CLINICAL REVIEW

Application Type	NDA pediatric (PREA) efficacy supplement
Application Number(s)	22285 (018)
Priority or Standard	Standard
Submit Date(s)	10/3/13
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PDUFA Goal Date	8/4/14
Division / Office	DNP/ODE I
Reviewer Name(s)	Norman Hershkowitz
Review Completion Date	7/23/14
Established Name	Levetiracetam extended-release tablets
(Proposed) Trade Name	Keppra XR
Therapeutic Class	Anticonvulsant
Applicant	UCB
Formulation(s)	Extended-release tablets
Indication(s)	Partial Onset seizures,
Intended Population(s)	Patients ≥12 (Presently indicated in patients ≥ 16 years old)

Table of Contents

APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based upon clinical review, this may be approved. The final decision must await the outcome of the OCP review.

1.2 Risk Benefit Assessment

Acceptable, but will need to await the OCP review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Keppra (levetiracetam) is an anticonvulsant, the immediate release formulation of which is indicated for a variety of seizures disorders. In 2008, an extended release formulation of Keppra (Keppra XR) was approved for only partial onset seizures (POS). This approval was based upon pharmacokinetic data demonstrating similar bioavailability between the XR and the immediate release 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. At that time the drug was approved only for adults use.

To promote its use in a pediatric population the division and PERC decided to require the following PREA PMR (PMR #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."

The present application is a response to that PMR.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Appears adequate, but also refer to the OCP review.

3.2 Compliance with Good Clinical Practices

Appears adequate, but also refer to the OCP review.

3.3 Financial Disclosures

Financial Disclosure Template, filled out by this reviewer, is separately entered into DARRTS. Please see separate entry in DARRTS.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable (no change in drug manufacturing).

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable (no new data on the pharm/tox for the moiety- all relevant studies were previously performed for prior approval).

4.4 Clinical Pharmacology

See the OCP review.

5 Sources of Clinical Data

This review examines a single PK study, which is described below.

6 Review of Efficacy

No new efficacy data is submitted. Efficacy is based upon: 1) the previous demonstration of efficacy of the IR formulation in both pediatric and adult populations, which was based upon clinical trials, 2) the previous double-blind placebo-controlled trial demonstrating efficacy of the XR product in the adult population, 3) the previous demonstration of the similarities in bioavailability for this XR formulation to the IR population in adults 4) the present data that explores the similarities of bioavailability of the XR formulations in adult and pediatric populations ages 12 to 16 years of age (refer to OCP's review).

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The submitted study report was that of an open label, multicenter, parallel-group, two-arm study comparing the pharmacokinetics of Keppra XR in children (aged 12-16 years old) with epilepsy and in adults (aged 18-55 years old) with epilepsy. For PK conclusions the reader is referred to the OCP's review.

This study compared a total of 12 children, ages 12 to 16 years old, to 13 adults, ages 18 to 55 years old, with epilepsy. All subjects had either been under treatment with an IR formulation of Keppra (solution or tablet) of 1,000 to 3,000 mg/day (administered BID and on concomitant anticonvulsants) for at least 1 week prior to screening. Subjects entered a 7 day screening period, and an drug treatment evaluation period of 4 to 7 days during which time patients were switched to an equivalent daily dose of the XR formulation.

7.2 Adequacy of Safety Assessments

Prior studies included

The primary objective of the submitted trial (N01340) data was to determine the pharmacokinetic similarity of the XR formulation of Keppra in 12 to 16 years old patients and adult patients. For conclusion on bioavailability the reader is referred to the OCP review.

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, all of these are described in the efficacy section of this review. Safety data, derived from the small PK study included in this submission, is reviewed in this document (see below), but cannot be considered a primary source for the conclusion of safety.

