Cross-Discipline Team Leader Review

Date	7/18/2014
From	Angela Yuxin Men., MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22285/S-18 Pediatric (PREA) Efficacy supplement
Applicant	UCB, Inc.
Date of Submission	10/4/2013
PDUFA Goal Date	8/4/2014
Proprietary/ Established (USAN) Name	Keppra XR (levetiracetam) extended release tablets
Dosage forms / Strength	500 mg and 750 mg tablets
Proposed Indication(s)	An antiepileptic drug indicated for adjunctive therapy in the treatment of partial onset seizure (POS)s in patients ≥12 years of age
Recommended:	Approval

1. Introduction

Levetiracetam (LEV), an antiepileptic drug, was first approved in 1999 as Keppra®, an immediate release (IR) tablet and oral solution, for a variety of seizures disorders. In 2008, an extended release tablet, Keppra XR®, was approved for adjunctive therapy in the treatment of partial onset seizures in patients ≥16 years of age with epilepsy. This approval was based upon pharmacokinetic data demonstrating similar bioavailability between the XR and the IR formulation and a single double-blinded placebo-controlled trial. At the time of approval, although the study enrolled patients down to the age of 12, it was considered that the number was too small and that additional PK data would be required before dosing recommendations could be made down to 12 years old. This submission contains pharmacokinetic (PK), tolerability and safety data of Keppra XR in patients with epilepsy, ages 12-16 years (Study N01340). This information will support Keppra XR to be approved for adjunctive therapy in the treatment of partial onset seizure (POS)s in patients ≥12 years of age.

The followings are the key primary reviewers for this NDA 22285/S-18:

- Clinical: Norman Hershkowitz, M.D., Ph.D.
- PMHS: Donna L. Snyder, M.D. (Team Leader: Hari Cheryl Sachs, M.D., Associate Director: Lynne Yao, M.D.)
- Clinical Pharmacology: Kristina Dimova, Ph.D. (Team Leader: Angela Yuxin Men, M.D., Ph.D.)
- CMC: Martha R. Heimann, Ph.D., CMC Lead (Branch Chief: Hasmukh Patel, Ph.D.)
- Project Manager: Laurie Kelley, PA-C

Reference ID: 3602274

2. Regulatory Background

In the approval letter dated September 12, 2008, the Agency waived the pediatric study requirement for ages 0 to 12 years because Keppra XR is not an appropriate formulation for that age group and Keppra is currently available in oral solution, which can be used for the pediatric population ages 0 to 12 years. However, the pediatric studies for ages 12 to 16 years was deferred because the drug is ready for approval for use in adults and the pediatric studies were not adequate in 2008.

The effectiveness of KEPPRA XR as adjunctive therapy (added to other antiepileptic drugs) was established in one multicenter, randomized, double-blind, placebo-controlled clinical study across 7 countries in patients who had refractory partial onset seizures with or without secondary generalization. Although this pivotal study enrolled patients down to the age of 12, the small number of patients exposed to drug below the age of 16 (only 7), together with the observation that the pharmacokinetics of this formulation seemed to be different between these younger patients and adults (see Dr. Burckart's review; however, only trough levels were available), made it difficult to offer adequate dosing recommendations for patients below the age of 16.

The following PMR was included in the NDA 22-285 Approval Letter (Sept 12, 2008):

> 1. Conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, in comparison to adult patients with epilepsy. The patient population can presently be receiving Keppra. The pharmacokinetic study would include at least 6 pharmacokinetic samples. The comparison group will be an equal number of adult patients studied under the same conditions.
>
> For each group (adolescents and adults), the mean Cmax and AUC must be estimated with a standard error of 20% or less, and this would be the basis for the original sample size calculation. As study data are evaluated, the sample size can be re-assessed if necessary for precise estimation of these pharmacokinetic parameters.

To fulfill this PMR, the sponsor submitted this NDA 22285/S-18 Pediatric (PREA) Efficacy supplement in the current submission. The Sponsor's original submission only planned to update Section 8 and did not ask for a new indication for 12 and older. In the 74 day letter we asked them to include that language.

> "The purpose of the requested studies included in the present submission was to label Keppra XR down to 12 years of age. Your submitted label does not include these recommended label changes. Please provide a revised label incorporating these recommended changes".

