CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21035Orig1s102

Trade Name:	**KEPPRA, for oral use**
Generic or Proper Name:	(levetiracetam)
Sponsor:	**UCB INC**
Approval Date:	October 23, 2019
Indication:	KEPPRA is indicated for the treatment of partial-onset seizures in patients 1 month of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

NDA 21035/S-102
NDA 21505/S-42
NDA 21872/S-28
NDA 22285/S-28

SUPPLEMENT APPROVAL

UCB, Inc.
Attention: Queen Arukwe, MS, RAC
Regulatory Strategic Partnership Lead
8010 Arco Corporate Drive
Suite 100
Raleigh, NC 27617

Dear Ms. Arukwe:

Please refer to your supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for the following:

Application	Product Name	Submitted & Received on:
NDA 21035/S-102	Keppra (levetiracetam) tablets	December 21, 2018
NDA 21505/S-42	Keppra (levetiracetam) oral solution	
NDA 21872/S-28	Keppra (levetiracetam) injection	
These supplements provide for:		
The use of Keppra (levetiracetam) as monotherapy in treatment of partial-onset seizures (POS) in patients 1 month of age and older; and updated labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR).		

Application	Product Name	Submitted & Received on:
NDA 22285/S-28	Keppra XR (levetiracetam) tablets	December 21, 2018
These supplements provide for:		
The use of Keppra XR (levetiracetam) as monotherapy in treatment of POS in patients 12 years of age and older; updated labeling to comply with the PLLR.		

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information for Keppra (levetiracetam) tablets and oral solution.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

CONTINUED ASSESSMENT OF PREGNANCY OUTCOMES

We request that you report outcomes in infants exposed to Keppra during pregnancy from the North American Antiepileptic Drug Pregnancy Registry and from EURAP (International Registry of Antiepileptic Drugs and Pregnancy) on an annual basis. Although human data have thus far not indicated a risk, continued surveillance is warranted in light of the developmental toxicity observed in animal studies at doses similar to human therapeutic doses.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Heather Bullock, Regulatory Project Manager, via email at heather.bullock@fda.hhs.gov or via telephone at 301-796-1126.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
10/23/2019 07:20:12 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KEPPRA® safely and effectively. See full prescribing information for KEPPRA.

KEPPRA (levetiracetam) tablets, for oral use
KEPPRA (levetiracetam) oral solution
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	10/2019
Dosage and Administration (2 2, 2.6)	10/2019

----------INDICATIONS AND USAGE----------

KEPPRA is indicated for the treatment of partial-onset seizures in patients 1 month of age and older (1.1)

KEPPRA is indicated for adjunctive therapy for the treatment of:

- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy (1.2)
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Use the oral solution for pediatric patients with body weight ≤ 20 kg (2.1)
- For pediatric patients, use weight-based dosing for the oral solution with a calibrated measuring device (not a household teaspoon or tablespoon) (2.1)

Partial-Onset Seizures (monotherapy or adjunctive therapy)

- 1 Month to < 6 Months: 7 mg/kg twice daily; increase by 7 mg/kg twice daily every 2 weeks to recommended dose of 21 mg/kg twice daily (2.2)
- 6 Months to < 4 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 25 mg/kg twice daily (2.2)
- 4 Years to < 16 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily (2.2)
- Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to a recommended dose of 1500 mg twice daily (2.2)

Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older

- 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.3)

Primary Generalized Tonic-Clonic Seizures

- 6 Years to < 16 Years: 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily (2.4)
- Adults 16 Years and Older: 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.4)

Adult Patients with Impaired Renal Function

- Dose adjustment is recommended, based on the patient's estimated creatinine clearance (2.5, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

- 250 mg, 500 mg, 750 mg, and 1000 mg film-coated, scored tablets (3)
- 100 mg/mL solution (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to levetiracetam; angioedema and anaphylaxis have occurred (4, 5.4)

----------WARNINGS AND PRECAUTIONS----------

- Behavioral abnormalities including psychotic symptoms, suicidal ideation, irritability, and aggressive behavior have been observed; monitor patients for psychiatric signs and symptoms (5.1)
- Suicidal Behavior and Ideation: Monitor patients for new or worsening depression, suicidal thoughts/behavior, and/or unusual changes in mood or behavior (5.2)
- Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on KEPPRA (5.3)
- Serious Dermatological Reactions: Discontinue KEPPRA at the first sign of rash unless clearly not drug related. (5.5)
- Coordination Difficulties: Monitor for ataxia, abnormal gait, and incoordination. Advise patients to not drive or operate machinery until they have gained experience on KEPPRA. (5.6)
- Withdrawal Seizures: KEPPRA must be gradually withdrawn (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 5% more than placebo) include:

- Adult patients: somnolence, asthenia, infection and dizziness (6.1)
- Pediatric patients: fatigue, aggression, nasal congestion, decreased appetite, and irritability (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 866-822-0068 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Plasma levels of levetiracetam may be decreased and therefore need to be monitored closely during pregnancy. Based on animal data, may cause fetal harm (5.10, 8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Partial-Onset Seizures

KEPPRA is indicated for the treatment of partial-onset seizures in patients 1 month of age and older.

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

KEPPRA is indicated as adjunctive therapy for the treatment of myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy.

1.3 Primary Generalized Tonic-Clonic Seizures

KEPPRA is indicated as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

KEPPRA is given orally with or without food. The KEPPRA dosing regimen depends on the indication, age group, dosage form (tablets or oral solution), and renal function.

Prescribe the oral solution for pediatric patients with body weight ≤ 20 kg. Prescribe the oral solution or tablets for pediatric patients with body weight above 20 kg.

When using the oral solution in pediatric patients, dosing is weight-based (mg per kg) using a calibrated measuring device (not a household teaspoon or tablespoon).

KEPPRA tablets should be swallowed whole. KEPPRA tablets should not be chewed or crushed.

2.2 Dosing for Partial-Onset Seizures

The recommended dosing for monotherapy and adjunctive therapy is the same; as outlined below.

Adults 16 Years of Age and Older

Initiate treatment with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Pediatric Patients

1 Month to < 6 Months

Initiate treatment with a daily dose of 14 mg/kg in 2 divided doses (7 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 14 mg/kg to the recommended daily dose of 42 mg/kg (21 mg/kg twice daily). In the clinical trial, the mean daily dose was 35 mg/kg in this age group.

6 Months to < 4 Years:

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose in 2 weeks by an increment of 20 mg/kg to the recommended daily dose of 50 mg/kg (25 mg/kg twice

daily). If a patient cannot tolerate a daily dose of 50 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 47 mg/kg in this age group.

4 Years to < 16 Years

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg twice daily). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 44 mg/kg. The maximum daily dose was 3000 mg/day.

For KEPPRA tablet dosing in pediatric patients weighing 20 to 40 kg, initiate treatment with a daily dose of 500 mg given as twice daily dosing (250 mg twice daily). Increase the daily dose every 2 weeks by increments of 500 mg to a maximum recommended daily dose of 1500 mg (750 mg twice daily).

For KEPPRA tablet dosing in pediatric patients weighing more than 40 kg, initiate treatment with a daily dose of 1000 mg/day given as twice daily dosing (500 mg twice daily). Increase the daily dose every 2 weeks by increments of 1000 mg/day to a maximum recommended daily dose of 3000 mg (1500 mg twice daily).

KEPPRA Oral Solution Weight-Based Dosing Calculation For Pediatric Patients

The following calculation should be used to determine the appropriate daily dose of oral solution for pediatric patients:

$$\text{Total daily dose (mL/day)} = \frac{\text{Daily dose (mg/kg/day)} \times \text{patient weight (kg)}}{100 \text{ mg/mL}}$$

2.3 Dosing for Myoclonic Seizures in Patients 12 Years of Age and Older with Juvenile Myoclonic Epilepsy

Initiate treatment with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Increase the dosage by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been studied.

2.4 Dosing for Primary Generalized Tonic-Clonic Seizures

Adults 16 Years of Age and Older

Initiate treatment with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Increase dosage by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been adequately studied.

Pediatric Patients 6 to <16 Years of Age

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg twice daily). The effectiveness of doses lower than 60 mg/kg/day has not been adequately studied. Patients with body weight ≤20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution *[see Dosage and Administration (2.1)]*. Only whole tablets should be administered.

2.5 Dosage Adjustments in Adult Patients with Renal Impairment

KEPPRA dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults are shown in Table 1. In order to calculate the dose recommended for patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CLcr) in mL/min must first be calculated using the following formula:

$$CLcr = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Then CLcr is adjusted for body surface area (BSA) as follows:

$$CLcr\ (mL/min/1.73m^2) = \frac{CLcr\ (mL/min)}{BSA\ subject\ (m^2)} \times 1.73$$

Table 1: Dosing Adjustment Regimen for Adult Patients with Renal Impairment

Group	Creatinine Clearance (mL/min/1.73m^2)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 hours
Mild	50 ─ 80	500 to 1,000	Every 12 hours
Moderate	30 ─ 50	250 to 750	Every 12 hours
Severe	< 30	250 to 500	Every 12 hours
ESRD patients using dialysis	----	500 to 1,000[1]	Every 24 hours[1]

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

2.6 Discontinuation of KEPPRA

Avoid abrupt withdrawal from KEPPRA in order to reduce the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.7)]*.

3 DOSAGE FORMS AND STRENGTHS

KEPPRA Tablets

- 250 mg: blue, oblong-shaped, scored, film-coated, and debossed with "ucb 250" on one sid.
- 500 mg: yellow, oblong-shaped, scored, film-coated, and debossed with "ucb 500" on one side
- 750 mg: orange, oblong-shaped, scored, film-coated, and debossed with "ucb 750" on one side
- 1000 mg: white, oblong-shaped, scored, film-coated, and debossed with “ucb 1000” on one side

KEPPRA Oral Solution

- 100 mg/mL: a clear, colorless, grape-flavored liquid

4 CONTRAINDICATIONS

KEPPRA is contraindicated in patients with a hypersensitivity to levetiracetam. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Behavioral Abnormalities and Psychotic Symptoms

KEPPRA may cause behavioral abnormalities and psychotic symptoms. Patients treated with KEPPRA should be monitored for psychiatric signs and symptoms.

Behavioral abnormalities

In clinical studies, 13% of adult KEPPRA-treated patients and 38% of pediatric KEPPRA-treated patients (4 to 16 years of age) compared to 6% and 19% of adult and pediatric placebo-treated patients, experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder).

A randomized double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of KEPPRA as adjunctive therapy in pediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in KEPPRA-treated patients on aggressive behavior (one of eight behavior dimensions) as measured in a standardized and systematic way using a validated instrument, the Achenbach Child Behavior Checklist (CBCL/6-18).

In clinical studies in pediatric patients 1 month to < 4 years of age, irritability was reported in 12% of the KEPPRA-treated patients compared to 0% of placebo-treated patients.

In clinical studies, 1.7% of adult KEPPRA-treated patients discontinued treatment due to behavioral adverse reactions, compared to 0.2% of placebo-treated patients. The treatment dose was reduced in 0.8% of adult KEPPRA-treated patients and in 0.5% of placebo-treated patients. Overall, 11% of KEPPRA-treated pediatric patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6% of placebo-treated patients.

Psychotic symptoms

In clinical studies, 1% of KEPPRA-treated adult patients, 2% of KEPPRA-treated pediatric patients 4 to 16 years of age, and 17% of KEPPRA-treated pediatric patients 1 month to <4 years of age experienced psychotic symptoms, compared to 0.2%, 2%, and 5% in the corresponding age groups treated with placebo. In a controlled study that assessed the neurocognitive and behavioral effects of KEPPRA in pediatric patients 4 to 16 years of age, 1.6% of KEPPRA-treated patients experienced paranoia, compared to 0% of placebo-treated patients. In the same study, 3.1% of KEPPRA-treated patients experienced confusional state, compared to 0% of placebo-treated patients *[see Use in Specific Populations (8.4)]*.

In clinical studies, two (0.3%) KEPPRA-treated adult patients were hospitalized and their treatment was discontinued due to psychosis. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. There was no difference between drug and placebo-treated patients in the incidence of the pediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

5.2 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including KEPPRA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four

suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing KEPPRA or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.3 Somnolence and Fatigue

KEPPRA may cause somnolence and fatigue. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on KEPPRA to gauge whether it adversely affects their ability to drive or operate machinery.

Somnolence

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 15% of KEPPRA-treated patients reported somnolence, compared to 8% of placebo-treated patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of KEPPRA-treated patients, compared to 0% in the placebo group. About 3% of KEPPRA-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo-treated patients. In 1.4% of KEPPRA-treated patients and 0.9% of placebo-treated patients, the dose was reduced, while 0.3% of the KEPPRA-treated patients were hospitalized due to somnolence.

Asthenia

In controlled clinical studies of adult patients with epilepsy experiencing partial-onset seizures, 15% of KEPPRA-treated patients reported asthenia, compared to 9% of placebo-treated patients. Treatment was discontinued due to

asthenia in 0.8% of KEPPRA-treated patients as compared to 0.5% of placebo-treated patients. In 0.5% of KEPPRA-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to asthenia.

Somnolence and asthenia occurred most frequently within the first 4 weeks of treatment. In general, the incidences of somnolence and fatigue in the pediatric partial-onset seizure studies, and in pediatric and adult myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult partial-onset seizure studies.

5.4 Anaphylaxis and Angioedema

KEPPRA can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the postmarketing setting have included hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. In some reported cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, KEPPRA should be discontinued and the patient should seek immediate medical attention. KEPPRA should be discontinued permanently if a clear alternative etiology for the reaction cannot be established *[see Contraindications (4)]*.

5.5 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients treated with KEPPRA. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with KEPPRA has also been reported. KEPPRA should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

5.6 Coordination Difficulties

KEPPRA may cause coordination difficulties.

In controlled clinical studies in adult patients with partial-onset seizure studies, 3.4% of adult KEPPRA-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo-treated patients. A total of 0.4% of patients in controlled clinical studies discontinued KEPPRA treatment due to ataxia, compared to 0% of placebo-treated patients. In 0.7% of KEPPRA-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to coordination difficulties, while one of the KEPPRA-treated patients was hospitalized due to worsening of pre-existing ataxia. These events occurred most frequently within the first 4 weeks of treatment.

Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on KEPPRA to gauge whether it could adversely affect their ability to drive or operate machinery.

5.7 Withdrawal Seizures

As with most antiepileptic drugs, KEPPRA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

5.8 Hematologic Abnormalities

KEPPRA can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in white blood cell (WBC), neutrophil, and red blood cell (RBC) counts; decreases in hemoglobin and hematocrit; and increases in eosinophil counts. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported in the postmarketing setting. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.

Partial-Onset Seizures

Adults
Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 106/mm3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in KEPPRA-treated patients in controlled trials.

A total of 3.2% of KEPPRA-treated and 1.8% of placebo-treated patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC, and 2.4% of KEPPRA-treated and 1.4% of placebo-treated patients had at least one possibly significant (≤1.0 x 10^9/L) decreased neutrophil count. Of the KEPPRA-treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Pediatric Patients 4 Years to < 16 Years
Statistically significant decreases in WBC and neutrophil counts were seen in KEPPRA-treated patients as compared to placebo. The mean decreases from baseline in the KEPPRA-treated group were -0.4 × 10^9/L and -0.3 × 10^9/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in KEPPRA-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

In the controlled trial, more KEPPRA-treated patients had a possibly clinically significant abnormally low WBC value (3% of KEPPRA-treated patients versus 0% of placebo-treated patients), however, there was no apparent difference between treatment groups with respect to neutrophil count (5% of KEPPRA-treated patients versus 4.2% of placebo-treated patients). No patient was discontinued secondary to low WBC or neutrophil counts.

In the controlled cognitive and neuropsychological safety study, 5 patients (8.6%) in the KEPPRA-treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant (≥10% or ≥0.7X109/L).

5.9 Increase in Blood Pressure

In a randomized, placebo-controlled study in patients 1 month to <4 years of age, a significantly higher risk of increased diastolic blood pressure was observed in the KEPPRA-treated patients (17%), compared to the placebo-treated patients (2%). There was no overall difference in mean diastolic blood pressure between the treatment groups. This disparity between the KEPPRA and placebo treatment groups was not observed in the studies of older children or in adults.

Monitor patients 1 month to <4 years of age for increases in diastolic blood pressure.

5.10 Seizure Control During Pregnancy

Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during

pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more details in other sections of labeling:

- Behavior Abnormalities and Psychotic Symptoms *[see Warnings and Precautions (5.1)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.2)]*
- Somnolence and Fatigue *[see Warnings and Precautions (5.3)]*
- Anaphylaxis and Angioedema *[see Warnings and Precautions (5.4)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.5)]*
- Coordination Difficulties *[see Warnings and Precautions (5.6)]*
- Hematologic Abnormalities *[see Warnings and Precautions (5.8)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Partial-Onset Seizures

Adults
In controlled clinical studies in adults with partial-onset seizures *[see Clinical Studies (14.1)]*, the most common adverse reactions in patients receiving KEPPRA in combination with other AEDs, for events with rates greater than placebo, were somnolence, asthenia, infection, and dizziness. Of the most common adverse reactions in adults experiencing partial-onset seizures, asthenia, somnolence, and dizziness occurred predominantly during the first 4 weeks of treatment with KEPPRA.

Table 3 lists adverse reactions that occurred in at least 1% of adult epilepsy patients receiving KEPPRA in placebo-controlled studies and were numerically more common than in patients treated with placebo. In these studies, either KEPPRA or placebo was added to concurrent AED therapy.

Table 3: Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Studies in Adults Experiencing Partial-Onset Seizures

	KEPPRA (N=769) %	Placebo (N=439) %
Asthenia	15	9
Somnolence	15	8
Headache	14	13
Infection	13	8
Dizziness	9	4
Pain	7	6
Pharyngitis	6	4
Depression	4	2
Nervousness	4	2
Rhinitis	4	3
Anorexia	3	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Cough Increased	2	1
Diplopia	2	1
Emotional Lability	2	0
Hostility	2	1
Paresthesia	2	1
Sinusitis	2	1

In controlled adult clinical studies, 15% of patients receiving KEPPRA and 12% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. Table 4 lists the most common (>1%) adverse reactions that resulted in discontinuation or dose reduction and that occurred more frequently in KEPPRA-treated patients than in placebo-treated patients.

