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NDA 21872/S-012 & S-013
Keppra Injection
FDA Approved Labeling text dated Jul 2013

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KEPPRA® (levetiracetam) injection for intravenous use
Initial U.S. Approval: 1999

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

Dosage and Administration, Partial Onset Seizures (2.6)	[07/2013]
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.7)	[07/2013]

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

KEPPRA injection is an antiepileptic drug indicated for adjunct therapy in adults (≥16 years of age) with the following seizure types when oral administration of KEPPRA is temporarily not feasible:

- Partial Onset Seizures (1.1)
- Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy (1.2)
- Primary Generalized Tonic-Clonic Seizures (1.3)

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

KEPPRA injection should be diluted in 100 mL of a compatible diluent and administered intravenously as a 15-minute infusion (2.1).

Initial Exposure to KEPPRA (2.2):

- Partial Onset Seizures: 1000 mg/day, given as twice-daily dosing (500 mg twice daily), increased as needed and as tolerated in increments of 1000 mg/day additional every 2 weeks to a maximum recommended daily dose of 3000 mg.
- Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy: 1000 mg/day, given as twice-daily dosing (500 mg twice daily), increased 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.
- Primary Generalized Tonic-Clonic Seizures: Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Dosage should be increased 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.

Replacement Therapy (2.3):
When switching from oral KEPPRA, the initial total daily intravenous dosage of KEPPRA should be equivalent to the total daily dosage and frequency of oral KEPPRA. At the end of the intravenous treatment period, the patient may be switched to KEPPRA oral administration at the equivalent daily dosage and frequency of the intravenous administration.

See full prescribing information for dosing instructions (2.5), adult patients with impaired renal function (2.6), and compatibility and stability (2.7).

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

- 500 mg/5 mL single-use vial (3)

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

- None (4)

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

- Psychiatric Reactions: Behavioral abnormalities including psychotic symptoms, suicidal ideation, irritability, and aggressive behavior have been observed. Monitor patients for psychiatric signs and symptoms (5.1)
- Somnolence and Fatigue: Monitor patients for these symptoms and advise patients not to drive or operate machinery until they have gained sufficient experience on KEPPRA (5.2)
- Withdrawal Seizures: KEPPRA must be gradually withdrawn. (5.5)

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

- Most common adverse reactions (incidence in KEPPRA-treated patients is ≥5% more than in placebo-treated patients) include: somnolence, asthenia, infection, and dizziness (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 (5.7, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [07/2013]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 3343504

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1 INDICATIONS AND USAGE

KEPPRA injection is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible.

1.1 Partial Onset Seizures

KEPPRA is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

KEPPRA is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy.

1.3 Primary Generalized Tonic-Clonic Seizures

KEPPRA is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.

2 DOSAGE AND ADMINISTRATION

2.1 General Information

KEPPRA injection is for intravenous use only and must be diluted prior to administration. KEPPRA injection (500 mg/5 mL) should be diluted in 100 mL of a compatible diluent [*see Dosage and Administration (2.7)*] and administered intravenously as a 15-minute IV infusion.

Product with particulate matter or discoloration should not be used.

Any unused portion of the KEPPRA injection vial contents should be discarded.

2.2 Initial Exposure to KEPPRA

KEPPRA can be initiated with either intravenous or oral administration.

Partial Onset Seizures
In clinical trials of oral KEPPRA, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice-daily dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose [*see Clinical Studies (14.1)*], a consistent increase in response with increased dose has not been shown.

Treatment should be initiated 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. Doses greater than 3000 mg/day have been used in open-label studies with KEPPRA tablets for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy
Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Dosage should be increased 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.

Primary Generalized Tonic-Clonic Seizures
Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Dosage should be increased 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.

2.3 Replacement Therapy

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When switching from oral KEPPRA, the initial total daily intravenous dosage of KEPPRA should be equivalent to the total daily dosage and frequency of oral KEPPRA and should be administered as a 15-minute intravenous infusion following dilution in 100 mL of a compatible diluent.

2.4 Switching to Oral Dosing

At the end of the intravenous treatment period, the patient may be switched to KEPPRA oral administration at the equivalent daily dosage and frequency of the intravenous administration.

2.5 Dosing Instructions

KEPPRA injection is for intravenous use only and must be diluted prior to administration. One vial of KEPPRA injection contains 500 mg levetiracetam (500 mg/5 mL). See Table 1 for the recommended preparation and administration of KEPPRA injection to achieve a dose of 500 mg, 1000 mg, or 1500 mg.

Table 1: Preparation And Administration Of KEPPRA Injection

Dose	Withdraw Volume	Volume of Diluent	Infusion Time
500 mg	5 mL (5 mL vial)	100 mL	15 minutes
1000 mg	10 mL (two 5 mL vials)	100 mL	15 minutes
1500 mg	15 mL (three 5 mL vials)	100 mL	15 minutes

For example, to prepare a 1000 mg dose, dilute 10 mL of KEPPRA injection in 100 mL of a compatible diluent [*see Dosage and Administration (2.7)*] and administer intravenously as a 15-minute infusion.

2.6 Adult Patients with Impaired Renal Function

KEPPRA dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in Table 2. 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:

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

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

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

Table 2: Dosing Adjustment Regimen For Adult Patients With Impaired Renal Function

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.