Per the request, the sponsor proposed to update the dosing regimen for 12 to 16 years of age for Keppra XR and proposed incorporation of new pediatric safety information based on data derived from a required pediatric postmarketing requirement pharmacokinetics and safety/tolerability study (N01340) in the Keppra XR labeling.

3. CMC

The supplement does not provide for any CMC changes or revisions to CMC related labeling information. The initial submission did not contain an updated environmental assessment or claim for categorical exclusion. At Agency request, the applicant submitted a claim for categorical exclusion in accordance with 21 CFR 25.31(a) on January 31, 2014. Approval of the supplement will not increase the use of the active moiety; the revised labeling does not provide for new indications or otherwise expand the current patient population. Thus, a categorical exclusion may be granted.

From a CMC perspective, approval of S-18 is recommended.

4. Nonclinical Pharmacology/Toxicology

There is no updated information as the information in these fields remaining unchanged from those in the approved NDA.

5. Biopharmaceutics

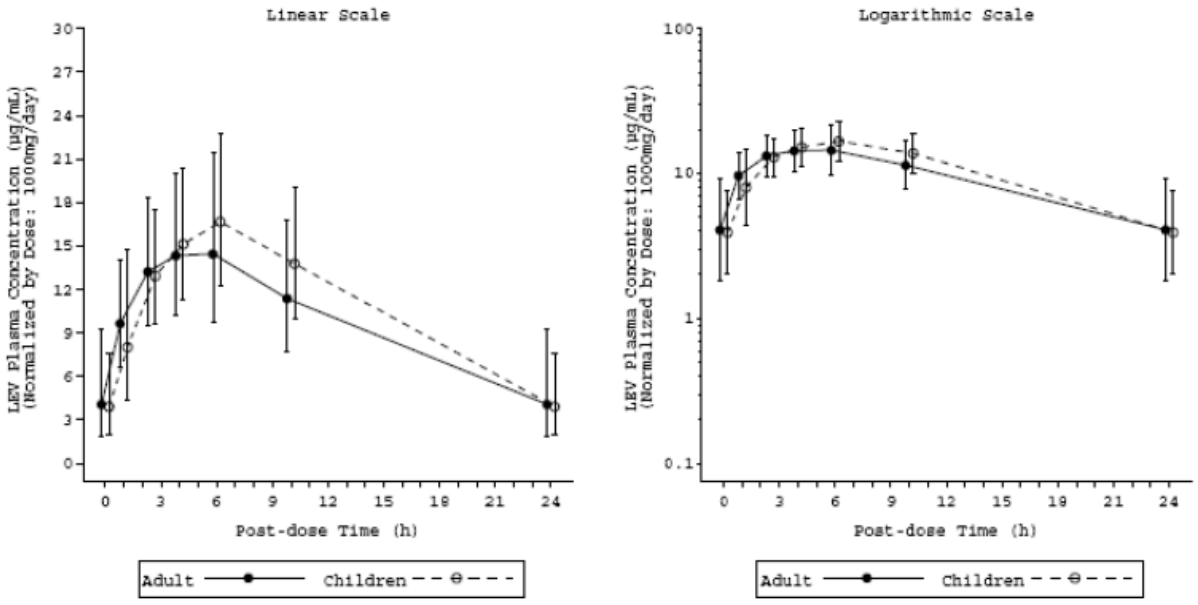
Levetiracetam is a BCS class 1 drug (high solubility, high permeability per Keppra labels). No new Biopharmaceutics information is available in this submission.

6. Clinical Pharmacology

The proposed labeling text changes are based on data from a pediatric post marketing requirement PK and safety/tolerability study (N01340), a multicenter, parallel-group, two-arm study conducted to compare the pharmacokinetics of Keppra XR in pediatric patients (aged 12-16 years old) with epilepsy and in adults (aged 18-55 years old) with epilepsy.

This study showed comparable levetiracetam pharmacokinetic exposures in children aged 12 years-16 years and adults aged 18 years-55 years receiving equivalent doses, i.e. 1000 mg to 3000 mg per day, as shown in Figure 1 and Table 1. The PK variability was low for both AUCτ and Cmax in children and adults, 5.7% and 10.8% for AUCτ and 4.8% and 7.8% for Cmax in children and adults, as expressed as %SE, respectively, when normalized to LEV 1mg/kg.