Table 4: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Placebo-Controlled Studies in Adult Patients Experiencing Partial-Onset Seizures

Adverse Reaction	KEPPRA (N=769) %	Placebo (N=439) %
Somnolence	4	2
Dizziness	1	0

Pediatric Patients 4 Years to <16 Years

The adverse reaction data presented below was obtained from a pooled analysis of two controlled pediatric clinical studies in pediatric patients 4 to 16 years of age with partial-onset seizures. The most common adverse reactions in pediatric patients receiving KEPPRA in combination with other AEDs, for events with rates greater than placebo, were fatigue, aggression, nasal congestion, decreased appetite, and irritability.

Table 5 lists adverse reactions from the pooled pediatric controlled studies (4 to 16 years of age) that occurred in at least 2% of pediatric KEPPRA-treated patients and were numerically more common than in pediatric patients treated with placebo. In these studies, either KEPPRA or placebo was added to concurrent AED therapy.

Table 5: Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Studies in Pediatric Patients Ages 4 to 16 Years Experiencing Partial-Onset Seizures

	KEPPRA (N=165) %	Placebo (N=131) %
Headache	19	15
Nasopharyngitis	15	12
Vomiting	15	12
Somnolence	13	9
Fatigue	11	5
Aggression	10	5
Cough	9	5
Nasal Congestion	9	2
Upper Abdominal Pain	9	8
Decreased Appetite	8	2
Abnormal Behavior	7	4
Dizziness	7	5
Irritability	7	1
Pharyngolaryngeal Pain	7	4
Diarrhea	6	2
Lethargy	6	5
Insomnia	5	3
Agitation	4	1
Anorexia	4	3
Head Injury	4	0
Altered Mood	3	1
Constipation	3	1
Contusion	3	1
Depression	3	1
Fall	3	2
Influenza	3	1
Affect Lability	2	1
Anxiety	2	1
Arthralgia	2	0
Confusional State	2	0
Conjunctivitis	2	0
Ear Pain	2	1
Gastroenteritis	2	0
Joint Sprain	2	1
Mood Swings	2	1
Neck Pain	2	1
Rhinitis	2	0
Sedation	2	1

In the controlled pooled pediatric clinical studies in patients 4-16 years of age, 7% of patients receiving KEPPRA and 9% receiving placebo discontinued as a result of an adverse reaction.

Pediatric Patients 1 Month to < 4 Years

In the 7-day, controlled pediatric clinical study in children 1 month to less than 4 years of age with partial-onset seizures, the most common adverse reactions in patients receiving KEPPRA in combination with other AEDs, for events with rates greater than placebo, were somnolence and irritability. Because of the shorter exposure period, incidences of adverse reactions are expected to be lower than in other pediatric studies in older patients. Therefore, other controlled pediatric data, presented above, should also be considered to apply to this age group.

Table 6 lists adverse reactions that occurred in at least 5% of pediatric epilepsy patients (ages 1 month to < 4 years) treated with KEPPRA in the placebo-controlled study and were numerically more common than in patients treated with placebo. In this study, either KEPPRA or placebo was added to concurrent AED therapy.

Table 6: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Pediatric Patients Ages 1 Month to < 4 Years Experiencing Partial-Onset Seizures

	KEPPRA (N=60) %	Placebo (N=56) %
Somnolence	13	2
Irritability	12	0

In the 7-day controlled pediatric clinical study in patients 1 month to < 4 years of age, 3% of patients receiving KEPPRA and 2% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. There was no adverse reaction that resulted in discontinuation for more than one patient.

Myoclonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from that seen in patients with partial-onset seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse reaction pattern for patients with JME is expected to be essentially the same as for patients with partial seizures.

In the controlled clinical study in patients 12 years of age and older with myoclonic seizures *[see Clinical Studies (14.2)],* the most common adverse reactions in patients receiving KEPPRA in combination with other AEDs, for events with rates greater than placebo, were somnolence, neck pain, and pharyngitis.

Table 7 lists adverse reactions that occurred in at least 5% of juvenile myoclonic epilepsy patients experiencing myoclonic seizures treated with KEPPRA and were numerically more common than in patients treated with placebo. In this study, either KEPPRA or placebo was added to concurrent AED therapy.

Table 7: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Patients 12 Years of Age and Older with Myoclonic Seizures

	KEPPRA (N=60) %	Placebo (N=60) %
Somnolence	12	2
Neck pain	8	2
Pharyngitis	7	0
Depression	5	2
Influenza	5	2
Vertigo	5	3

In the placebo-controlled study, 8% of patients receiving KEPPRA and 2% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. The adverse reactions that led to discontinuation or dose reduction and that occurred more frequently in KEPPRA-treated patients than in placebo-treated patients are presented in Table 8.

Table 8: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in a Placebo-Controlled Study in Patients with Juvenile Myoclonic Epilepsy

Adverse Reaction	KEPPRA (N=60) %	Placebo (N=60) %
Anxiety	3	2
Depressed mood	2	0
Depression	2	0
Diplopia	2	0
Hypersomnia	2	0
Insomnia	2	0
Irritability	2	0
Nervousness	2	0
Somnolence	2	0

Primary Generalized Tonic-Clonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from that seen in patients with partial-onset seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse reaction pattern for patients with primary generalized tonic-clonic (PGTC) seizures is expected to be essentially the same as for patients with partial seizures.

In the controlled clinical study that included patients 4 years of age and older with PGTC seizures *[see Clinical Studies (14.3)]*, the most common adverse reaction in patients receiving KEPPRA in combination with other AEDs, for events with rates greater than placebo, was nasopharyngitis.

Table 9 lists adverse reactions that occurred in at least 5% of idiopathic generalized epilepsy patients experiencing PGTC seizures treated with KEPPRA and were numerically more common than in patients treated with placebo. In this study, either KEPPRA or placebo was added to concurrent AED therapy.

Table 9: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Patients 4 Years of Age and Older with PGTC Seizures

	KEPPRA (N=79) %	Placebo (N=84) %
Nasopharyngitis	14	5
Fatigue	10	8
Diarrhea	8	7
Irritability	6	2
Mood swings	5	1

In the placebo-controlled study, 5% of patients receiving KEPPRA and 8% receiving placebo either discontinued or had a dose reduction during the treatment period as a result of an adverse reaction.

This study was too small to adequately characterize the adverse reactions that could be expected to result in discontinuation of treatment in this population. It is expected that the adverse reactions that would lead to discontinuation in this population would be similar to those resulting in discontinuation in other epilepsy trials (see tables 4 and 8).

In addition, the following adverse reactions were seen in other controlled adult studies of KEPPRA: balance disorder, disturbance in attention, eczema, memory impairment, myalgia, and blurred vision.

Comparison of Gender, Age and Race

The overall adverse reaction profile of KEPPRA was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse reactions by age and race.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KEPPRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported in patients receiving marketed KEPPRA worldwide. The listing is alphabetized: abnormal liver function test, acute kidney injury, anaphylaxis, angioedema, agranulocytosis, choreoathetosis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, muscular weakness, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, and weight loss. Alopecia has been reported with KEPPRA use; recovery was observed in majority of cases where KEPPRA was discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), including KEPPRA, during pregnancy. Encourage women who are taking KEPPRA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

Prolonged experience with KEPPRA in pregnant women has not identified a drug-associated risk of major birth defects or miscarriage, based on published literature, which includes data from pregnancy registries and reflects experience over two decades *[see Human Data]*. In animal studies, levetiracetam produced developmental toxicity (increased embryofetal and offspring mortality, increased incidences of fetal structural abnormalities, decreased embryofetal and offspring growth, neurobehavioral alterations in offspring) at doses similar to human therapeutic doses *[see Animal Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Levetiracetam blood levels may decrease during pregnancy *[see Warnings and Precautions (5.10)]*.

Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester. Dose adjustments may be necessary to maintain clinical response.

Data

Human Data

While available studies cannot definitively establish the absence of risk, data from the published literature and pregnancy registries have not established an association with levetiracetam use during pregnancy and major birth defects or miscarriage.

Animal Data

When levetiracetam (0, 400, 1200, or 3600 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, reduced fetal weights and increased incidence of fetal skeletal variations were observed at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on embryofetal developmental in rats (1200 mg/kg/day) is approximately 4 times the maximum recommended human dose (MRHD) of 3000 mg on a body surface area (mg/m^2) basis.

Oral administration of levetiracetam (0, 200, 600, or 1800 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and incidence of fetal skeletal variations at the mid and high dose and decreased fetal weights and increased incidence of fetal malformations at the high dose, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m^2 basis.

Oral administration of levetiracetam (0, 70, 350, or 1800 mg/kg/day) to female rats throughout pregnancy and lactation led to an increased incidence of fetal skeletal variations, reduced fetal body weight, and decreased growth in offspring at the mid and high doses and increased pup mortality and neurobehavioral alterations in offspring at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on pre- and postnatal development in rats (70 mg/kg/day) is less than the MRHD on a mg/m^2 basis.

Oral administration of levetiracetam to rats during the latter part of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Levetiracetam is excreted in human milk. There are no data on the effects of KEPPRA on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KEPPRA and any potential adverse effects on the breastfed infant from KEPPRA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of KEPPRA for the treatment of partial-onset seizures in patients 1 month to 16 years of age have been established *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*. The dosing recommendation in these pediatric patients varies according to age group and is weight-based *[see Dosage and Administration (2.2)]*.

The safety and effectiveness of KEPPRA as adjunctive therapy for the treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy have been established *[see Clinical Studies (14.2)]*.

The safety and effectiveness of KEPPRA as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established *[see Clinical Studies (14.3)]*.

Safety and effectiveness for the treatment of partial-onset seizures in pediatric patients below the age of 1 month; adjunctive therapy for the treatment of myoclonic seizures in pediatric patients below the age of 12 years; and adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients below the age of 6 years have not been established.

A 3-month, randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of KEPPRA as adjunctive therapy in 98 (KEPPRA N=64, placebo N=34) pediatric patients, ages 4 to 16 years old, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter-R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no substantive differences were observed between the placebo and drug treated groups in the median change from baseline in this battery, the study was not adequate to assess formal statistical non-inferiority of the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/6-18), a standardized validated tool used to assess a child's competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL/6-18 indicated on average a worsening in KEPPRA-treated patients in aggressive behavior, one of the eight syndrome scores *[see Warnings and Precautions (5.1)]*.

Juvenile Animal Toxicity Data

Studies of levetiracetam in juvenile rats (dosed on postnatal days 4 through 52) and dogs (dosed from postnatal weeks 3 through 7) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m^2 basis) did not demonstrate adverse effects on postnatal development.

8.5 Geriatric Use

There were 347 subjects in clinical studies of KEPPRA that were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of KEPPRA in these patients.

Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance *[see Clinical Pharmacology (12.3)]*. Dose adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

10.1 Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest known dose of KEPPRA received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of

somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with KEPPRA overdoses in postmarketing use.

10.2 Management of Overdose

There is no specific antidote for overdose with KEPPRA. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with KEPPRA.

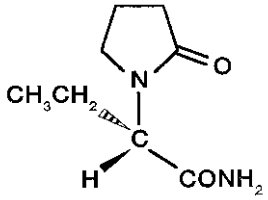
10.3 Hemodialysis

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

11 DESCRIPTION

KEPPRA is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow), 750 mg (orange), and 1000 mg (white) tablets and as a clear, colorless, grape-flavored liquid (100 mg/mL) for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C8H14N2O2 and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:



Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent.)

KEPPRA tablets contain the labeled amount of levetiracetam. Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyethylene glycol 3350, polyethylene glycol 6000, polyvinyl alcohol, talc, titanium dioxide, and additional agents listed below:

250 mg tablets: FD&C Blue #2/indigo carmine aluminum lake
500 mg tablets: iron oxide yellow
750 mg tablets: FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide red

KEPPRA oral solution contains 100 mg of levetiracetam per mL. Inactive ingredients: ammonium glycyrrhizinate, citric acid monohydrate, glycerin, maltitol solution, methylparaben, potassium acesulfame, propylparaben, purified water, sodium citrate dihydrate and natural and artificial flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown.

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

12.2 Pharmacodynamics

Effects on QTc Interval

The effect of KEPPRA on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of KEPPRA (1000 mg or 5000 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of significant QTc prolongation in this study.

12.3 Pharmacokinetics

The pharmacokinetics of levetiracetam are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures.

Absorption and Distribution

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite

ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment *[see Use in Specific Populations (8.6) and Dosage and Administration (2.5)]*.

Specific Populations

Elderly
Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61-88 years) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pediatric Patients
Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after single dose (20 mg/kg). The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults.

A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4-12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a T_{max} of about 1 hour and a $t_{1/2}$ of 5 hours across the three dosing levels. The pharmacokinetics of levetiracetam in children was linear between 20 to 60 mg/kg/day. The potential interaction of levetiracetam with other AEDs was also evaluated in these patients. Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate or lamotrigine. However, there was about a 22% increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED (e.g. carbamazepine).
Following single dose administration (20 mg/kg) of a 10% oral solution to children with epilepsy (1 month to < 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 mL/min/kg) than for adults (0.96 mL/min/kg).

Population pharmacokinetic analysis showed that body weight was significantly correlated to the clearance of levetiracetam in pediatric patients; clearance increased with an increase in body weight.

Pregnancy
Levetiracetam levels may decrease during pregnancy *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]*.

Gender
Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for body weight were comparable.

Race
Formal pharmacokinetic studies of the effects of race have not been conducted. Cross-study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Renal Impairment
The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr =

50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min) and 60% in the severe renal impairment group (CLcr <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr >80 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure *[see Dosage and Administration (2.5)]*.

Hepatic Impairment
In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

Drug Interactions
In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Phenytoin
KEPPRA (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate
KEPPRA (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

Other Antiepileptic Drugs
Potential drug interactions between KEPPRA and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Effect of AEDs in Pediatric Patients
There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

Oral Contraceptives
KEPPRA (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that

impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin
KEPPRA (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin
KEPPRA (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid
Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of KEPPRA on probenecid was not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300, and 1800 mg/kg/day. Plasma exposure (AUC) at the highest dose was approximately 6 times that in humans at the maximum recommended daily human dose (MRHD) of 3000 mg. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a body surface area (mg/m^2) basis.
Mutagenesis
Levetiracetam was negative in in vitro (Ames, chromosomal aberration in mammalian cells) and in vivo (mouse micronucleus) assays. The major human metabolite of levetiracetam (ucb L057) was negative in in vitro (Ames, mouse lymphoma) assays.

Impairment of Fertility
No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1800 mg/kg/day, which were associated with plasma exposures (AUC) up to approximately 6 times that in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Partial-Onset Seizures

Effectiveness in Partial-Onset Seizures in Adults
The effectiveness of KEPPRA for the treatment of partial-onset seizures in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial-onset seizures with or without secondary generalization. The tablet formulation was used in all these studies. In

these studies, 904 patients were randomized to placebo, 1000 mg, 2000 mg, or 3000 mg/day. Patients enrolled in Study 1 or Study 2 had refractory partial-onset seizures for at least two years and had taken two or more classical AEDs. Patients enrolled in Study 3 had refractory partial-onset seizures for at least 1 year and had taken one classical AED. At the time of the study, patients were taking a stable dose regimen of at least one and could take a maximum of two AEDs. During the baseline period, patients had to have experienced at least two partial- onset seizures during each 4-week period.

Study 1

Study 1 was a double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States comparing KEPPRA 1000 mg/day (N=97), KEPPRA 3000 mg/day (N=101), and placebo (N=95) given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, patients were randomized to one of the three treatment groups described above. The 18-week treatment period consisted of a 6-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial-onset seizure frequency). The results of the analysis of Study 1 are displayed in Table 10.

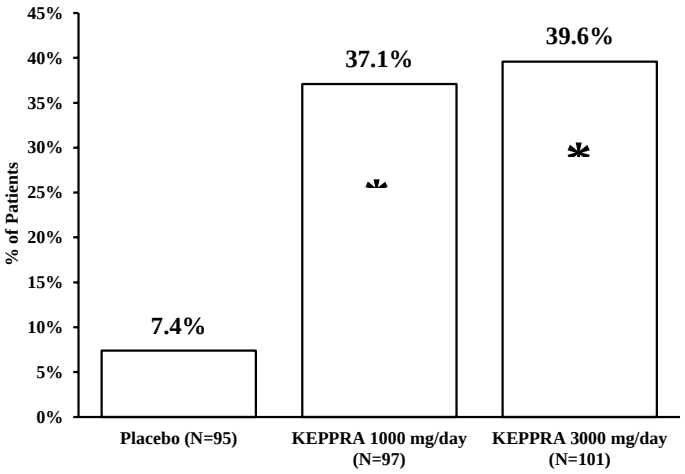
Table 10: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 1

	Placebo (N=95)	KEPPRA 1000 mg/day (N=97)	KEPPRA 3000 mg/day (N=101)
Percent reduction in partial seizure frequency over placebo	–	26.1%*	30.1%*

*statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in partial-onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the three treatment groups (x-axis) is presented in Figure 1.

Figure 1: Responder Rate (≥50% Reduction from Baseline) in Study 1



*statistically significant versus placebo

Study 2

Study 2 was a double-blind, placebo-controlled, crossover study conducted at 62 centers in Europe comparing KEPPRA 1000 mg/day (N=106), KEPPRA 2000 mg/day (N=105), and placebo (N=111) given in equally divided doses twice daily.

The first period of the study (Period A) was designed to be analyzed as a parallel-group study. After a prospective baseline period of up to 12 weeks, patients were randomized to one of the three treatment groups described above. The 16-week treatment period consisted of the 4-week titration period followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial-onset seizure frequency). The results of the analysis of Period A are displayed in Table 11.

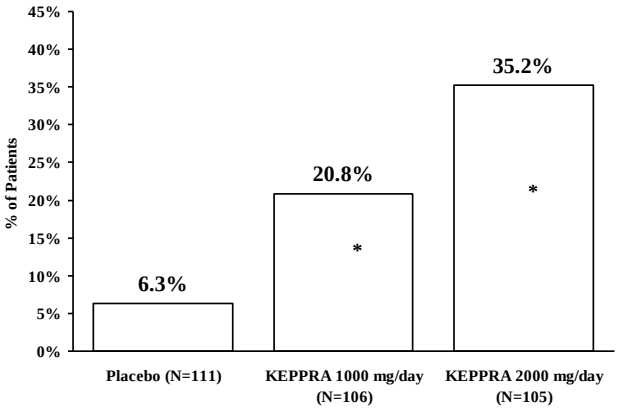
Table 11: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 2: Period A

	Placebo (N=111)	KEPPRA 1000 mg/day (N=106)	KEPPRA 2000 mg/day (N=105)
Percent reduction in partial seizure frequency over placebo	–	17.1%*	21.4%*

*statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in partial-onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the three treatment groups (x-axis) is presented in Figure 2.

