at 2-week intervals thereafter, by increments of 20 mg/kg to a maximum recommended daily dose of 60 mg/kg. A deferral for children less than 4 years old was requested.

The pharmacokinetic studies performed included study N01010, in which children 4 to 12 years old with partial onset seizure were administered 20, 40 and 60 mg/kg/day of levetiracetam. This study was an open label, multi-center trial. The study consisted of a 2 week titration period, a 4-week withdrawal period and final two visits after the last intake of levetiracetam, for a total of up to 14 weeks of study participation. Subjects were to be on Carbamazepine (CBZ) or Valproic acid (VPA) for at least 2 weeks. During the titration period, the dose of levetiracetam was gradually increased by administering 20 mg/kg/day for the first 2 weeks, followed by 40 mg/kg/day for 2 weeks, and then followed by 60 mg/kg/day of levetiracetam for the last 2 weeks. In addition, plasma concentrations were monitored in the pivotal safety and efficacy studies consistent with sparse sampling population pharmacokinetic approach. Data from all studies were subjected to population pharmacokinetic meta-analysis. Exposure-Response analyses were performed using data from the current studies in pediatrics and previous studies in adults.

The overall conclusions from the pharmacokinetic study in children were:

1) Levetiracetam is rapidly absorbed in epileptic children greater than 4 years old. The mean Tmax is achieved in about 1 hour post-administration. T ½ was about 5 to 6 hours in children. The pharmacokinetics of levetiracetam was linear in children receiving doses from 20 to 60 mg/kg. The primary metabolite (ucb L057) was present in children.

2) Population pharmacokinetic analyses indicated that the only significant effect was weight on clearance (CL/F) and apparent volume (V/F) and anti-epileptic drug (AED) category on CL/F.

3) Apparent clearance in children increased with increase in body weight. Therefore, exposure (e.g. AUC) in children decreased with increase in body weight.

4) Enzyme inducing AEDs as a class (e.g. CBZ) were found to increase the clearance of levetiracetam by about 22%. But, dose adjustments are not recommended.

5) Levetiracetam does not affect the concentrations (trough) of Carbamazepine, Valproic acid, Lamotrigine and Topiramate when they are co-administered.

6) Exposure-Response analyses using data from the current studies in pediatrics and previous studies in adults indicated the percent change in seizures from baseline in pediatrics and adults seem to be different. This might be due to the differences in the background therapies between adults and pediatrics.

7) The concentration (trough) – percent change in seizures from baseline relationship is similar between adults and pediatrics.

Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, this sNDA is acceptable with the labeling recommendations suggested by the reviewer.

The sponsor's proposed dosing recommendations for the pediatric patients 4 years to less than 16 years old are acceptable provided the medical reviewer from a clinical perspective agrees that it is a safe and effective dose.

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/s/

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