Figure 1 Mean observed levetiracetam plasma concentrations versus time profies for adults and children in study N01340



Source: Figure 9:1 on page 50 in sponsor's clinical study report N01340

Table 1 Comparison of levetiracetam PK exposures between children and adults in study N01340

Parameter	Normalization	Geometric mean (SE)	
		Children (N=12)	Adults (N=10)
C_{max} (µg/mL)	normalized to LEV 1000mg	17.3 (8.6)	14.9 (11.1)
AUC_τ (µg*h/mL)		265 (8.8)	236 (12.7)
C_{max} (µg/mL)	normalized to LEV 1mg/kg	1.27 (4.8)	1.24 (7.8)
AUC_τ (µg*h/mL)		19.4 (5.7)	19.6 (10.8)
CL/F (L/h)	Not applicable	3.78 (8.9)	4.23 (12.7)
		Median (range)	
t_{max} (h)		5.90 (2.50 to 6.07)	5.93 (2.45 to 6.05)

Source: Table 9:1 on page 52 in sponsor's clinical study report N01340

These results allow providing dosing recommendations in the 12-16 age groups, similar to those in adults: treatment should be initiated with a dose of 1000 mg once daily in pediatrics 12-16. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg. The proposed dosage regimens for Keppra XR in pediatric patients aged 12– 16 years are adequately supported by PK bridging between pediatrics and adults.

Drs. Kristina and Men reviewed the submission and the team concluded that NDA 22285/S018 is approval from an OCP perspective.

7. Efficacy

There is no clinical efficacy trial conducted.

8. Safety

Dr. Hershkowitz reviewed the safety information obtained from Study N01340.

No deaths, serious adverse events and discontinuation were observed. It is noted that two patients, one adult and one "child" experienced psychiatric event. The adult experienced mild irritability and a 16 year old experienced mild "abnormal behavior. This 16 year old patient had a history of "high dose behavioral problems" from Keppra in the past. Such Psychiatric events ranging from irritability to abnormal behavior to confusional state have been observed with the IR formulation in the pediatric population and are labeled in the Warnings Section. Thus, none of these require any labeling change.

The most commonly reported adverse events were somnolence, nausea and vomiting. All events were mild in nature. Keppra XR was well tolerated in both adult and pediatric patients. There are no obvious changes in mean chemistry or hematology values and no significant changes in vital signs observed.

The principal support of safety is based upon a number of priors including trial information derived from the IR formulation, previous adult XR clinical trial data, and data describing PK similarity between these two formulations. Safety data, derived from the small Study N01340 in this submission cannot be considered a primary source for the conclusion of safety. In summary, from a clinical perspective, there is no obvious new safety signals were observed. It is therefore recommended approval.

9. Advisory Committee Meeting

None

10. Pediatrics

There is one outstanding postmarketing study for Keppra XR® required under the Pediatric Research and Equity Act (PREA):
• An open-label, single-dose, two-arm study comparing the pharmacokinetics (PK) of Keppra XR in pediatric patients 12 to 16 years of age with epilepsy to an equal number of adults ages 18 to 55 years with epilepsy

This NDA 22285/S-18 Pediatric (PREA) Efficacy supplement is to update the dosing regimen for 12 to 16 years of age for Keppra XR and to incorporate new pediatric safety information based on data derived from a required pediatric PMR pharmacokinetics and safety/tolerability study (N01340) in the Keppra XR labeling.

The Division of Neurologic Products (DNP) consulted the Pediatric and Maternal Health

Staff (PMHS) to participate in meetings related to the review of the supplement, assist with preparation of paperwork for presentation of the pediatric assessment to the Pediatric Review Committee (PeRC), and to provide input on pediatric labeling.

PeRC meeting was held on May 21, 2014 for Keppra XR. The Division clarified that the PREA PMRs for Keppra XR were issued prior the PeRC policy to require development of long-acting formulations for younger patients. Therefore, this PREA requirement only required studies down to 12 years of age. The PeRC agreed that no further studies are necessary for the existing Keppra XR because there are approved alternatives for treating patients with POS down to 1 month of age (e.g., the IR and IV formulations).

11. Labeling

See labeling included in the Divisions action letter.

12. Recommended Regulatory Action

The Sponsor's submission provides adequate information for regulatory approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUXIN MEN
07/30/2014