Figure 2: Responder Rate (≥50% Reduction from Baseline) in Study 2: Period A



*statistically significant versus placebo

The comparison of KEPPRA 2000 mg/day to KEPPRA 1000 mg/day for responder rate was statistically significant (P=0.02). Analysis of the trial as a cross-over yielded similar results.

Study 3

Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing KEPPRA 3000 mg/day (N=180) and placebo (N=104) in patients with refractory partial-onset seizures, with or without secondary generalization, receiving only one concomitant AED. Study drug was given in two divided doses.

After a prospective baseline period of 12 weeks, patients were randomized to one of two treatment groups described above. The 16-week treatment period consisted of a 4-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED doses were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly seizure frequency relative to placebo over the entire randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial-onset seizure frequency). Table 12 displays the results of the analysis of Study 3.

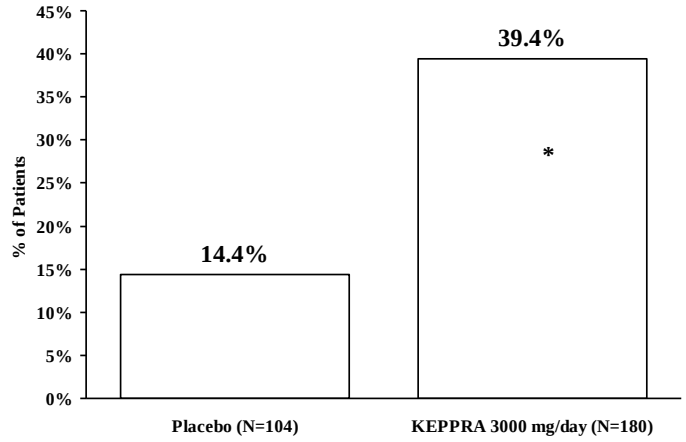
Table 12: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 3

	Placebo (N=104)	KEPPRA 3000 mg/day (N=180)
Percent reduction in partial seizure frequency over placebo	–	23.0%*

*statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in partial-onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in Figure 3.

Figure 3: Responder Rate (≥50% Reduction from Baseline) in Study 3



*statistically significant versus placebo

Effectiveness in Partial-Onset Seizures in Pediatric Patients 4 to 16 Years of Age

The effectiveness of KEPPRA for the treatment of partial-onset seizures in pediatric patients was established in one multicenter, randomized double-blind, placebo-controlled study (Study 4), conducted at 60 sites in North America, in pediatric patients 4 to 16 years of age with partial seizures uncontrolled by standard antiepileptic drugs (AEDs). Eligible patients on a stable dose of 1-2 AEDs, who still experienced at least 4 partial- onset seizures during the 4 weeks prior to screening, as well as at least 4 partial-onset seizures in each of the two 4-week baseline periods, were randomized to receive either KEPPRA or placebo. The enrolled population included 198 patients (KEPPRA N=101, placebo N=97) with refractory partial-onset seizures, whether or not secondarily generalized. The study consisted of an 8-week baseline period and 4-week titration period followed by a 10-week evaluation period. Dosing was initiated at a dose of 20 mg/kg/day in two divided doses. During the treatment period, KEPPRA doses were adjusted in 20 mg/kg/day increments, at 2-week intervals to the target dose of 60 mg/kg/day. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative

to placebo over the entire 14-week randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥ 50% reduction from baseline in partial-onset seizure frequency per week). Table 13 displays the results of this study.

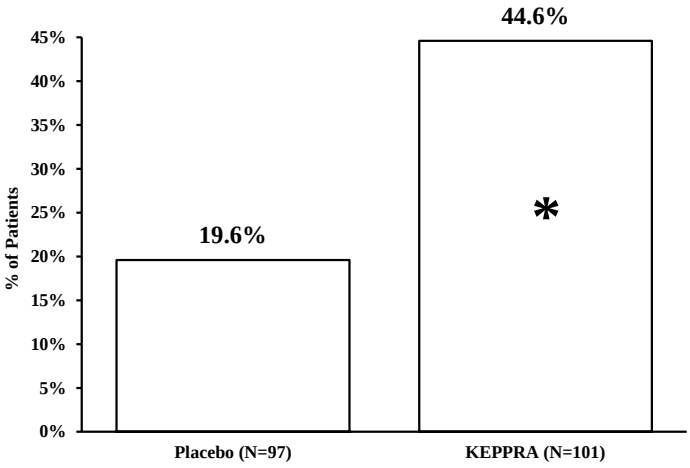
Table 13: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 4

	Placebo (N=97)	KEPPRA (N=101)
Percent reduction in partial seizure frequency over placebo	-	26.8%*

*statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥ 50% reduction in weekly seizure rates from baseline in partial-onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in Figure 4.

Figure 4: Responder Rate (≥ 50% Reduction from Baseline) in Study 4



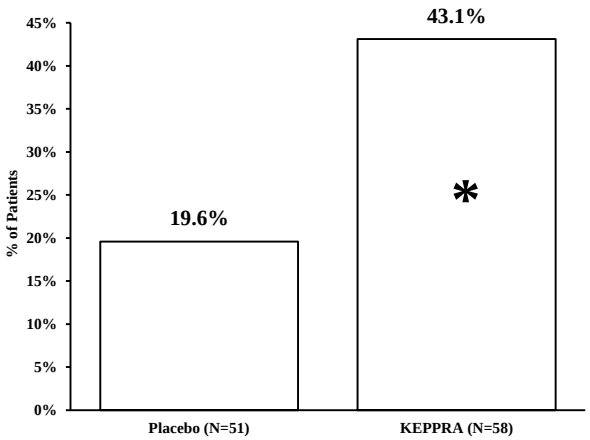
*statistically significant versus placebo

Effectiveness in Partial-Onset Seizures in Pediatric Patients 1 Month to <4 Years of Age

The effectiveness of KEPPRA for the treatment of partial-onset seizures in pediatric patients was established in one multicenter, randomized double-blind, placebo-controlled study (Study 5), conducted at 62 sites in North America, South America, and Europe in pediatric patients 1 month to less than 4 years of age with partial seizures, uncontrolled by standard epileptic drugs (AEDs). Eligible patients on a stable dose of 1-2 AEDs, who experienced at least 2 partial -onset seizures during the 48-hour baseline video EEG were randomized to receive either KEPPRA or placebo. The enrolled population included 116 patients (KEPPRA N=60, placebo N=56) with refractory partial-onset seizures, whether or not secondarily generalized. Randomization was stratified by age range as follows: 1 month to less than 6 months of age (N=4 treated with KEPPRA), 6 months to less than 1 year of age (N=8 treated with KEPPRA), 1 year to less than 2 years of age (N=20 treated with KEPPRA), and 2 years to less than 4 years of age (N=28 treated with KEPPRA). The study consisted of a 5-day evaluation period which included a 1-day titration period followed by a 4-day maintenance period. KEPPRA dosing was determined by age and weight as follows: children 1 month to less than 6 months old were randomized to a target dose of 40 mg/kg/day, and children 6 months to less than 4 years old were randomized to a target dose of 50 mg/kg/day. The primary measure of effectiveness was the responder rate (percent of patients with ≥ 50% reduction from baseline in average daily partial-onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG performed during

the last two days of the 4-day maintenance period. A total of 109 patients were included in the efficacy analysis. A statistically significant difference between KEPPRA and placebo was observed (see Figure 5). The treatment effect associated with KEPPRA was consistent across age groups.

Figure 5: Responder Rate for All Patients Ages 1 Month to < 4 Years (≥ 50% Reduction from Baseline) in Study 5



*statistically significant versus placebo

14.2 Myoclonic Seizures in Patients With Juvenile Myoclonic Epilepsy

The effectiveness of KEPPRA as adjunctive therapy in patients 12 years of age and older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 6), conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 antiepileptic drug (AED) experiencing one or more myoclonic seizures per day for at least 8 days during the prospective 8-week baseline period were randomized to either KEPPRA or placebo (KEPPRA N=60, placebo N=60). Patients were titrated over 4 weeks to a target dose of 3000 mg/day and treated at a stable dose of 3000 mg/day over 12 weeks (evaluation period). Study drug was given in 2 divided doses.

The primary measure of effectiveness was the proportion of patients with at least 50% reduction in the number of days per week with one or more myoclonic seizures during the treatment period (titration + evaluation periods) as compared to baseline. Of the 120 patients enrolled, 113 had a diagnosis of confirmed or suspected JME. Table 14 displays the results for the 113 patients with JME in this study.

Table 14: Responder Rate (≥50% Reduction from Baseline) in Myoclonic Seizure Days per Week for Patients with JME in Study 6

	Placebo (N=59)	KEPPRA (N=54)
Percentage of responders	23.7%	60.4%*

*statistically significant versus placebo

14.3 Primary Generalized Tonic-Clonic Seizures

The effectiveness of KEPPRA as adjunctive therapy in patients 6 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic (PGTC) seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 7), conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 antiepileptic drugs (AEDs) experiencing at least 3 PGTC seizures during the 8-week

combined baseline period (at least one PGTC seizure during the 4 weeks prior to the prospective baseline period and at least one PGTC seizure during the 4-week prospective baseline period) were randomized to either KEPPRA or placebo. The 8-week combined baseline period is referred to as "baseline" in the remainder of this section. Patients were titrated over 4 weeks to a target dose of 3000 mg/day for adults or a pediatric target dose of 60 mg/kg/day and treated at a stable dose of 3000 mg/day (or 60 mg/kg/day for children) over 20 weeks (evaluation period). Study drug was given in 2 equally divided doses per day. The primary measure of effectiveness was the percent reduction from baseline in weekly PGTC seizure frequency for KEPPRA and placebo treatment groups over the treatment period (titration + evaluation periods). The population included 164 patients (KEPPRA N=80, placebo N=84) with idiopathic generalized epilepsy (predominately juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening) experiencing primary generalized tonic-clonic seizures. Each of these syndromes of idiopathic generalized epilepsy was well represented in this patient population.

There was a statistically significant decrease from baseline in PGTC frequency in the KEPPRA-treated patients compared to the placebo-treated patients.

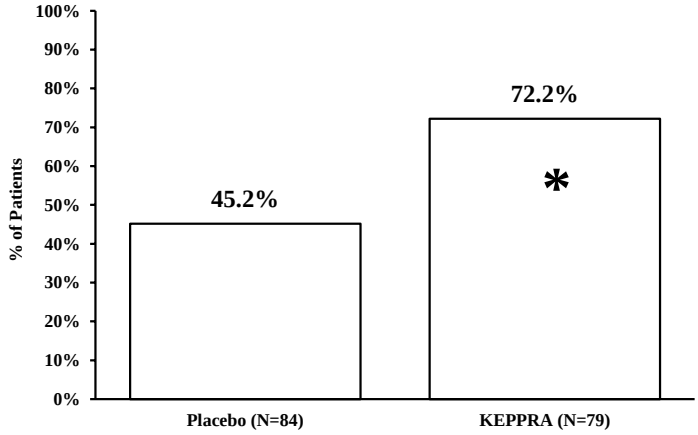
Table 15: Median Percent Reduction from Baseline in PGTC Seizure Frequency per Week in Study 7

	Placebo (N=84)	KEPPRA (N=78)
Percent reduction in PGTC seizure frequency	44.6%	77.6%*

*statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from baseline in PGTC seizure frequency over the entire randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in Figure 6.

Figure 6: Responder Rate (≥50% Reduction from Baseline) in PGTC Seizure Frequency per Week in Study 7



*statistically significant versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

KEPPRA Tablets

- 250 mg: blue, oblong-shaped, scored, film-coated tablets debossed with "ucb 250" on one side. They are supplied in white HDPE bottles containing 120 tablets (NDC 50474-594-40).
- 500 mg: yellow, oblong-shaped, scored, film-coated tablets debossed with "ucb 500" on one side. They are supplied in white HDPE bottles containing 120 tablets (NDC 50474-595-40).

- 750 mg: orange, oblong-shaped, scored, film-coated tablets debossed with "ucb 750" on one side. They are supplied in white HDPE bottles containing 120 tablets (NDC 50474-596-40).

- 1000 mg: white, oblong-shaped, scored, film-coated tablets debossed with “ucb 1000” on one side. They are supplied in white HDPE bottles containing 60 tablets (NDC 50474-597-66).

KEPPRA Oral Solution

- 100 mg/mL: a clear, colorless, grape-flavored liquid. It is supplied in 16 fl. oz. white HDPE bottles (NDC 50474-001-48).

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Psychiatric Reactions and Changes in Behavior

Advise patients that KEPPRA may cause changes in behavior (e.g. aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms *[see Warnings and Precautions (5.1)]*.

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and/or families that antiepileptic drugs (AEDs), including KEPPRA, may increase the risk of suicidal thoughts and behavior and advise patients to be alert for the emergence or worsening of symptoms of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their caregivers, and/or families to immediately report behaviors of concern to a healthcare provider *[see Warnings and Precautions (5.2)]*.

Effects on Driving or Operating Machinery

Inform patients that KEPPRA may cause dizziness and somnolence. Inform patients not to drive or operate machinery until they have gained sufficient experience on KEPPRA to gauge whether it adversely affects their ability to drive or operate machinery *[see Warnings and Precautions (5.3)]*.

Anaphylaxis and Angioedema

Advise patients to discontinue KEPPRA and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema *[see Warnings and Precautions (5.4)]*.

Dermatological Adverse Reactions

Advise patients that serious dermatological adverse reactions have occurred in patients treated with KEPPRA and instruct them to call their physician immediately if a rash develops *[see Warnings and Precautions (5.5)]*.

Withdrawal of KEPPRA

Advise patients and caregivers not to discontinue use of KEPPRA without consulting with their healthcare provider. KEPPRA should normally be gradually withdrawn to reduce the potential of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.7)]*.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during KEPPRA therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry if they become pregnant *[see Use in Specific Populations (8.1)]*.

KEPPRA Tablets and KEPPRA Oral Solution manufactured for
UCB, Inc.
Smyrna, GA 30080

MEDICATION GUIDE
KEPPRA® (KEPP-ruh*)* (levetiracetam)
tablets, for oral use, and oral solution

Read this Medication Guide before you start taking KEPPRA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about KEPPRA?
Like other antiepileptic drugs, KEPPRA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it.
Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Do not stop KEPPRA without first talking to a healthcare provider.

- Stopping KEPPRA suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus).
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms

What is KEPPRA?
KEPPRA is a prescription medicine taken by mouth that is used to treat partial-onset seizures in people 1 month of age and older.
KEPPRA is a prescription medicine taken by mouth that is used with other medicines to treat:

- myoclonic seizures in people 12 years of age and older with juvenile myoclonic epilepsy.
- primary generalized tonic-clonic seizures in people 6 years of age and older with certain types of generalized epilepsy.

It is not known if KEPPRA is safe or effective in children under:

- 1 month of age to treat partial-onset seizures
- 12 years of age to treat myoclonic seizures
- 6 years of age to treat primary generalized tonic-clonic seizures

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your bottle and the appearance of your medicine with the description of KEPPRA provided below. Tell your pharmacist immediately if you think you have been given the wrong medicine.

Who should not take KEPPRA?
Do not take KEPPRA if you are allergic to levetiracetam.

What should I tell my healthcare provider before starting KEPPRA?

Before taking KEPPRA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior.
- have kidney problems.
- are pregnant or planning to become pregnant. It is not known if KEPPRA will harm your unborn baby. You and your healthcare provider will have to decide if you should take KEPPRA while you are pregnant. If you become pregnant while taking KEPPRA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334 or go to http://www.aedpregnancyregistry.org. The purpose of this registry is to collect information about the safety of KEPPRA and other antiepileptic medicine during pregnancy.
- are breastfeeding or plan to breastfeed. KEPPRA can pass into your breast milk. It is not known if the KEPPRA that passes into your breast milk can harm your baby. Talk to your doctor about the best way to feed your baby while you receive KEPPRA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the counter medicines, vitamins, and herbal supplements. Do not start a new medicine without first talking with your healthcare provider.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take KEPPRA?

- Take KEPPRA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much KEPPRA to take and when to take it. KEPPRA is usually taken 2 times each day.
- Your healthcare provider may change your dose. **Do not** change your dose without talking to your healthcare provider.
- Take KEPPRA with or without food.
- Swallow the tablets whole. **Do not** chew or crush tablets. Ask your healthcare provider for KEPPRA oral solution if you cannot swallow tablets.
- If your healthcare provider has prescribed KEPPRA oral solution, be sure to ask your pharmacist for a medicine dropper or medicine cup to help you measure the correct amount of KEPPRA oral solution. Do not use a household teaspoon. Ask your pharmacist for instructions on how to use the measuring device the right way.
- If you take too much KEPPRA, call your local Poison Control Center or go to the nearest emergency room right away.

What should I avoid while taking KEPPRA?

Do not drive, operate machinery or do other dangerous activities until you know how KEPPRA affects you. KEPPRA may make you dizzy or sleepy.

What are the possible side effects of KEPPRA?

KEPPRA can cause serious side effects including:

See **"What is the most important information I should know about KEPPRA?"**

Call your healthcare provider right away if you have any of these symptoms:

- mood and behavior changes such as aggression, agitation, anger, anxiety, apathy, mood swings, depression, hostility, and irritability. A few people may get psychotic symptoms such as hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs) and unusual behavior.
- extreme sleepiness, tiredness, and weakness
- allergic reactions such as swelling of the face, lips, eyes, tongue, and throat, trouble swallowing or breathing, and hives.
- a skin rash. Serious skin rashes can happen after you start taking KEPPRA. There is no way to tell if a mild rash will become a serious reaction.
- problems with muscle coordination (problems walking and moving)

The most common side effects seen in people who take KEPPRA include:

- sleepiness
- infection
- weakness
- dizziness

The most common side effects seen in children who take KEPPRA include, in addition to those listed above include:

- tiredness
- decreased appetite
- irritability
- acting aggressive
- nasal congestion

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of KEPPRA. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KEPPRA?

- **Store KEPPRA** at room temperature, between 59°F to 86°F (15°C to 30°C) away from heat and light.
- **Keep KEPPRA and all medicines out of the reach of children.**

General information about the safe and effective use of KEPPRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KEPPRA for a condition for which it was not prescribed. Do not give KEPPRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider information about KEPPRA that is written for health professionals.

What are the ingredients in KEPPRA?

