Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 22285/S-18
Applicant Name	UCB, Inc.
Date of Submission	10/3/2013
PDUFA Goal Date	8/4/2014
Proprietary Name / **Established (USAN) Name**	Keppra XR (levetiracetam) extended release tablets
Dosage Forms / Strength	500 mg and 750 mg tablets
Proposed Indication(s)	Adjunctive therapy in the treatment of partial onset seizures in patients ≥12 years of age with epilepsy
Action	Approval

Material Reviewed/Consulted Office of New Drugs Action Package, including:	**Names of discipline reviewers**
Cross-Discipline Team Leader Review	Angela Yuxin Men., MD PhD
Medical Officer Review	Norman Hershkowitz, MD PhD
CMC Review	Martha R. Heimann, PhD
Clinical Pharmacology Review	Hristina Dimova, PhD and Xiaofeng Wang, PhD
Office of Prescription Drug Promotion (OPDP) Review	Melinda McLawhorn, PharmD, BCPS
Division of Medical Policy Programs (DMPP) Review	Sharon W. Williams, MSN, BSN, RN
Pediatric and Maternal Health Staff (PMHS) Review	Donna L. Snyder, MD

1. Introduction

The submission under review provides for the addition of new pediatric information to the KEPPRA XR labeling following completion of a pediatric pharmacokinetic, tolerability and safety study in response to a postmarketing requirement (PMR) under PREA.

2. Background

Levetiracetam was first approved in 1999, as an immediate release (IR) tablet and oral solution, for a variety of seizures disorders. In 2008, an extended release tablet, Keppra XR, was approved as adjunctive therapy for the treatment of partial onset seizures in patients ≥16 years of age. At the time of approval, because of insufficient data to support use in pediatric patients ages 12 to 16 years, additional data in that population were requested as a PMR.

3. CMC

The supplement does not provide for any CMC changes.

4. Nonclinical Pharmacology/Toxicology

The supplement does not provide for any new pharmacology/toxicology information.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. This submission contains the results of a pharmacokinetic parallel-group, two-arm study (N01340), comparing Keppra XR between pediatric patients (12-16 years of age) and adult patients (18-55 years of age) with epilepsy. Study N01340 shows comparable levetiracetam exposures between adults and adolescents receiving equivalent doses of KEPPRA XR, i.e., 1000 mg to 3000 mg per day. Therefore, dosing recommendations for the adult population are also applicable to pediatric patients ages 12– 16 years.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The supplement does not provide for any new efficacy information. As discussed by Dr. Hershkowitz, the primary basis for the determination of efficacy of KEPPRA XR in the adolescent population comes from the previous demonstration of efficacy of the levetiracetam immediate-release formulation in both pediatric and adult populations, the previous double-blind placebo-controlled trial demonstrating efficacy of the XR product in the adult population, the previous demonstration of similar bioavailability of the XR and immediate-release formulation in adults, and the pharmacokinetic bridging between the adult and the pediatric population (12-16 years of age) provided in this submission.

8. Safety

There was minimal new safety information submitted in this supplement, and no new safety signal identified. The primary information in support of the safety of Keppra XR in the adolescent population comes from the prior determination of safety in the adult population for Keppra XR, and in the adolescent population for immediate-release Keppra. As discussed above, adequate bridging to these populations was provided in this supplement.

9. Advisory Committee Meeting

No advisory meeting was necessary for this efficacy supplement.

10. Pediatrics

A PeRC meeting was held on May 21, 2014. PeRC agreed that the PREA requirement for Keppra XR has been fulfilled.

11. Other Relevant Regulatory Issues

There are no other unresolved regulatory issues.

12. Labeling

There are no unresolved labeling issues.

13. Decision/Action/Risk Benefit Assessment

As the sponsor has provided adequate pharmacokinetic bridging between the adult and the pediatric population (age 12-16 years), the indication of adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy can be extended down to age 12 years. Also, PREA requirements for KEPPRA XR are fulfilled.

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

/s/

ERIC P BASTINGS
08/01/2014