The Sponsor intends to label this Keppra formulation at dosages similar to that used in the immediate release formulation (1,000 to 3,000 mg/day). Of the pediatric patient randomized, 10 were taking 1,000 mg/day, 1 was talking 1500 mg/day and 1 was taking 3,000 mg/day. Adults tended to take a higher dose, with most taking 3,000 mg/day.

What follows below is a discussion of the safety data from the above described PK study.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were observed.

7.3.2 Nonfatal Serious Adverse Events

No subject has an event categorized as a serious adverse event.

7.3.3 Dropouts and/or Discontinuations

No subject discontinued.

7.3.4 Significant Adverse Events

The Sponsor did not have a pre-established definition of events constituting “significant adverse events,” but they note two patients, one adult and one “child” experiences psychiatric event. 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, a 16 year old experienced mild “abnormal behavior.” This patient had a history of “high dose behavioral problems” from Keppra in the past. The adult experienced mild irritability. This does not require any labeling change.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Three children (25.0%) reported 7 treatment emergent adverse events and 3 adults (23.1%) reported 11 treatment emergent adverse events. All events were mild in nature. The below table, transcribed form the Sponsor's study report, lists all adverse events observed.

Table 3.1.2
Number (%) of Subjects with at Least One Treatment-Emergent Adverse Events Presented by Primary System Organ Class, Preferred Term, Age Group
ITT Population

Primary System Organ Class (MedDRA Version 13.0) Preferred Term	Children (N=12) n (%)	Adults (N=13) n (%)	Overall (N=25) n (%)
Nervous system disorders	1 (8.3)	2 (15.4)	3 (12.0)
Paraesthesia	0	1 (7.7)	1 (4.0)
Somnolence	1 (8.3)	1 (7.7)	2 (8.0)
Psychiatric disorders	1 (8.3)	0	1 (4.0)
Abnormal behaviour	1 (8.3)	0	1 (4.0)
Reproductive system and breast disorders	0	1 (7.7)	1 (4.0)
Dysmenorrhoea	0	1 (7.7)	1 (4.0)
Skin and subcutaneous tissue disorders	0	1 (7.7)	1 (4.0)
Hypoaesthesia facial	0	1 (7.7)	1 (4.0)
Pruritus	0	1 (7.7)	1 (4.0)
Rash	0	1 (7.7)	1 (4.0)

The adverse events, although largely consistent with what is known about the drug or the population studied, is not sufficient to draw any conclusions regarding the need for a change in the labeling.

7.4.2 Laboratory Findings

No obvious changes in mean chemistry or hematology values occurred. Only one potentially significant laboratory change was noted in a 30 year old female with a MCV of 106 (normal values 81-98). Such an isolated event is uninterpretable.

7.4.3 Vital Signs

No significant changes in blood pressure was observed, except for a transient elevation in the diastolic blood pressure in two patients, one in an adult and the other in a child, up to 92 and 96, respectively. A transient increase in blood pressure in such a small sample is hard to interpret in this limited population, particularly against the background of a lack of any such prior definitive signal. Of note, a more consistent increase in blood pressure was observed in patients 1 month to 4 years, and such information is contained in the label for the IR formulation. Because this formulation does not include labeling for this younger population and these results are unclear, I do not recommend changes to the XR label.

7.4.4 Electrocardiograms (ECGs)

While EKG changes were observed, none where considered significant, nor was there any consistent. No significant changes in mean blood pressure were obvious. It is difficult to conclude anything from such data, but prior analysis indicated no significant

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

None.

7.5 Other Safety Explorations

The database was of insufficient size to make any other explorations

7.6 Additional Safety Evaluations

No new data and not applicable.

7.7 Additional Submissions / Safety Issues

None.

7.7 Conclusions

The Sponsor concludes that XR was tolerated. I would note that the principal conclusions that could be drawn from such data are that no obvious new safety signals were observed. Additional safety conclusions need to be drawn for the findings of bioavailability conclusion of OCP.

8 Postmarket Experience

No new data submitted.

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/s/

NORMAN HERSHKOWITZ
07/23/2014