Keppra tablet active ingredient**:** levetiracetam
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyethylene glycol 3350, polyethylene glycol 6000, polyvinyl alcohol, talc, titanium dioxide, and additional agents listed below:

250 mg tablets: FD&C Blue #2/indigo carmine aluminum lake
500 mg tablets: iron oxide yellow
750 mg tablets: FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide red

Keppra oral solution active ingredient: levetiracetam
inactive ingredients: ammonium glycyrrhizinate, citric acid monohydrate, glycerin, maltitol solution, methylparaben, potassium acesulfame, propylparaben, purified water, sodium citrate dihydrate and natural and artificial flavor.

KEPPRA does not contain lactose or gluten. KEPPRA oral solution does contain carbohydrates. The liquid is dye-free.

Distributed by
UCB, Inc.
Smyrna, GA 30080

For more information, go to www.keppra.com or call 1-866-822-0068.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 10/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 16, 2019
From	Philip Sheridan, MD Nick Kozauer, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21035/S-102 NDA 21505/S-42 NDA 21872/S-28 NDA 22285/S-28
Applicant	UCB, Inc.
Date of Submission	12/21/2018
PDUFA Goal Date	10/21/2019
Proprietary Name / Non-Proprietary Name	Keppra (levetiracetam)
Dosage form(s) / Strength(s)	Tablet (250 mg, 500 mg, 750 mg, 1000 mg), extended release tablet (500 mg and 750 mg), oral solution (100 mg/mL), injection (500 mg/5 mL)
Applicant Proposed Indication(s)/Population(s)	For tablet, oral solution, and injection: treatment of partial-onset seizures in patients 1 month of age and older For extended release tablet: treatment of partial-onset seizures in patients 12 years of age and older
Recommendation on Regulatory Action	Approval

1. Background

Keppra (levetiracetam) is currently approved in the U.S. for adjunctive use in the treatment of partial onset seizures (POS) in patients 1 month of age and older, for adjunctive use in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients 6 years and older, and adjunctive use in the treatment of myoclonic seizures in patients 12 years and older. These approvals were based on several randomized, placebo-controlled efficacy and safety trials in adults and pediatric patients.

This prior approval supplemental application seeks to expand the use of Keppra as monotherapy for the treatment of POS in patients with epilepsy aged 1 month and older (12 years and older for the extended release tablet) based on extrapolation from adjunctive use of Keppra in this population. The applicant included a request for waiver of pediatric studies for Keppra XR formulations in this sNDA submission. This waiver is unnecessary since this submission did not trigger PREA.

The Division of Neurology Products issued a General Advice letter on September 13, 2016, indicating that it is acceptable to extrapolate the efficacy and safety of drugs approved as adjunctive therapy for the treatment of POS to their use as monotherapy for the treatment of POS. To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. A sponsor must provide pharmacokinetic information adequate to demonstrate such similarity, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

This application also provided for an update to the currently approved product labeling for these supplements to adopt the Pregnancy and Lactation Labeling Rule (PLLR) format.

2. Product Quality

No new data submitted or required.

3. Nonclinical Pharmacology/Toxicology

No new data with respect to the proposed monotherapy labeling have been submitted or required. The nonclinical reviewers provided input into the applicant's proposed PLLR labeling revisions.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by Dr. Michael Bewernitz and Dr. Dawei Li with Team Leaders Dr. Atul Bhattaram and Dr. Angela Men.

The applicant proposes a dosing regimen for monotherapy use in POS that is the same as the current approved dosing for adjunctive use for POS in the absence of concomitant enzyme-inducing antiepileptic drugs (EIAEDs). The applicant utilized population pharmacokinetic (PPK) modeling and simulation as well as population pharmacokinetic pharmacodynamic (PKPD) modeling and simulation to provide support for the proposed monotherapy indication and dosing.

Population Pharmacokinetic (PPK) Modeling

The OCP reviewers find that the PPK modeling supports the conclusion that the co-administration of AEDs does not have a clinically-relevant effect on Keppra PK in POS patients. Therefore, under the same dosing regimen, Keppra exposure in epilepsy patients with POS receiving Keppra monotherapy comparable to Keppra exposure in epilepsy patients with POS receiving Keppra adjunctive therapy.

Based on their review of the prior OCP analyses from the original NDA review and of the PPK modeling, the OCP reviewers determined that the proposed dosing regimen for monotherapy use of Keppra in POS should provide similar exposures as adjunctive use of Keppra for POS in the absence of EIAEDs (refer to Clinical Pharmacology review by Dr. Bewernitz and Dr. Li for additional details).

Pharmacokinetic Pharmacodynamic Modeling and Simulation

The applicant expanded on the population PK (PPK) model to create a pharmacokinetic pharmacodynamic (PKPD) model to assess how the PK-based interactions of the concomitant AEDs against LEV may manifest in terms of a change in monthly seizure rate. The applicant concludes that their PKPD simulations demonstrate no clinically-relevant efficacy difference between Keppra monotherapy versus Keppra adjunctive therapy across the range of approved adjunctive Keppra dose levels in adult patients and pediatric patients. The OCP reviewers state that, although these PKPD analyses may provide support for extrapolating efficacy in an adjunctive scenario to efficacy in a monotherapy scenario, they are not necessary to derive monotherapy dosing recommendations for this application since the pivotal support for this supplement is based on PK analyses.

OCP recommends that the supplement supporting the monotherapy use of Keppra in POS patients 1 month of age and older be approved. I agree with OCP's recommendation. The prescribing information (PI) for Keppra will be revised to remove the condition of use of "adjunctive therapy" from the Indications in Section 1.1 Partial-Onset Seizures. Dosing for monotherapy use and adjunctive use will be described in Section 2.1 Dosage for Partial-Onset Seizures. Section 8.4 Pediatric Use will include a statement of the safety and effectiveness of Keppra as monotherapy for POS in patients age 1 month to 16 years.

5. Clinical/Statistical- Efficacy

Evidence for the effectiveness of monotherapy use of Keppra in POS is based on the prior demonstration of efficacy when used as adjunctive therapy for the treatment of POS in patients age 1 month and older and the expectation of similar exposures with monotherapy use of Keppra to adjunctive use of Keppra. Refer to Section 4 for a more detailed discussion of this approach.

6. Safety

The clinical review by Dr. Natalie Getzoff focuses on the review of safety. The primary assessment of safety derives from the previously reviewed data from the placebo-controlled adjunctive trials of Keppra in adult and pediatric patients with POS. These data are summarized in current labeling.

New safety data were primarily generated from four active-controlled monotherapy studies, mainly in adult patients with epilepsy. One study enrolled adolescent patients 12 years of age and older. However, none of these four studies included a concurrent placebo control group for comparison.

- Study N01280: Historical-controlled, double-blind, 2-arm, multicenter study of Keppra in adolescent and adult patients with POS.
- Study N01061: Active-controlled, randomized, double-blind, parallel-group, non-inferiority, multicenter study of Keppra in adult patients with POS and PGTCS.
- Study N01364: Active-controlled, randomized, double-blind, parallel-group, non-inferiority, multicenter study of Keppra in adult patients with POS.
- Study N01375: Uncontrolled, 2-arm, randomized, open-label, comparison-to-threshold-value, multicenter study of Keppra in adult patients with POS.

A total of 1313 patients, 805 of whom received Keppra, were included in the safety datasets for Studies N01280, N01061, N01364, and N01375.

The safety analysis focused on treatment-emergent adverse events (TEAEs). The incidences of treatment emergent serious adverse effects (SAEs) in the Keppra groups ranged from 3-5% to 6% during the four monotherapy trials, similar to the incidence seen in the placebo-controlled trials. The most frequent SAEs in the monotherapy trials were seizure-related, as is commonly seen in AED trials.

The frequently reported TEAEs are consistent both with commonly observed illnesses in this population and TEAEs observed in the controlled trials of Keppra. Review of the TEAEs did not identify any new safety signals.

Overall, the safety findings from this submission are consistent with data from the NDA submissions for adjunctive use of Keppra in patients with POS. No new safety signals were identified in Studies N01280, N01061, N01364, and N01375

I agree with Dr. Getzoff's conclusion that the safety profile of Keppra as adjunctive therapy has been previously well-characterized in patients 1 month of age and older. The safety data in patients taking Keppra as monotherapy included in this sNDA submission did not raise any new clinical concerns, and the frequently seen adverse events in these studies were similar to those seen in the placebo-controlled trials. No new safety signals were identified.

7. Labeling

Please see final labeling appended to the approval letter, including the agreed-upon PLLR labeling revisions.

8. Recommendations

- Recommended Regulatory Action: Approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies: None required.
- Recommendation for other Postmarketing Requirements and Commitments: None.

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/s/

PHILIP H SHERIDAN
10/17/2019 09:21:19 PM

NICHOLAS A KOZAUER
10/23/2019 07:16:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Prior Approval Supplement
Application Number(s)	021035 (b) (4) 021505 (b) (4) 021872 (b) (4) 022285 (b) (4)
Priority or Standard	Standard
Submit Date(s)	21 DEC 2018
Received Date(s)	21 DEC 2018
PDUFA Goal Date	21 OCT 2019
Division/Office	DNP/ODE-1/OND
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	1 OCT 2019
Established/Proper Name	Levetiracetam
(Proposed) Trade Name	Keppra
Applicant	UCB Inc
Dosage Form(s)	Tablet (250 mg, 500 mg, 750 mg, 1000 mg), extended release tablet (500 mg and 750 mg), oral solution (100 mg/mL), injection (500 mg/5 mL)
Applicant Proposed Dosing Regimen(s)	For tablet, oral solution, and injection: • 1 Month to < 6 Months: 7 mg/kg twice daily; increase by 7 mg/kg twice daily every 2 weeks to recommended dose of 21 mg/kg twice daily • 6 Months to < 4 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 25 mg/kg twice daily • 4 Years to < 16 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily • Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to a recommended dose of 1500 mg twice daily For extended release tablet: • Initiate treatment with a dose of 1000 mg once daily. The once daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg/day once daily
Applicant Proposed Indication(s)/Population(s)	For tablet, oral solution, and injection: indicated for the treatment of partial-onset seizures in patients 1 month of age and older For extended release tablet: treatment of partial-onset seizures in patients 12 years of age and older
Recommendation on Regulatory Action	Approval

Recommended Indication(s)/Population(s) (if applicable)	Same as above

Table of Contents

1. Overview

1.1. Introduction

The applicant proposes to market levetiracetam (LEV, proprietary name Keppra) as monotherapy use in patients with partial onset seizures ages 1 month and older based on extrapolation. Keppra is an oral and intravenous drug-product currently approved for the adjunctive treatment of partial onset seizures (POS), myoclonic seizures, and primary tonic clonic seizures.

Proposed dosing is unchanged from the currently approved dosing for adjunctive treatment of POS, as seen in Table 1 below.

Table 1: Approved dosing for levetiracetam formulations

Age Range	Dosing for tablet, oral solution, and injection		Dosing for XR tablets (≥ 12 yrs only)	
	Initiation/ Titration	Maintenance	Initiation/ Titration	Maintenance
1 to < 6 mos	7 mg/kg BID / increase by 7 mg/kg BID every 2 weeks	21 mg/kg BID	N/A	N/A
6 mos to < 4 yrs	10 mg/kg BID / increase by 10 mg/kg BID every 2 weeks	25 mg/kg BID	N/A	N/A
4 to < 16 yrs	10 mg/kg BID / increase by 10 mg/kg BID every 2 weeks	30 mg/kg BID	N/A	N/A
≥16 years	500 mg BID / increase by 500 mg BID every 2 weeks	1500 mg BID	1000 mg QD / increase by 1000 mg every 2 weeks	3000 mg/day QD

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of a drug for monotherapy use in the treatment of partial onset seizures in patients 1 month of age and older is extrapolated from adult and pediatric efficacy as adjunctive use based on adequate dose-exposure data. In Studies N01280, N01061, N01375, and N01364, the applicant provided sufficient dose-exposure pharmacokinetic data to support extrapolation of efficacy of monotherapy use of levetiracetam in patients with partial onset seizures.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Keppra (levetiracetam) is approved in the U.S. for adjunctive use in the treatment of partial onset seizures (POS) in patients 1 month of age and older, for adjunctive use in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients 6 years and older, and adjunctive use in the treatment of myoclonic seizures in patients 12 years and older. These

approvals were based on several randomized, placebo-controlled efficacy and safety trials in adults and pediatric patients. POS are commonly seen in patients with a multitude of epilepsy disorders and, when refractory to treatment, are associated with significant adverse consequences, such as severe trauma, depression, anxiety, and sudden death.

FDA has determined that extrapolation of efficacy from adjunctive use to monotherapy use is appropriate for partial-onset seizures based on a review of several marketed antiepileptic drugs showing similar exposure-response relationships when used as monotherapy and adjunctive therapy in patients with POS. Keppra was initially approved for marketing in the US in 1999 for treatment of POS with subsequent approvals in younger pediatric patients following in 2006. The clinical trials supporting the approvals for Keppra as adjunctive therapy, along with PK data from four monotherapy studies, support evidence of effectiveness of monotherapy use in patients with POS.

The safety profile of levetiracetam is well-characterized in patients 1 month of age and older. The safety data in patients taking levetiracetam as monotherapy included in this supplemental NDA submission did not raise any new clinical concerns, and the frequently seen adverse events in these studies were similar to those seen in the placebo-controlled trials. No new safety signal was identified. Therefore, I recommend approval of levetiracetam for monotherapy use for treatment of POS in patients 1 month of age and older and approval of extended release levetiracetam for monotherapy use for treatment of POS in patients 1 month of age and older.

2. Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

Keppra was originally approved for adjunctive treatment of partial onset seizures in adult patients on November 11, 1999. This approval was based on results of three randomized, placebo-controlled efficacy trials. Keppra was subsequently approved for adjunctive treatment of POS in pediatric patients ≥ 4 years of age in 2005, based on a single, controlled efficacy trial. It was approved as adjunctive therapy in the treatment of myoclonic seizures in patients ≥ 12 years in 2006 and as adjunctive treatment of primary generalized tonic clonic seizures (PGTCS) in patients ≥ 6 years in 2007. In 2011, Keppra was approved as adjunctive therapy to treat POS in patients 1 month to 4 years of age. A single controlled clinical trial for each of these indications was the basis for these subsequent approvals. An extended release formulation (Keppra-XR) was approved for use in 2008 with approval in patients 12-17 years of age in 2014.

2.2. Summary of Presubmission/Submission Regulatory Activity

See below for timeline of key regulatory activity regarding the monotherapy use sNDA:

- General advice letter (9/13/2016) on the acceptability of extrapolation to POS

monotherapy in AEDs approved for adjunctive therapy in POS (see Section 3.4 below);

- Email response to Advice/Information Request (7/24/2018) stating that a waiver for submission of legacy datasets are unnecessary, the PK/PD data sets must be in a format that will allow the CDER reviewers to conduct their own analyses as part of the review process, and that there is no user fee for the planned supplement.
- The applicant included a request for waiver of pediatric studies for Keppra XR formulations in this sNDA submission. This waiver is unnecessary, as this submission did not trigger PREA.

2.3. Background Information Regarding Monotherapy Extrapolation

A General Advice Letter was sent to sponsors dated September 13, 2016, which stated that the Division of Neurology Products (DNP) had *"determined that it is acceptable to extrapolate efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS. This extrapolation applies to both adult and pediatric populations, provided that efficacy and safety as adjunctive therapy for the treatment of POS have been previously established in the respective age range."* This determination was based on FDA analysis of drugs approved for both adjunctive and monotherapy demonstrating that dosages and exposures of drugs when used as monotherapy are within the ranges of dosages and exposures for those drugs when used as adjunctive therapy for POS.

3. Summary of Clinical Pharmacology Evaluation

Please see The Office of Clinical Pharmacology (OCP) review for a full discussion of the pharmacokinetics data.

The OCP review concludes that *"[t]he findings from the* [Applicant's] *PPK modeling … support the conclusion that the co-administration of AEDs do not have a clinically-relevant effect on LEV PK in POS patients. Therefore, under the same dosing regimen, LEV exposure in epilepsy patients with POS receiving LEV monotherapy is likely to be comparable to LEV exposure in epilepsy patients with POS receiving LEV adjunctive therapy. As such, the* ***Applicant's proposal to use the same recommended dose in monotherapy as in adjunctive therapy is acceptable****."*

4. Sources of Clinical Data and Review Strategy

Four monotherapy studies of levetiracetam form the primary basis of this review and are summarized in Table 2 below.

Table 2: Clinical Studies in Patients Contributing PK and Safety Data

Study #	Study Design	Doses	No. enrolled	Study Population
N01280	Double-blind, parallel, randomized, 2-arm, historical-controlled	LEV XR Tablet QD; 1000 or 2000 mg/day.	1000 mg: 57 2000 mg: 171	Patients 12 to 70 yrs of age with refractory epilepsy (POS)
N01061	Active-controlled, randomized, double-blind, parallel-group, non-inferiority	LEV: 1000 to 3000 mg/day (divided BID) CBZ-CR: 400 to 1200 mg/day (divided BID).	LEV: 285 CBZ-CR: 291	Adults (≥ 16 yrs) with newly or recently diagnosed epilepsy (POS or PGTCS).
N01364	Open-label, randomized, active-controlled, non-inferiority	LEV: 1000 mg/day (divided BID) CBZ-IR (BID) 400mg/day	LEV: 218 CBZ: 215	Chinese patients (≥16 yrs) with newly or recently diagnosed with epilepsy, unprovoked POS
N01375	Uncontrolled, 2-arm, randomized, open-label	LEV Tablet: 1000 to 3000mg/day (divided BID).	1000-2000 mg: 61 3000 mg: 10	Japanese patients ≥16 yrs with newly or recently diagnosed with POS

5. Review of Relevant Individual Trials Used to Support Efficacy

As noted in Section 2.3 above, DNP and OCP conducted a lengthy review and determined that it is acceptable to extrapolate the safety and efficacy of drugs used in the adjunctive treatment of POS to their use as monotherapy for the same population. This determination was based on FDA analysis of drugs approved for both adjunctive and monotherapy demonstrating that dosages and exposures of drugs when used as monotherapy are within the ranges of dosages and exposures for those drugs when used as adjunctive therapy for POS.

As part of their development program, UCB conducted four studies of levetiracetam used as monotherapy in patients with epilepsy (primarily POS, some with PGTCS). The efficacy results of these will not be commented upon further, as efficacy is based upon extrapolation of adjunctive treatment.

6. Review of Safety

6.1. Safety Review Approach

The primary safety data were primarily generated from four controlled monotherapy studies, primarily in adult patients with epilepsy. One study enrolled adolescent patients 12 years of age and older. None of the studies included a concurrent placebo control group for comparison.

- Study N01280: Historical-controlled, double-blind, 2-arm, multicenter study of LEV in adolescent and adult patients with POS.
- Study N01061: Active-controlled, randomized, double-blind, parallel-group, non-inferiority, multicenter study of LEV in adult patients with POS and PGTCS.
- Study N01364: Active-controlled, randomized, double-blind, parallel-group, non-inferiority, multicenter study of LEV in adult patients with POS.
- Study N01375: Uncontrolled, 2-arm, randomized, open-label, comparison-to-threshold-value, multicenter study of LEV in adult patients with POS.

The safety analysis focused on treatment-emergent adverse events (TEAEs), SAEs, severe TEAEs, most common TEAEs, and TEAEs that led to discontinuation. because these are legacy studies completed years ago under different MedDRA categorizations, safety is analyzed separately for all four studies.,

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Reviewer's comment: There were no placebo-controlled data for review; therefore, any conclusions regarding the clinical meaningfulness of observed adverse effects are not definitive.

6.2. Description of Clinical Trials Used to Support Safety

6.2.1. Study N01280

Study N01280 was a double-blind, parallel, randomized, two-arm, historical-controlled study of the efficacy and safety of high and low dose levetiracetam as compared to a historical control exit rate. Patients ages 12 and older with refractory POS were randomized 3:1 to receive LEV 2000 mg or 1000 mg once daily. After an 8-week baseline period during which baseline seizure frequency was prospectively assessed, patients were randomized 3:1 to either 2000 mg or 1000 mg LEV, provided they met the randomization eligibility criteria. Titration for both arms was over 2 weeks with all patients receiving LEV 1000 mg the first week. Concomitant AEDs were tapered over a 6-week period. The monotherapy phase was 10 weeks, during which patients remained on their assigned dose of LEV-XR until study completion or occurrence of any of the four exit criteria. Down titration occurred over 2 weeks following the monotherapy period. Safety outcomes included adverse events, laboratory tests, physical exam, vital signs, and ECGs.

6.2.2. Study N01061

Study N01061 was a randomized, double-blind, parallel-group, active-controlled, non-inferiority trial of levetiracetam 1000-3000 mg/day as compared to controlled release carbamazepine 400-1200 mg/day. Patients 16 years and older with newly or recently unprovoked POS or PGTCS were randomized 1:1 to receive either LEV or CBZ. LEV 250 mg and CBZ CR 200 mg oral tablets were over-encapsulated to allow a double-blind design.

Initial titration was over 2 weeks to either LEV 1000 mg or CBZ 400 mg, followed by a one-week

stabilization period and a 26-week evaluation period and a maintenance period of 26 additional weeks. If a seizure occurred during the evaluation period, the dose was escalated over 2 weeks to the second target daily dose (LEV 2000 mg / CBZ 800 mg), followed by a 1-week stabilization period, a new evaluation period of 26 weeks and a maintenance period of 26 additional weeks. If a seizure occurred during the second evaluation period, the dose was titrated to LEV 3000 mg or CBZ 1200 mg, followed by a stabilization period, a new evaluation period and a new maintenance period. Safety outcomes included adverse events, laboratory tests, physical exam, vital signs, and ECGs.

6.2.3. Study N01364

Study N01364 was a randomized, double-blind, parallel-group, active-controlled non-inferiority study of efficacy and safety of levetiracetam 1000 mg/day as compared to immediate release carbamazepine 400 mg/day. Patients ages 16 and older with newly or recently unprovoked POS were randomized 1:1 to receive either LEV or CBZ.

Initial titration was over 2 weeks to either LEV 1000 mg or CBZ 400 mg, followed by a one-week stabilization period, 26-week evaluation period, and a maintenance period of 26 additional weeks. Safety outcomes included adverse events, laboratory tests, physical exam, vital signs, and ECGs.

6.2.4. Study N01375

Study N01375 was an uncontrolled, 2-dose, randomized, open-label study of efficacy and safety of LEV 1000-2000 mg or 3000 mg as monotherapy. Patients ages 16 and older with newly or recently diagnosed POS were randomized 6:1 to receive either LEV 1000-2000 mg or LEV 3000 mg per day.

Starting dose for all patients was 1000 mg/day. Patients in the 3000 mg group were titrated to 3000 mg/day over 4 weeks (1000 mg/day x 2 weeks, then 2000 mg/day x 2 weeks, then 3000 mg/day). In both groups, the evaluation period began after the stabilization period, and lasted 26 weeks. The evaluation period was followed by a maintenance period of 26 additional weeks.

Safety outcomes included adverse events, laboratory tests, physical exam, vital signs, and ECGs.

6.3. Review of the Safety Database

6.3.1. Overall Exposure

A total of 1313 patients, 805 of whom received LEV, were included in the safety datasets for Studies N01280, N01061, N01364, and N01375.

In Study N01280, 228 patients were randomized and received at least one dose of study drug. Ten patients discontinued participation due to AEs, 3 (5%) in the 1000 mg group and 7 (4%) in the 2000 mg group.

In Study N01061, 576 patients received at least one dose of study drug (LEV 285 and CBZ 291). A greater percentage of patients discontinued the study because of an adverse event in the CBZ group (19%) than in the LEV group (15%), while more patients discontinued the study because of lack of efficacy in the LEV group (18%) than in the CBZ group (10%).

In Study N01364, 443 patients received at least one dose of drug (LEV: 218 and CBZ-IR: 215). A greater percentage of patients discontinued the study because of an adverse event in the CBZ group (12%) than in the LEV group (3%), while more patients discontinued the study because of lack of efficacy in the LEV group (43%) than in the CBZ group (19%).

A total of 71 patients were randomized into Study N01375 and received at least one dose of study drug, 61 in the 1000-2000 mg group and 10 in the 3000 mg group).

Reviewer's Comments: The primary limitation of the safety data included in this NDA is that there were no placebo controls for comparison; therefore, the primary assessment of safety remains dependent on data from the placebo-controlled trials of levetiracetam in patients with POS.

6.4. Safety Results

6.4.1. Deaths

No deaths were reported during Studies N01280 and N01364. During Study N01061, no deaths were reported in the LEV group, although one patient who had taken LEV died about 2 months after the drug had been discontinued and she had been withdrawn from the study. Two patients in the CBZ group died during Study N01061, one from a (b) (6) and the other from (b) (6). One death in a patient taking LEV occurred during Study N01375 with the cause related to seizures.

Reviewer's Comments: The few deaths that occurred during the monotherapy studies do no raise any new safety concerns.

6.4.2. Serious Adverse Events

The incidences of treatment emergent SAEs in the LEV groups ranged from 3-6% during the four monotherapy trials, similar to those seen in the placebo-controlled trials. The most frequent SAEs in the monotherapy trials were seizure-related, as is commonly seen in AED trials.

Reviewer's Comments: No new safety signals related to SAEs were identified during the monotherapy trials.

6.4.3. Treatment Emergent Adverse Events and Adverse Reactions

Due to the differing structures of legacy datasets, it was not possible to assemble a pooled safety dataset for all four studies; therefore, the safety was assessed separately for each study.

The incidences of treatment emergent adverse events (TEAEs) in Studies N01280, N01061, N01364, and N01375 overall ranged from 50.5% in Study N01280 to 95.8% in Study N01375, with 49.6% to 95.8% occurring in the LEV groups. Overall, the most common TEAEs in the LEV groups were headache, dizziness/vertigo, nasopharyngitis, somnolence, nausea, and fatigue. Keppra is already labeled for all of these AEs.

Reviewer's comment: The frequently reported TEAEs are consistent both with commonly observed illnesses in this population and TEAEs observed in the controlled trials of levetiracetam. Review of the TEAEs did not identify any new safety signal.

6.4.4. Laboratory Findings

Clinical laboratory testing (hematology, serum chemistry, urinalysis, oxygen saturation, urine drug, alcohol, and tobacco screening, and pregnancy) was performed. A number of patients had reported clinical laboratory findings that were abnormal (marginally above or below the normal range). However, the majority of these were considered either not clinically significant, single findings, observed during the screening, or observed at baseline.

Reviewer's comment: Review of the clinical laboratory data did not identify any safety signal.

6.5. Integrated Assessment of Safety

This review briefly summarizes the safety data collected from 1313 patients with epilepsy overall and 805 patients exposed to levetiracetam in four monotherapy trials. The clinical safety tests conducted in the studies were appropriate and capable of identifying major safety signals. Overall, the safety findings from this submission are consistent with data from the NDA submissions for adjunctive use of levetiracetam (Keppra) in patients with POS. No new safety signals were identified in Studies N01280, N01061, N01364, and N01375.

7. Labeling Recommendations

7.1. Prescription Drug Labeling

The labeling has not been finalized at the time of this review.

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/s/

NATALIE B GETZOFF
10/18/2019 10:46:41 AM

PHILIP H SHERIDAN
10/18/2019 10:50:52 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Numbers: NDA 21-035 / S-102 and NDA 21-505 / S-042**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement	PAS	12/21/2018	12/21/2018	12/26/2018	10/21/2019	09/10/2019

3. **Provides For from the Cover Letter:** (1) expansion of the indication to include monotherapy for the treatment of partial onset seizures in patients one month of age and older with epilepsy and (2) revisions to the prescribing information in accordance with the "Pregnancy and Lactation Labeling Rule" (PLLR) published in December 2014.

4. **Review #**: 1

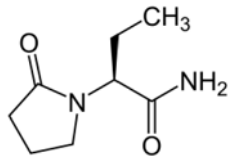
5. **Clinical Review Division**: CDER/ODEI/DNP

6. **Name and Address of Applicant**:
   UCB, Inc.
   1950 Lake Park Drive / Building 2100
   Smyrna, Georgia 30080

7. **Drug Product**:

NDA	Drug Name	Dosage Form	Strengths	Route of Administration	Rx or OTC	Special Product
21-035	Keppra®	Tablets	250 mg, 500 mg, 750 mg, and 1000 mg	Oral	Rx	No
21-505	Keppra®	Oral Solution	100 mg/mL	Oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

	USAN: Levetiracetam, USP CAS Number: 102767-28-2 Chemical name: (-)-(*S*)-α-Ethyl-2-oxo-1-pyrrolidine acetamide Molecular formula: $C_8H_{14}N_2O_2$ MW: 170.21

9. **Indication**: adjunctive therapy in the treatment of partial onset seizures in patients one month of age and older with epilepsy.

10. **Supporting/Relating Documents**: See pages 3-4.

11. Consults: None

12. Executive Summary:

In both Prior Approval efficacy supplemental submissions, namely NDA-021035-SUPPL-102 and NDA-021505-SUPPL-42, the sponsor proposes to expand the indication of Keppra® to include "monotherapy" in treatment of partial onset seizures in patients one month of age and older with epilepsy. NDA-021035-SUPPL-102 pertains to Keppra® (levetiracetam) Tablets and NDA-021505-SUPPL-42 pertains to Keppra® (levetiracetam) Oral Solution. Both drug product presentations are currently indicated for only "adjunctive therapy" in the treatment of partial onset seizures in patients one month of age and older with epilepsy. No changes or updates are being proposed to the approved chemistry, manufacturing and controls (CMC) for the drug substance levetiracetam or to either of the drug product presentations. Regarding the label common to both drug product presentations, no changes are being made in CMC sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", or "16 HOW SUPPLIED/STORAGE AND HANDLING" within the "full prescribing information" in the proposed USPI.

The sponsor also proposes to revise the common prescribing information for these two drug products in accordance with the "Pregnancy and Lactation Labeling Rule" (PLLR) published in December 2014 and as described in the corresponding draft *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products –Content and Format*. All proposed changes to (b) (4) (b) (4) are not CMC-related and, hence, were not evaluated in this review.

The sponsor claims categorical exclusion from the requirement to prepare an Environmental Assessment because approval will not increase the "estimated concentration of the drug substance at the point of entry into the aquatic environment" above 1 part per billion (in accordance with 21 CFR 25.31(b)). Based upon the calculations provided (see details in the body of the review), the claim of categorical exclusion appears to be warranted for both supplemental submissions.

13. Conclusions & Recommendations:

This supplement is recommended for approval from a CMC point of view.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Richard T. Matsuoka, CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

David B. Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC Assessment

I. Background Information

Keppra® (levetiracetam) Tablets, approved on 11/30/1999, come in four different strengths regarding the labeled amount of the drug substance levetiracetam: 250 mg, 500 mg, 750 mg, and 1000 mg. The tablets are for oral administration and contain the following common inactive ingredients: "colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyethylene glycol 3350, polyethylene glycol 6000, polyvinyl alcohol, talc", and titanium dioxide.

Keppra® (levetiracetam) Oral Solution, approved on 07/15/2003, contains 100 mg of levetiracetam per milliliter as a "clear, colorless, grape-flavored liquid". Keppra Oral Solution is supplied in 16 fl. oz. white-colored HDPE bottles at a volume of 473 mL. The oral solution contains the following inactive ingredients: "ammonium glycyrrhizinate, citric acid monohydrate, glycerin, maltitol solution, methylparaben, potassium acesulfame, propylparaben, purified water, sodium citrate dihydrate and natural and artificial flavor". Currently, Keppra is approved as adjunctive therapy in the treatment of partial onset seizures in patients one month of age and older with epilepsy.

The Agency published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR), on 12/03/2014. The "PLLR" became effective on 06/30/2015 and amends the Physician Labeling Rule (PLR) of 2006. The "PLLR" expands and revises the "original stipulations to help providers get additional, more useful information that can help them more accurately and effectively assess risks and benefits of using medications and vaccines during pregnancy". Per the "PLLR", all prescription drugs approved on or after June 30, 2001 must revise the labeling content and format of the Pregnancy and Nursing Mothers (Lactation) subsections. More specifically, all prescription drugs are required to remove pregnancy letter categories and replace them with an integrated risk summary. A draft guidance document entitled *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (Guidance for Industry)* was issued concurrently with the PLLR's publishing to assist the drug manufacturers "in complying with the new labeling content and format requirements".

II. Proposed Changes

The sponsor proposes to:

- add the monotherapy use of Keppra® in the treatment of partial onset seizures (POS) in patients one month of age and older with epilepsy. Currently, both drug product presentations are only approved as adjunctive treatment of POS in the identical patient population.
- revise the prescribing information for the drug product in accord with the "Pregnancy and Lactation Labeling Rule" (PLLR) published in December 2014 and as described in a corresponding guidance for industry.

III. Data Submitted to Support the Proposed Changes

Module "1.12.14. Environmental Analysis"

Comments: The sponsor has provided a request for a Categorical Exclusion under 21 CFR 25.31(b) as the EIC (Expected Introduction Concentration) "of levetiracetam in the aquatic environment is < 1 ppb." Moreover, the sponsor certifies that to the best of their knowledge "no extraordinary circumstances exist where the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(d)." More specifically, the sponsor calculates that the EIC (b) (4) (b) (4) (b) (4) This value is well below the 1.0 ppb limit and, hence, the claim of categorical exclusion appears to be warranted for both supplemental submissions.

Evaluation: ***Adequate***

Module "1.14.1.3. Draft Labeling Text"

Comments: The "1 INDICATIONS AND USAGE" and "2 DOSAGE AND ADMINISTRATION" sections of the proposed prescribing information document common to both drug products have been amended to add reference to the proposed use of Keppra as monotherapy in treatment of partial onset seizures in patients one month of age and older with epilepsy. No changes have been made in the CMC sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", or "16 HOW SUPPLIED/STORAGE AND HANDLING" of the proposed prescribing information document. No changes to the formulation or strengths of the two drug product presentations are being proposed in this efficacy supplemental submission.

Evaluation: ***Adequate***

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety:

Low since both supplemental submissions provide no updates/changes to the approved chemistry, manufacturing and controls (CMC) regarding the drug substance or the drug product presentations.

Richard Matsuoka

Digitally signed by Richard Matsuoka
Date: 9/10/2019 01:16:21PM
GUID: 58405a2d00b8e6d18c2b669521269752

David Lewis

Digitally signed by David Lewis
Date: 9/10/2019 01:20:30PM
GUID: 508da72000029f287fa31e664741b577

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 21035, Supplement 102 (IR tablets) NDA 21505, Supplement 42 (oral solution) NDA 21872, Supplement 28 (IV solution) NDA 22285, Supplement 28 (XR tablets)
Link to EDR	\\CDSESUB1\evsprod\NDA021872\0069
Submission Date	12/21/2018
Submission Type	Standard
Brand Name	KEPPRA®
Generic Name	Levetiracetam
Dosage Form and Strength	Tablets (250, 500, 700, 1000 mg) Solution for injection (100 mg/mL) Oral solution (100 mg/mL) XR tablets (500, 750 mg)
Route of Administration	Oral, intravascular
Proposed Indication	Monotherapy and adjunctive treatment of partial onset seizures in patients with epilepsy
Applicant	UCB Inc.
OCP Review Team	Michael Bewernitz, Ph.D. Dawei Li, Ph.D. Atul Bhattaram, Ph.D. Angela Men, M.D., Ph.D.

1 EXECUTIVE SUMMARY

Keppra® (levetiracetam, LEV) is currently approved in the U.S. for adjunctive therapy in the treatment of partial onset seizures (POS) in patients with epilepsy age 1 month and older. Efficacy supplement 102/42/28/28 was submitted under NDA 21035/21505/21872/22285 to pursue an indication for monotherapy or adjunctive therapy in the treatment of POS in patients with epilepsy age 1 month and older. The current submission involves efficacy extrapolation from adjunctive therapy to monotherapy.

To support use of LEV as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. Although there are some drugs that interact with LEV in the adjunctive setting (i.e. carbamazepine, oxcarbazepine, and vigabatrin), the interactions are not clinically-relevant and thus do not require a dose adjustment. Based on these considerations, it is reasonable to apply the same dosing to monotherapy as is applied to adjunctive therapy.

Overall, the Applicant's submission is acceptable and supports a monotherapy indication from the OCP perspective. The final labeling language will reflect ongoing internal and external discussions which may occur after this review is archived.

2 RECOMMENDATIONS

The Office of Clinical Pharmacology has determined that the submission is acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the Applicant and the Agency regarding the label language.

3 BACKGROUND

Keppra® (Levetiracetam; LEV) is currently approved in the U.S. for the adjunctive treatment of POS in patients with epilepsy age 1 month and older. Efficacy Supplement 102/42/28/28 was submitted under NDA 21035/21505/21872/22285 to pursue an indication for Keppra for monotherapy and adjunctive therapy of POS in patients with epilepsy age 1 month and older. Specifically the current submission involves extrapolation from adjunctive therapy to monotherapy. The Applicant utilized population pharmacokinetic (PPK) modeling and simulation as well as population pharmacokinetic pharmacodynamic (PKPD) modeling and simulation to provide support for the proposed indication.

2 GENERAL ADVICE FOR MONOTHERAPY EXTRAPOLATION

On September 13, 2016 the Division of Neurology Products sent a General Advice Letter to the Sponsor indicating that it is acceptable to extrapolate the efficacy and safety of drugs approved as adjunctive therapy for the treatment of POS to their use as monotherapy for the treatment of POS. In order to support use as monotherapy treatment for POS based on extrapolation, an Applicant must provide pharmacokinetic information supportive of the proposed dose regimen, which when used as monotherapy, is expected to result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. Potential drug interactions that may alter the pharmacokinetics of the drug should be taken into consideration.

4 CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

Phase 3 studies of Keppra in pediatric subjects include N159 and N01009. Both of these studies involved Keppra administration under an adjunctive therapy scenario. There is no clinical experience of monotherapy treatment in pediatric patients in this submission. The Applicant submitted report CL0444 which describes modeling of the pharmacokinetic (PK) and pharmacodynamic (PD) data obtained from these studies as well as PK simulations and PD simulations.

[*Reviewer comment: Studies N159 and N01009 have been previously-reviewed by the Office of Clinical Pharmacology during their assessment of efficacy supplement 73. Efficacy supplement 73 was submitted under NDA 021035 to pursue an indication for the use of Keppra as adjunctive therapy in the treatment*

of partial onset seizures in children age 1 month to less than 4 years. Please refer to the clinical pharmacology review of NDA 021035 archived on 9/8/2008 for details.]

N159 (complete): Phase 3, double-blind, randomized, placebo-controlled, multi-center, pharmacokinetic, efficacy, and safety trial of 14 weeks of adjunctive Keppra treatment for POS in n=194 patients with epilepsy age 4 years to 17 years receiving stable treatment with 1-2 other anti-epilepsy drugs (AEDs). Subjects were randomized 1:1 to receive Keppra or matching placebo. Subjects randomized to Keppra underwent 6 weeks of fixed titration (two weeks at 20, 40, and 60 mg/kg/day, respectively), 8 weeks at the maximum tolerated dose, and a 6-week down-titration period. The total daily dose was administered as twice daily (bid). The primary efficacy parameter was partial onset seizure frequency normalized to a one-week period.

N01009 (complete): Phase 3, double-blind, randomized, placebo-controlled, multi-center, pharmacokinetic, safety, and efficacy trial of 20 days of adjunctive Keppra treatment for POS in n=110 patients with epilepsy age 1 month to < 4 years receiving stable treatment of 1-2 other AEDs. Subjects were randomized 1:1 to receive Keppra or matching placebo. Subjects age 1 month to < 6 months that were randomized to Keppra received 20 mg/kg/day on Day 1, 40 mg/kg/day Day 2 to Day 6, and 20 mg/kg/day from Day 6 to Day 20. Subjects age 6 months to < 4 years that were randomized to Keppra received 25 mg/kg/day on Day 1, 50 mg/kg/day Day 2 to Day 6, and 25 mg/kg/day from Day 6 to Day 20. The total daily dose was administered bid. The primary efficacy endpoint was responder rate computed as the proportion of subjects with a 50% reduction in daily seizure frequency. Subjects were stratified by arm and by age group for the primary efficacy analyses.

CL0444: Report CL0444 describes the development of a PPK model in pediatric patients age 1 month to 17 years. The model includes a term for each of 12 concomitant AEDs as a covariate on LEV apparent clearance (CL/F). The Applicant used the final PPK model to conduct PK simulations. The PK simulations assessed the effect of each individual concomitant medication on LEV exposure as well as all 12 concomitant medications combined on LEV exposure. Report CL0444 also describes the development of a PKPD model to link LEV PK to PD using daily seizure count as the PD measure. The PKPD model was used by the Applicant to conduct simulations to characterize the impact of the drug interactions in terms of seizure rate and ultimately to inform the comparison of monotherapy versus adjunctive therapy.

[*Reviewer comment: The support for approval of the current submission is based on PK matching and extrapolation. The PKPD analyses were not reviewed.*]

5 RESULTS OF APPLICANT'S ANALYSES

The Applicant conducted modeling and simulation exercises intended to support use of LEV in a monotherapy scenario. The results of these analyses are available in the file cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf submitted to module 5342, sequence 0069, under NDA 021872 (supplement 28).

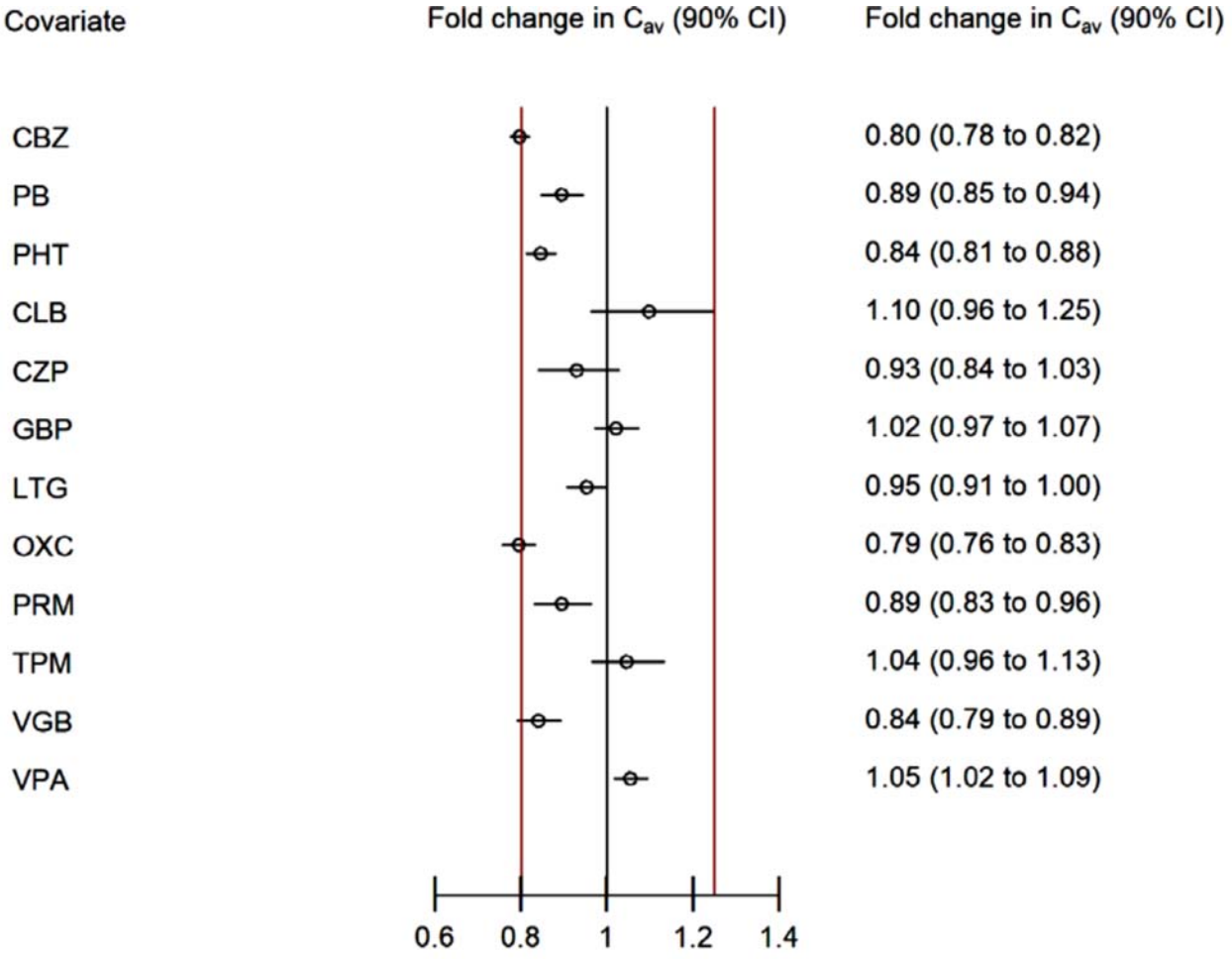
Pharmacokinetic Modeling and Simulation

The Applicant built a PPK model to quantify the effect of concomitant AEDs on LEV apparent clearance (CL/F) in adult and pediatric epilepsy patients with POS. Please refer to the Appendix for details regarding the PPK model and the clinical studies from which the PK data were obtained.

PK Simulations: Effect of Individual Concomitant Medications

Using the PPK model, the Applicant simulated the LEV average concentration (C_{av}) at steady-state (C_{avss}) in a monotherapy scenario as well as an adjunctive therapy scenario with one of each of the 12 concomitant AEDs included in the final PPK model. The effect of the drug interaction for each concomitant AED was computed as the fold-change in simulated C_{avss} when the concomitant AED is added on to LEV versus LEV alone. The point estimates and 90% confidence intervals (CI) for the drug interaction effects are presented **Figure 1**.

Figure 1: Forest Plot of the Predicted Change in Levetiracetam Average Concentration at Steady-State when Co-Administered with a Concomitant Antiepileptic Drug Using the Final PPK Model (run009)



Red lines indicate the limits associated with 0.8- to 1.25-fold change in C_{avss}. CBZ: carbamazepine, CLB: clobazam, CZP: clonazepam, GBP: gabapentin, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PHT: phenytoin, PRM: primidone, TPM: topiramate, VGB: vigabatrin, VPA: valproic acid

Source: NDA 021872, sequence 0069, module 5342, cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf, page 9 of 98

Out of all the concomitant AEDs presented in **Figure 1**, carbamazepine, oxcarbazepine, and vigabatrin have the highest magnitudes of effect on LEV exposure. Carbamazepine, oxcarbazepine, and vigabatrin produce provide point estimates of 0.8, 0.79, and 0.84 which translates to a 20%, 21%, and 16% reduction in LEV C_{avss} when LEV is used with these medications, respectively. Thus, when using LEV in a monotherapy scenario, the LEV C_{avss} is expected to be 25%, 27%, and 19% higher (1/0.8 = 1.25, 1/0.79 = 1.27, and 1/0.84 = 1.19) than for levetiracetam with carbamazepine, or levetiracetam with oxcarbazepine, or levetiracetam with vigabatrin, respectively.

[*Reviewer comment: The reviewer compared the results of the Applicant's PPK-based drug interaction assessment with the drug interaction knowledge from the current Keppra label. At the time of this submission, the current Keppra label provides the following information regarding drug interactions:*

- *Section 2 does not require any dose adjustments to Keppra based on concomitant medication use*
- *There is no "7 Drug Interactions" section in the Keppra label*
- *Section 12.3, Drug Interactions, states: "In Vitro data on metabolic interactions indicate that levetiracetam is unlikely to … be subject to, pharmacokinetic interactions"*

The current findings from the Applicant's PPK analyses of drug interaction are consistent with the statements in the current approved label regarding drug interactions.

Overall, when comparing LEV used in monotherapy to LEV used in adjunctive therapy, exposure changes of these magnitudes (i.e. 19% to 27% higher LEV C_{avss} in monotherapy versus when used adjunctively with carbamazepine, oxcarbazepine, or vigabatrin, respectively) are not expected to result in a clinically relevant worsening of safety or tolerability.]

PK Simulations: Effect of All Concomitant Medications Simultaneously

The Applicant conducted additional PK simulations to compare LEV monotherapy versus LEV adjunctive therapy when combined with all 12 concomitant medications from in the final PPK model simultaneously (CBZ, PB, PHT, CLB, CZP, GBP, LTG, OXC, PRM, TPM, VGB, and VPA combined; "full AED add-on profile"). The final LEV PPK Model (run009) was used with these concomitant medication terms "active" along with representative age and weight information from the Nhanes database to simulate C_{avss} for pediatric patients at dose levels utilized in Phase 3 studies N01009 and N159 and simulate C_{avss} for adult patients at an approved adjunctive Keppra dose level (see **Table 1**).

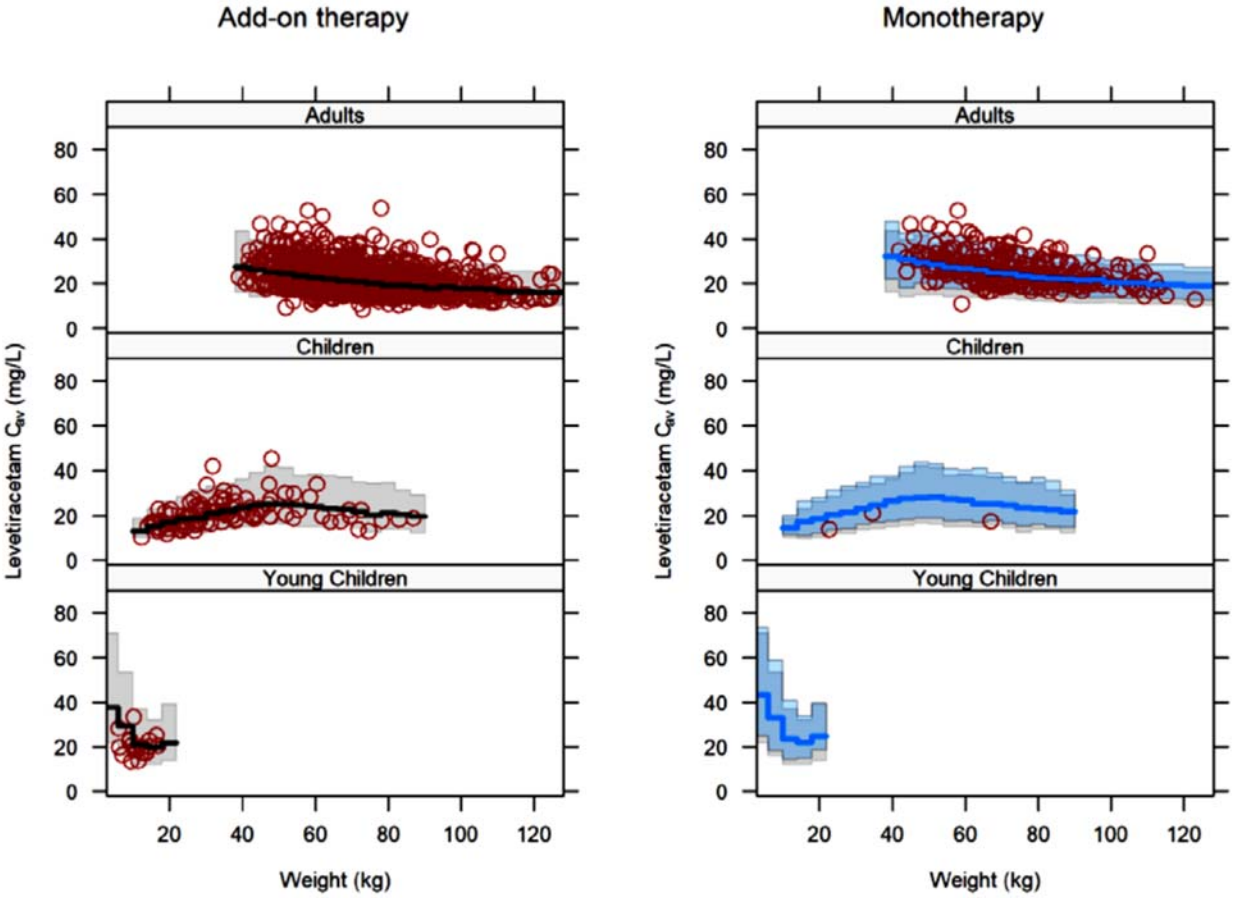
Table 1: Dose Regimens Administered to Virtual Subjects for PK Simulations

Group of Virtual Subjects			Dose	Notes
Pediatric Patients	1 month to < 0.5 years		40 mg/kg/day	Within dose range used in study N01009
	0.5 to < 4 years		50 mg/kg/day	
	4 to 16 years	< 50 kg	40 mg/kg/day	Within dose range used in study N159
		≥ 50 kg	2000 mg/day	
Adult Patients			2000 mg/day	approved adult range is 1000 to 3000 mg/day

Source: NDA 021872, sequence 0069, module 5342, cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf, page 44 of 98

The results of the Applicant's PK simulations are presented in **Figure 2**.

Figure 2: Simulated Average Plasma Concentration at Steady-State (C_{avss}) versus Body Weight by Age Group for Monotherapy and Full Add-on Adjunctive Therapy



Doses: adults (≥ 18 years) receive 2000 mg/day, children (≥ 4 years and <18 years) receive 40 mg/kg/day with a maximum of 2000 mg/day, young children (≥ 6 months to <4 years) receive 50 mg/kg/day, and young children (<6 months) receive 40 mg/kg/day. Gray shaded area: 90% of simulated patients (90% prediction interval; 5th percentile to 95th percentile of the distribution of predicted exposures within the virtual population) with observed add-on AEDs as used in the trials. Blue shaded area (right): 90% of patients without add-on AEDs. Solid lines: median simulated value. Brown circles are predicted individual C_{avss} values using the individual PK parameter estimates for LEV add-on therapy patients (left) and monotherapy patients (right) from the final PPK model (run009). The x-axis starts at 2 kg. The "full AED add-on profile" refers to LEV used with a cocktail of all 12 concomitant medications (CBZ, PB, PHT, CLB, CZP, GBP, LTG, OXC, PRM, TPM, VGB, and VPA) that are present in the final PPK model (run009).

Source: NDA 021872, sequence 0069, module 5342,
cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf, page 46 of 98

In **Figure 2**, the distribution of simulated LEV C_{avss} for pediatric patients under the monotherapy scenario (right panel; middle and bottom boxes; blue shaded area) is comparable to the distribution of simulated LEV C_{avss} for pediatric patients under the adjunctive scenario (left panel, middle and bottom boxes; grey shaded area) across the range of weight groups. The individual predicted LEV C_{avss} for children receiving Keppra monotherapy (**Figure 2**, right panel, middle box; brown circles) as well as for children receiving

Keppra adjunctive therapy (**Figure 2**, left panel, middle box and bottom box; brown circles) are mostly contained within the 90% prediction interval for the virtual population.

Based on the PK simulations, the Applicant states that for a 70 kg adult, the median predicted LEV C_{avss} increases 17% when switching from the "full add-on scenario" to monotherapy due to the absence of enzyme-inducing AEDs. The Applicant turns to the PKPD simulations in order to interpret the effect of this PK difference in terms of a PD difference.

[*Reviewer comment: The virtual population selected for the PK simulation as well as the dose levels selected for the virtual population are reasonable.*

The "full add-on scenario" is intended to represent the combined effect on LEV PK of all concomitant medications included in the final population model. However, this simulation exercise was built on the assumption that the individual drug interaction effects from each concomitant medication can be combined to predict the interaction effect of all drugs combined. Specifically, this approach assumes that the change in LEV CL/F from simultaneous use of all 12 concomitant AEDs on is equal to the product of the proportional change in LEV CL/F from each of the 12 concomitant AEDs. However, the population PK analysis included data from adult and pediatric patients receiving LEV with up to a maximum of 2 concomitant medications. Thus, it is not clear that the LEV PK data provided by patients receiving Keppra with 2 concomitant medications can be used to inform the effect of 12 simultaneous concomitant medications (the so-called "full AED add-on profile") on LEV PK. In addition, 12 concomitant medications is likely in excess of the number of concomitant medications typically used in clinical practice.

Overall, it is not clear that the "full AED add-on profile" represents a "worst-case scenario" as this approach does not address the complex set of interactions of the various concomitant medications against one another. For this reason, it is not clear that the PK simulations for the "full AED add-on profile" are a reliable piece of support for the proposed dosing regimen.]

Pharmacokinetic Pharmacodynamic Modeling and Simulation

The Applicant expanded on the population PK (PPK) model to create a pharmacokinetic pharmacodynamic (PKPD) model to assess how the PK-based interactions of the concomitant AEDs against LEV may manifest in terms of a change in monthly seizure rate. The Applicant concludes that their PKPD simulations demonstrate no clinically-relevant efficacy difference between Keppra monotherapy versus Keppra adjunctive therapy across the range of approved adjunctive Keppra dose levels in adult patients and pediatric patients.

[*Reviewer comment: Although these analyses may provide support for extrapolating efficacy in an adjunctive scenario to efficacy in a monotherapy scenario, they are not necessary to derive monotherapy dosing recommendations for this application. The support for this supplement is based on PK analyses. As such, the Applicant's PKPD modeling will not be further discussed.*]

Applicant's Proposed Dosing Recommendations

The Applicant concludes that when converting from LEV adjunctive therapy to LEV monotherapy, or when initiating LEV monotherapy, the same dose as recommended for LEV adjunctive therapy can be used in adults and children down to 1 month of age.

[*Reviewer comment: The findings from the PPK modeling (e.g. the results presented in* ***Figure 1****) support the conclusion that the co-administration of AEDs do not have a clinically-relevant effect on LEV PK in POS patients.*

Therefore, under the same dosing regimen, LEV exposure in epilepsy patients with POS receiving LEV monotherapy is likely to be comparable to LEV exposure in epilepsy patients with POS receiving LEV adjunctive therapy. As such, the ***Applicant's proposal to use the same recommended dose in monotherapy as in adjunctive therapy is acceptable****.*]

6 LABEL RECOMMENDATIONS

This section addresses key label edits proposed by the Applicant. Text that the Applicant proposes for addition to the label is marked with blue font and an underline (e.g. text that Applicant proposes to add to the label). Text that the Applicant proposes to delete from the label is marked with red font and a strike-through (e.g. ~~text that the Applicant proposes to remove from the label~~).

Assuming this supplement is approved, the final label will reflect subsequent ongoing internal discussions and external discussions that may occur after this review is archived.

2.1 Dosing for Partial Onset Seizures

> "For adults and pediatric patients, the recommended dosing for monotherapy and adjunctive therapy is the same as outlined below."

[*Reviewer comment: This statement, proposed for addition to section 2.1, is supported by the PPK data analyses and is acceptable.*]

8.4 Pediatric Use

> "The safety and effectiveness of KEPPRA as monotherapy of partial- onset seizures in patients age 1 month to 16 years old with epilepsy have been established [*see Clinical Pharmacology (12.3)*]. The dosing recommendation in these pediatric patients varies according to age group and is weight-based [*see Dosage and Administration (2.2)*]."

[*Reviewer comment: This statement, proposed for addition to section 2.1, is supported by the PPK data analyses and is acceptable.*]

12.3 Pharmacokinetics

pharmacokinetics of levetiracetam are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures."]

Michael Bewernitz, Ph.D.
Reviewer, Division of Pharmacometrics (DPM)

Dawei Li, Ph.D.
Reviewer, Division of Clinical Pharmacology 1 (DCP1)

Atul Bhattaram, Ph.D.
Team Leader, DPM

Angela Men, M.D., Ph.D.
Team Leader DCP1

APPENDIX

Pediatric Population PK Model Review

The Applicant developed a PPK model to characterize LEV PK in adult and pediatric patients with epilepsy age 1 month and older. The results of these analyses are presented in report cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf (NDA 021872 [SUPP28] sequence 0069, module 5342). The model was utilized to conduct PPK simulations to compare LEV exposures in a monotherapy scenario to LEV exposures in an adjunctive therapy scenario.

For a discussion on the interpretation of these results, please refer to section "5 RESULTS OF APPLICANT'S ANALYSES ".

Summary of PK Data:

There were 5240 measureable LEV concentration values for PK analyses from n=1183 subjects that received LEV as adjunctive therapy or received LEV monotherapy. Out of the full dataset, there were 1317 LEV concentration values obtained from n=326 patients receiving LEV monotherapy.

Studies in Pediatric Patients: The Applicant utilized LEV PK data from n=101 pediatric patients age 4.1 to 17.0 years in Phase 3 study N159 and n=19 pediatric patients age 0.687 to 3.94 years in Phase 3 study N01009. All studies from which pediatric PK data originated for the PPK analyses in this submission were studies where Keppra was administered adjunctively.

Study N159 was a Phase 3, double-blind, randomized, placebo-controlled, multi-center, pharmacokinetic, efficacy, and safety trial of 14 weeks of adjunctive Keppra treatment in n=194 patients with epilepsy with POS age 4 years to 17 years. Subjects randomized to Keppra underwent 6 weeks of fixed titration (two weeks at 20, 40, and 60 mg/kg/day each, respectively), 8 weeks at the maximum tolerated dose, and a 6 week down-titration period. The total daily dose is administered as twice daily (bid).

Study N01009 was a Phase 3, double-blind, randomized, placebo-controlled, multi-center, pharmacokinetic, safety, and efficacy trial of 20 days of adjunctive Keppra treatment in n=110 patients with epilepsy with POS age 1 month to < 4 years of age receiving stable treatment of 1-2 other AEDs. Subjects were randomized 1:1 to receive Keppra or matching placebo. Subjects age 1 month to < 6 months that were randomized to Keppra received 20 mg/kg/day on Day 1, 40 mg/kg/day Day 2 to Day 6, and 20 mg/kg/day from Day 6 to Day 20. Subjects age 6 months to < 4 years that were randomized to Keppra received 25 mg/kg/day on Day 1, 50 mg/kg/day Day 2 to Day 6, and 25 mg/kg/day from Day 6 to Day 20. The total daily dose is administered bid.

[*Reviewer comment: Studies N159 and N01009 have been previously-reviewed by the Office of Clinical Pharmacology (please refer to the clinical pharmacology review of NDA 021035 archived on 9/8/2008 for details). Additional details regarding study N159 can be found in the clinical pharmacology review of NDA 21035 archived on 06/01/2005.*]

Studies in Adult Patients: Phase 3 studies of adjunctive LEV use from which adult PK data originated for the PPK analyses are N051, N052, and N0132. Phase 3 studies of monotherapy LEV use from which adult PK data originated for the PPK analyses are N138 and N01061 (with 197 PK samples from n=62 subjects in study N138; 1120 PK samples from n=264 subjects in study N01061).

[*Reviewer comment: For details regarding study N132, N138, N01009 please refer to the clinical pharmacology of NDA 21035 archived on 09/08/2008. Details regarding Phase 3 studies N132, N051, N138 and N052 can be found in the clinical pharmacology review of NDA 21035 archived on 06/01/2005. Study N01061 was conducted in order to approve LEV for monotherapy use in the European Union. Please refer to the meeting minutes for IND 45151 archived on 5/21/04 for details on Study N01061.*]

Pediatric Population PK Model:

The structural model is a one-compartment model with first order absorption. PK parameters include apparent clearance (Cl/F), apparent volume of distribution (V/F) and absorption rate constant (k_a).

Allometric scaling: Cl/F and V/F had allometric scaling applied using body weight normalized to 70 kg
Inter-individual variability: exponential
Residual variability: proportional error model
Covariates: A sigmoid E_{max} model was utilized to relate post-conceptional age to LEV CL/F. In addition, a covariate term was estimated for the effect of each of 12 concomitant medications as a proportional change in LEV CL/F.

The parameter estimates from the final population PK model (run009) are shown in **Table 2**.

Table 2: PK Parameter Estimates for the Final Levetiracetam Population Pharmacokinetic Model in Pediatric Epilepsy Patients with Partial Onset Seizures (run009)

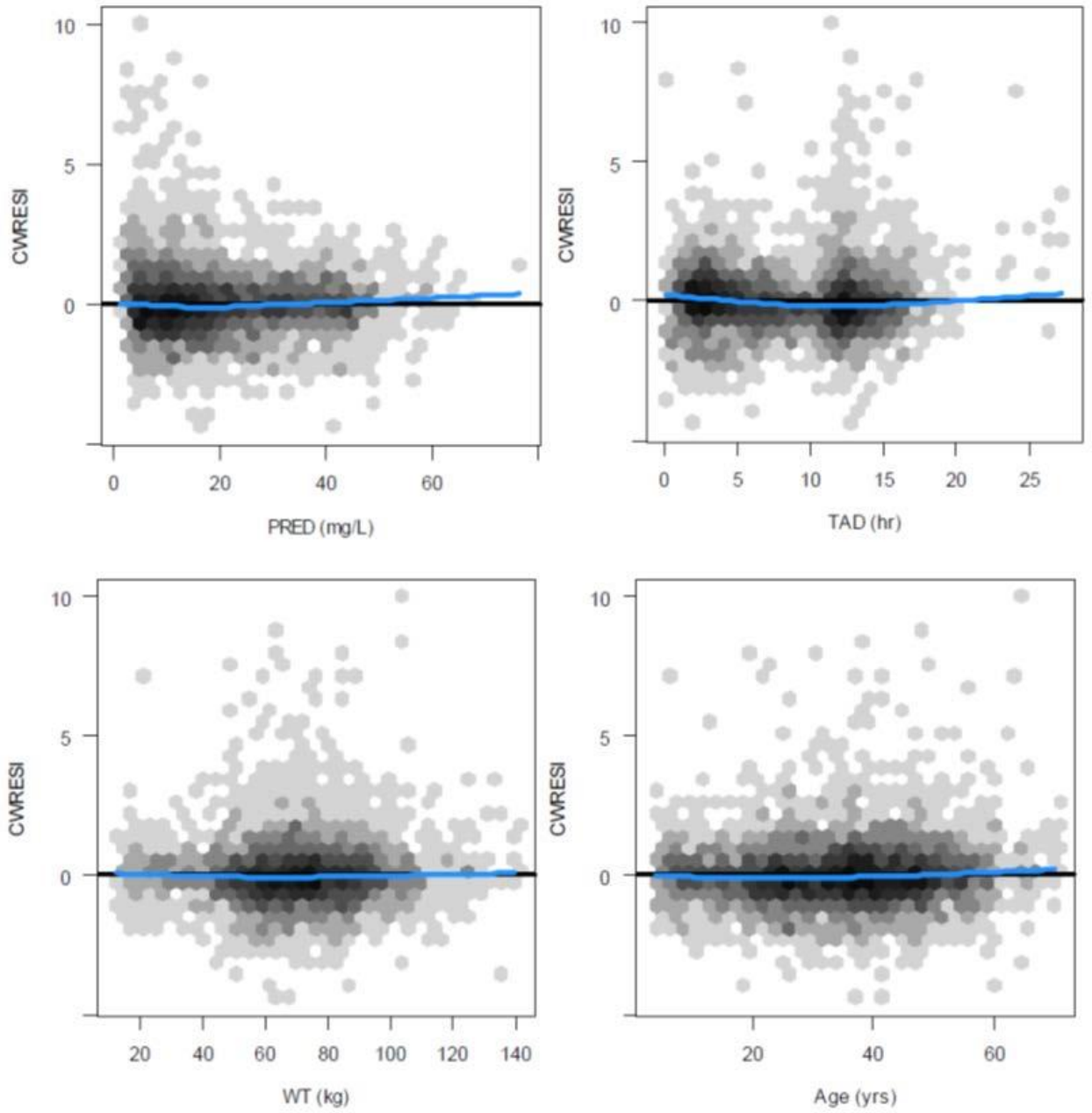
Parameter	*Estimate (90% CI)*[1]	*SE (%CV)*[2]	*IIV (%)*[3]	*Shrinkage (%)*[4]
CL (L/hr)[5]	3.38 (3.29/3.47)	1.6%	25.3%	18.8%
V (L)[5]	57.3 (53.6/60.9)	3.9%	48.3%	43.5%
Ka (1/hr)	1.85 (1.53/2.17)	10.4%		
Wt on CL	0.489 (0.440/0.539)	6.2%		
Wt on V	0.798 (0.697/0.900)	7.7%		
Fold change in Cav due to CBZ[6]	0.80 (0.78/0.82)	7.2%		
Fold change in Cav due to PB[6]	0.89 (0.85/0.94)	29.5%		
Fold change in Cav due to PHT[6]	0.84 (0.81/0.88)	14.5%		
Fold change in Cav due to CLB[6]	1.10 (0.96/1.25)	85.8%		
Fold change in Cav due to CZP[6]	0.93 (0.84/1.03)	82.2%		
Fold change in Cav due to GBP[6]	1.02 (0.97/1.07)	145.2%		
Fold change in Cav due to LTG[6]	0.95 (0.91/1.00)	60.2%		
Fold change in Cav due to OXC[6]	0.79 (0.76/0.83)	12.8%		
Fold change in Cav due to PRM[6]	0.89 (0.83/0.96)	40.3%		
Fold change in Cav due to TPM[6]	1.04 (0.96/1.13)	112.3%		
Fold change in Cav due to VGB[6]	0.84 (0.79/0.89)	21.3%		
Fold change in Cav due to VPA[6]	1.05 (1.02/1.09)	42.5%		
sigmoidicity for PCA-dependent CL maturation	2.65 (1.96/3.34)	15.8%		
half-maximal PCA-dependent CL maturation (years)	1.51 (1.25/1.77)	10.4%		
Res.error (SD/mean)	0.261 (0.250/0.271)	2.4%		10.3%

AED effects are back-transformed log-estimates of proportional change in LEV CL/F transformed to fold-change in C_{avss}. CBZ: carbamazepine, CI: confidence interval, CLB: clobazam, CV: coefficient of variation, CZP: clonazepam, GBP: gabapentin, IIV: interindividual variability, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PCA: post-conceptional age, PHT: phenytoin, PRM: primidone, TPM: topiramate, VGB: vigabatrin, VPA: valproic acid, Wt: body weight (reference value: 70 kg)

Source: NDA 021872, sequence 0069, module 5342,
cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf, page 30 of 98

Key model diagnostic plots are presented in **Figure 3** and **Figure 4**.

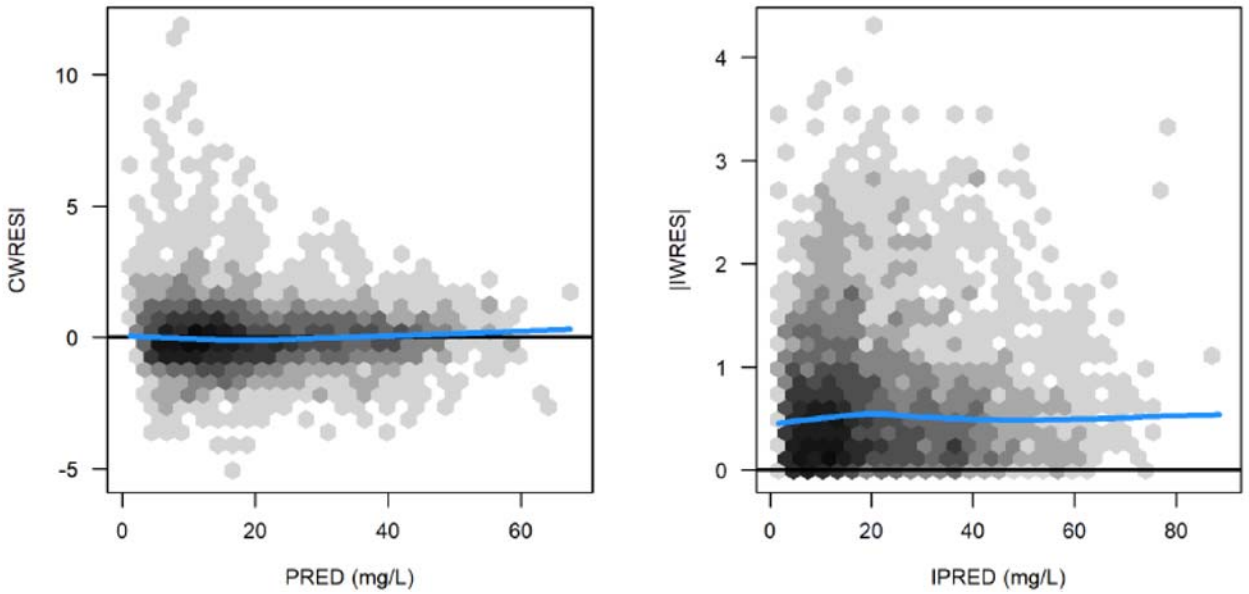
Figure 3: Diagnostic Plots For the Final Population PK Model (run009) Using Conditional Weighted Residual (CWRESI)



The horizontal black lines are zero lines, the blue lines are loess smoothers through the data. CWRESI = Conditional weighted residuals, TAD = time after dose, WT = body weight, PRED = population prediction. The darkness of the hexagons corresponds to the data density at that location.

Source: NDA 021872, sequence 0069, module 5342, cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf, page 33 to 34 of 98

Figure 4: Diagnostic Plots For the Final Population PK Model (run009) Using Population Predicted Values (PRED) and Individual Predicted Values (IPRED)



The horizontal black lines represent a y-axis value of zero, the blue curves are generated by locally-estimated scatterplot smoothing of the observed data. CWRESI = Conditional weighted residuals, |IWRES| = absolute value of individual weighted residuals, PRED = population prediction, IPRED = individual prediction. The darkness of the hexagons corresponds to the data density at that location.

Source: NDA 021872, sequence 0069, module 5342,
cl0444_levetiracetam_pediatric_monotherapy_pkpd_report_29-oc.pdf, page 34 of 98

[*Reviewer comment: The diagnostic plots presented in **Figure 3** and **Figure 4** do not suggest any obvious sign of systematic bias throughout the duration of a dosing interval nor with respect to the magnitude of predicted concentration.*

*Applicant has determined that weight is a covariate on LEV PK. Allometric scaling was applied to account for the change in LEV CL/F and LEV V/F with body weight, which is acceptable. The inclusion of age in a sigmoid E_{max} model to address renal maturation is acceptable. The bottom panels in **Figure 3** suggest that after inclusion of age and weight as covariates, there is no systemic bias across the range of weights nor across the range of ages present in the PK dataset.*

*Estimates of the proportional change in LEV CL/F attributed to concomitant use of gabapentin and concomitant use of topiramate provided highest standard error of all the drug interaction terms (145.2% and 112.3%; see **Table 2**), respectively. However, due to effect size of these two covariates (1.02 and 1.04 in terms of C_{avss}; a 2% and 4% increase in LEV C_{avss}) the low precision is not likely to affect model performance in a manner that is clinically-relevant.*

*The visual predictive check (figure not shown in review) indicates that the model provides reasonably accurate predictions of central tendency throughout the dosing interval for adult subjects (at 1000, 2000, and 3000 mg/day) and pediatric subjects (at 60 mg/kg/day). The model may be less accurate at predicting extreme values (e.g. concentrations ≤ 5th percentile and concentrations ≥ 95th percentile) regardless of dose level or age group. **Overall, the Applicant's pediatric PK model is acceptable**.*]

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/s/

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VENKATESH A BHATTARAM
09/19/2019 01:28:47 PM

YUXIN MEN
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

OTHER REVIEW(S)

Safety Team Leader Memo
NDA 21035, 21505, 21872, 22285

Safety Team Leader Memorandum

NDA:	21035, 21505, 21872, 22285
Drug:	Keppra (Levetiracetam)
Route:	Oral tablet, Oral solution, Oral extended release tablet, injectable
Indication:	PLLR labeling
Submission Date:	December 21, 2018
Sponsor:	UCB, Inc.

This memo reviews and summarizes the proposed labeling language, related to the human experience, in the Keppra label sections that address the Pregnancy and Lactation Labeling Rule (PLLR) in the Prior Approval Labeling Supplement submitted December 21, 2018. The Applicant's proposed labeling related to PLLR provided for edits in Sections 8.1 (Pregnancy) and 8.2 (Lactation) of the prescribing information. The focus of the review is on outcomes after Keppra monotherapy. The initial approval for Keppra was in 1999.

Background

UCB submitted the final study report of the Keppra pregnancy registry, a review of their safety database, and a published literature review on September 30, 2016. That submission was reviewed by Dr. Leyla Sahin, Division of Pediatric and Maternal Health (7/21/17) and by Danijela Stojanovic, Division of Epidemiology I (7/28/17). Please refer to the table below from Dr. Sahin's review, showing the rate of major congenital malformations (MCM) with levetiracetam monotherapy or polytherapy compared to a control group for the UCB Keppra registry, the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP), and the North American Antiepileptic Drug Pregnancy Registry (NAAED, also referred to as NAAPR).

Table 1: Rate of Major Congenital Malformations (MCM) with levetiracetam use in pregnancy observed in the Keppra, EURAP, NAAPR

Registry	MCM with Levetiracetam Monotherapy	MCM with Levetiracetam Polytherapy	MCM in Control Group (without AED use)
Keppra	9.4% (29 out of 309)	12.6 % (17 out of 129)	N/A
	6.8% (19 out of 280)*		
EURAP*	2.6% (18 out of 696)	4.1% (24 out of 580)	2.2% (3 out of 134)
NAAPR**	2.1% (15 of 759)	2.35% (11 of 485)	1.5% (8 out of 529) ***

*rate calculated by this reviewer based on first trimester exposures and exclusion of 3 cases with a cluster of > 2 minor birth defects, 3 genetic disorders, 1 chromosomal anomaly, and 1familial disorder
**cut-off date 5-20-2016
***cut-off date 1-1-2016; 46 of the Keppra Pregnancy Registry's enrollments report to be participating in the NAAPR concurrently, indicating overlap between the two registry populations.

Dr. Sahin found that although the prevalence of major malformations in the Keppra registry was higher than the NAAPR, EURAP, and the background rate in the general population, although there was no pattern of malformations. She noted that differences in methodology preclude comparing results across registries. She also noted that external independent review of the Keppra birth defect cases in the UCB registry, based on criteria used in the NAAPR and EURAP registries, confirmed the presence of a major birth defect in only 15.7% and 43.4% cases in the Keppra registry. She also noted that the NAAPR and EURAP registries, which had more than double the sample size of the

Keppra registry, showed no increased risk for MCM. Finally, she noted that the cumulative data based on the published literature and the sponsor's safety database did not identify a safety signal.

In addition to considering MCM, Dr. Sahin noted data from the sponsor's literature review in that submission that included data from EURAP that showed no difference in risk for stillbirth or spontaneous abortion in pregnancies exposed to levetiracetam (n=324) compared with pregnancies exposed to other antiepileptic drugs and data from the Norway medical Birth Register that showed no increased risk for small for gestational age or microcephaly in infants exposed to levetiracetam in utero (n=188) compared to other antiepileptic drugs.

Literature Review

In the present submission, the sponsor summarized pregnancy registry literature. I summarize the publications since the time of Dr. Sahin's review in the table below[1]. The rates of MCM are similar to those reported in Dr. Sahin's review from earlier EURAP and NAAPR data shown above supporting the finding of no safety signal in the available literature.

Registry	MCM with Levetiracetam Monotherapy	MCM with Levetiracetam Polytherapy	MCM in Control group (without AED use)
Australian Pregnancy Register through mid-2017[2]	3.1%		3.1%
EURAP Registry 1999-2016[3]	2.8% (17/599)		
North American Register, Australian Register, UK Register[4]	1.77% (and not associated with increased risk vs no medication in women with or without epilepsy.		
EURAP through May 22, 2018[5]	3.1% (27 of 885)		
NAAED (NAAPR)[6]	1.8% of 920 monotherapy pregnancies	2.4% of 584 polytherapy pregnancies	

[1] Additional references, not included here, reported information for fewer than 50 pregnancies exposed to levetiracetam.
[2] Vajda et al. Antiepileptic drug polytherapy in pregnant women with epilepsy. Acta Neurologica Scandinavica 2018; 138:115-121.
[3] Tomson T et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort drugs: a prospective cohort study of the EURAP registry. The Lancet Neurology. 2018;17(6):530-8.
[4] Weston Jet al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child (Review). Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224. DOI: 10.1002/14651858.CD010224.pub2.
[5] Interim May 2018 report provided to UCB, discussed in UCB Pregnancy Cumulative Review
[6] As of April 30, 2018, report provided to UCB, discussed in UCB Pregnancy Cumulative Review

Keppra Pharmacovigilance Database

The table below shows the findings from the Keppra pharmacovigilance database for levetiracetam exposure reported in the present submission compared to the information reviewed by Dr. Sahin from the 2016 submission. As noted in Dr. Sahin's 2017 review, limitations include lack of denominator data, lack of controls, and poor case documentation. The present findings are very similar to the findings previously reviewed by Dr. Sahin.

	UCB 2016 Database	UCB 2018 Database (thru June 15, 2018)
Live Births	1250 live births • 686 monotherapy (230 prospective) • 555 polytherapy	1892 live births • 1100 monotherapy (273 prospective) • 792 polytherapy
Spontaneous Abortions	287	339
Stillbirths	33	37
Congenital anomaly (among prospective monotherapy live births with first trimester exposure)	5%	5.5%

Fertility

Limited data do not allow for a conclusion regarding the effect on levetiracetam on fertility. The Sponsor provided summaries of 2 publications evaluating effects of levetiracetam on semen quality among other things in male adults with epilepsy. Wu et al evaluated 11 males with epilepsy treated with levetiracetam for 6 months and found no significant difference in semen results or in sex hormones[7]. Ceylan et al found decreased sperm quality in 26 males treated with levetiracetam monotherapy.[8]

Lactation

The Sponsor provided published literature on pharmacokinetics of levetiracetam during pregnancy and lactation. These data do not inform the effects of Keppra on the breastfed infant or the effects on milk production. I searched LactMed (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~Wf1HR4:1); I do not believe that the limited data available in LactMed informs the effects of Keppra on the breastfed infant or the effects on milk production.

Conclusions and Recommendations

A 2017 review by Dr Leyla Sahin did not find a signal for teratogenicity from levetiracetam exposure. Updated information available since that time, presented in the current submission, supports Dr. Sahin's conclusion. Based on approximately 20 years

[7] Wu D et al. The effects of oxcarbazepine, levetiracetam, and lamotrigine on semen quality, sexual function, and sex hormones in male adults with epilepsy. Epilepsia 2018; 59:1344-1350.
[8] Eylan et al. Effects of levetiracetam monotherapy on sperm parameters and sex hormones; Data from newly diagnosed patients with epilepsy. Seizure. 2016; 41:70-74.

of experience with levetiracetam, with data from some registries starting in 1999, I recommend including the following language in the Risk Summary in Section 8.1:

(b) (4)

[redacted]

I recommend including the following information in the Human Data section:

> While available studies cannot definitively establish the absence of risk, published data from the published literature and pregnancy registries have not established an association with levetiracetam use during pregnancy and major birth defects or miscarriage.

There are no sufficient data to inform labeling regarding lactation or fertility.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 26, 2019

To: Philip Sheridan, M.D.
Division of Neurology Products (DNP)

Heather Bullock, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for KEPPRA (levetiracetam) tablets, for oral use; oral solution; injection, for intravenous use; extended-release tablets, for oral use

NDA: 21035 s102
21505 s42
21872 s28
22285 s28

In response to the DNP consult request dated February 15, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guides for the supplemental NDA submissions for KEPPRA (levetiracetam) tablets, for oral use; oral solution; injection, for intravenous use; extended-release tablets, for oral use.

PIs and Medication Guides: OPDP's comments on the proposed labeling are based on the draft PIs received by electronic mail from DNP (Heather Bullock) on September 11, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guides was sent under separate cover on September 24, 2019.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

95 Pages Draft Labeling have been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

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DHARA SHAH
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 24, 2019
To:	William Dunn, M.D. Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	KEPPRA (levetiracetam) tablets KEPPRA (levetiracetam) oral solution KEPPRA XR (levetiracetam) extended-release tablets
Application Type/Number:	NDA 21035/S-102 NDA 21505/S-042 NDA 22285/S-028
Applicant:	UCB, Inc

1 INTRODUCTION

On December 21, 2018 UCB, Inc submitted for the Agency's review a prior approval labeling supplement for KEPPRA (levetiracetam) tablets, oral solution, injection and KEPPRA XR (levetiracetam) extended-release tablets. The purpose of the submission is to seek approval for the use of KEPPRA (levetiracetam) as a monotherapy in the treatment of partial-onset seizures in patients 1 month of age and older with epilepsy and for the use of KEPPRA XR (levetiracetam) as a monotherapy in the treatment of partial-onset seizures in patients 12 years of age and older with epilepsy. In addition, the labeling includes implementation of the Pregnancy and Lactation Labeling Rule (PLLR).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on April 4, 2019 for DMPP and OPDP to provide a review of the Applicant's proposed MGs for KEPPRA (levetiracetam) tablets, oral solution, and KEPPRA XR (levetiracetam) extended-release tablets.

2 MATERIAL REVIEWED

- Draft KEPPRA and KEPPRA XR (levetiracetam) MGs received on December 21, 2019 and received by DMPP and OPDP on September 11, 2019.
- Draft KEPPRA and KEPPRA XR (levetiracetam) Prescribing Information (PI) received on December 21, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 11, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG documents using the Arial font, size 10.

In our collaborative review of the MGs we have:

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MGs are free of promotional language or suggested revisions to ensure that it is free of promotional language

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/s/

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DHARA SHAH
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LASHAWN M GRIFFITHS
09/24/2019 09:55:29 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 24, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 021035/S-102 NDA 021505/S-042 NDA 021872/S-028 NDA 022285/S-028
Product Name and Strength:	Keppra (levetiracetam) tablets, 250 mg, 500 mg, 750 mg, 1000 mg Keppra (levetiracetam) oral solution, 100 mg/mL Keppra (levetiracetam) injection, 500 mg/5 mL (100 mg/mL) Keppra XR (levetiracetam) extended-release tablets, 500 mg, 750 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	UCB, Inc. (UCB)
FDA Received Date:	December 21, 2018
OSE RCM #:	2019-434
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 REASON FOR REVIEW

UCB, Inc. (UCB) submitted supplements for Keppra (levetiracetam) to: 1) expand the approved indication to include monotherapy in treatment of partial-onset seizures (POS), and 2) revise labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) requirements. Subsequently, the Division of Neurology Products (DNP) requested that we review the revised Keppra prescribing information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 EVALUATION

Our evaluation of the proposed revisions to the Keppra PI and MG did not identify areas of vulnerability that may lead to medication errors.

As part of our review, we considered whether the expansion of the indication or the PLLR conversion would require revisions to the carton labeling or container labels to ensure consistency and decrease risk of confusion and medication errors. We note no changes were proposed or required to the name, strength, dosing, or route of administration because of the proposed changes. As such, our evaluation did not identify any necessary revisions to the carton labeling or container labels at this time.

4 CONCLUSION

The proposed revisions to the Keppra PI and MG are acceptable from a medication safety perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Keppra that UCB, Inc. submitted on December 21, 2018.

Table 2. Relevant Product Information for Keppra	
Initial Approval Date	November 30, 1999 (250 mg, 500 mg, 750 mg tablets) July 15, 2003 (100 mg/mL oral solution) January 6, 2006 (1000 mg tablets) July 31, 2006 (100 mg/mL injection) September 12, 2008 (500 mg, 750 mg extended-release tablets)
Active Ingredient	Levetiracetam
Indication	Tablets, oral solution, and injection Adjunctive therapy in the treatment of: • Partial onset seizures (POS) • Myoclonic seizures • Primary generalized tonic-clonic seizures Extended-release tablets Adjunctive therapy in the treatment of: • Partial onset seizures (POS) All dosage forms (Proposed) Monotherapy in the treatment of POS
Route of Administration	Oral
Dosage Form	Tablet Oral solution Injection Extended-release tablets
Strength	Tablets: 250 mg, 500 mg, 750 mg, 1000 mg Oral solution: 100 mg/mL Injection: 500 mg/5 mL (100 mg/mL) Extended release tablets: 500 mg, 750 mg

Dose and Frequency	Tablets, Oral solution, and Injection Partial-Onset Seizures • 1 Month to < 6 Months: 7 mg/kg twice daily; increase by 7 mg/kg twice daily every 2 weeks to recommended dose of 21 mg/kg twice daily (2.2) • 6 Months to < 4 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 25 mg/kg twice daily (2.2) • 4 Years to < 16 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily (2.2) • Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to a recommended dose of 1500 mg twice daily (2.2) Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older • 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.3) Primary Generalized Tonic-Clonic Seizures • 6 Years to < 16 Years: 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily (2.4) • Adults 16 Years and Older: 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.4) Adult Patients with Impaired Renal Function • Dose adjustment is recommended, based on the patient's estimated creatinine clearance (2.5, 8.6) Extended-release tablets Initiate treatment with a dose of 1000 mg once daily; increase by 1000 mg every 2 weeks to a maximum recommended dose of 3000 mg once daily (2)
How Supplied	Tablets: 250 mg, 500 mg, 750 mg (bottles of 120 tablets) 1000 mg (bottles of 60 tablets) Oral solution: 100 mg/mL (bottles containing 16 fl. oz.) Injection: 500 mg/5 mL single-dose vial (carton of 10 vials) Extended-release tablets: (bottles of 60 extended release tablets)
Storage	Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
Container Closure	HDPE bottles (tablets, oral solution, extended-release tablets) Glass vial (injection)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 18, 2019, we searched for previous DMEPA reviews using the terms, Keppra and levetiracetam. Our search did not identify any previous reviews relevant to this current review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Keppra labeling submitted by UCB, Inc. on December 21, 2018

- Prescribing Information and Medication Guide (Images not shown) for Keppra tablets and oral solution,[b] and extended-release tablets[c]
- Prescribing Information (Image not Shown) for Keppra injection.[d]

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[b] Available in EDR via: \\cdsesub1\evsprod\nda021035\0061\m1\us\114-labeling\draft\labeling\cir-high-201814-sub-ir.docx

[c] Available in EDR via: \\cdsesub1\evsprod\nda022285\0057\m1\us\114-labeling\draft\labeling\cir-high-201814-sub-xr.docx

[d] Available in EDR via: \\cdsesub1\evsprod\nda021872\0069\m1\us\114-labeling\draft\labeling\cir-high-201814-sub-iv.docx

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
06/24/2019 03:39:05 PM

BRIANA B RIDER
06/24/2019 05:28:13 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21035Orig1s102

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21035/S-102
NDA 21505/S-42
NDA 21872/S-28
NDA 22285/S-28

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

UCB, Inc.
Attention: Queen Arukwe, MS, RAC
Regulatory Strategic Partnership Lead
8010 Arco Corporate Drive
Suite 100
Raleigh, NC 27617

Dear Ms. Arukwe:

Please refer to your supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for the following:

NDA Number/ Supplement Number	Drug Product	Submitted on:	Received on:
21035/S-102	Keppra (levetiracetam) tablets	December 21, 2018	December 21, 2018
21505/S-42	Keppra (levetiracetam) oral solution		
21872/S-28	Keppra (levetiracetam) injection		
22285/S-28	Keppra XR (levetiracetam) tablets		

We also refer to your amendment dated February 6, 2019.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), these applications are considered filed 60 days after the date we received your applications. The review classification for these applications is **Standard**. Therefore, the user fee goal date is October 21, 2019.

We are reviewing your applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g.,

submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 21, 2019. This date conforms to the 21st Century Review timeline for your applications.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the applications and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed prescribing information (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the prescribing information (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your applications, you are exempt from this requirement.

If you have any questions, call Heather Bullock, Regulatory Project Manager, at 301-796-1126.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
03/05/2019 07:27:22 AM
Signed for Dr. Dunn.