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2.7 Compatibility and Stability

KEPPRA injection was found to be physically compatible and chemically stable when mixed with the following diluents and antiepileptic drugs for at least 24 hours and stored in polyvinyl chloride (PVC) bags at controlled room temperature 15-30˚C (59-86˚F).

Diluents
Sodium chloride (0.9%) injection, USP
Lactated Ringer's injection
Dextrose 5% injection, USP

Other Antiepileptic Drugs
Lorazepam
Diazepam
Valproate sodium

There is no data to support the physical compatibility of KEPPRA injection with antiepileptic drugs that are not listed above.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

3 DOSAGE FORMS AND STRENGTHS

One vial of KEPPRA injection contains 500 mg levetiracetam (500 mg/5 mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Psychiatric Reactions

In some patients KEPPRA causes behavioral abnormalities. The incidences of behavioral abnormalities in the myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult partial onset seizure studies.

A total of 13.3% of adult KEPPRA-treated patients compared to 6.2% of placebo patients experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, and nervousness).

A total of 1.7% of adult KEPPRA-treated patients discontinued treatment due to behavioral adverse events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of adult KEPPRA-treated patients and in 0.5% of placebo patients.

One percent of adult KEPPRA-treated patients experienced psychotic symptoms compared to 0.2% of placebo patients.

Two (0.3%) adult KEPPRA-treated 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.

The above psychiatric signs and symptoms should be monitored.

5.2 Somnolence and Fatigue

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In some patients, KEPPRA causes somnolence and fatigue. The incidences of somnolence and fatigue provided below are from controlled adult partial onset seizure studies. In general, the incidences of somnolence and fatigue in the myoclonic and primary generalized tonic-clonic studies were comparable to those of the adult partial onset seizure studies.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.8% of KEPPRA-treated patients reported somnolence, compared to 8.4% of placebo 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 the 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 patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.7% of KEPPRA-treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued due to asthenia in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced due to asthenia.

Somnolence and asthenia 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 adversely affects their ability to drive or operate machinery.

5.3 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with levetiracetam. 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 levetiracetam 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.

5.4 Coordination Difficulties

Coordination difficulties were only observed in the adult partial onset seizure studies. A total of 3.4% of adult KEPPRA-treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued KEPPRA treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the 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.

5.5 Withdrawal Seizures

Antiepileptic drugs, including KEPPRA, should be withdrawn gradually to minimize the potential of increased seizure frequency.

5.6 Hematologic Abnormalities

Partial Onset Seizures

Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 10^6/mm^3), 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 treated and 1.8% of placebo patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤1.0 x 10^9/L) decreased neutrophil count. Of the 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.

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Juvenile Myoclonic Epilepsy

Although there were no obvious hematologic abnormalities observed in patients with JME, the limited number of patients makes any conclusion tentative. The data from the partial seizure patients should be considered to be relevant for JME patients.

5.7 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:

- Psychiatric Reactions [*see Warnings and Precautions (5.1)*]
- Somnolence and Fatigue [*see Warnings and Precautions (5.2)*]
- Serious Dermatological Reactions [*see Warnings and Precautions (5.3)*]
- Coordination Difficulties [*see Warnings and Precautions (5.4)*]
- Withdrawal Seizures [*see Warnings and Precautions (5.5)*]
- Hematologic Abnormalities [*see Warnings and Precautions (5.6)*]
- Seizure Control During Pregnancy [*see Warnings and Precautions (5.7)*]

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.

The adverse reactions that result from KEPPRA injection use include all of those reported for KEPPRA tablets and oral solution. Equivalent doses of intravenous (IV) levetiracetam and oral levetiracetam result in equivalent C_{max}, C_{min}, and total systemic exposure to levetiracetam when the IV levetiracetam is administered as a 15 minute infusion.

The prescriber should be aware that the adverse reaction incidence figures in the following tables, obtained when KEPPRA was added to concurrent AED therapy, cannot be used to predict the frequency of adverse reactions in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical trials. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse reaction incidences in the population studied.

Partial Onset Seizures

In controlled clinical studies using KEPPRA tablets in adults with partial onset seizures, the most frequently reported 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 frequently reported adverse reactions in adults experiencing partial onset seizures, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with KEPPRA.

Table 4 lists adverse reactions that occurred in at least 1% of adult epilepsy patients treated with KEPPRA tablets participating 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. Adverse reactions were usually mild to moderate in intensity.

Table 4: Incidence (%) Of Adverse Reactions In Placebo-Controlled, Add-On Studies In Adults Experiencing Partial Onset Seizures By Body System (Adverse Reactions Occurred In At Least 1% Of KEPPRA-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

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Body System/ Adverse Reaction	KEPPRA (N=769) %	Placebo (N=439) %
Body as a Whole		
Asthenia	15	9
Headache	14	13
Infection	13	8
Pain	7	6
Digestive System		
Anorexia	3	2
Nervous System		
Somnolence	15	8
Dizziness	9	4
Depression	4	2
Nervousness	4	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Hostility	2	1
Paresthesia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Diplopia	2	1

In controlled adult clinical studies using KEPPRA tablets, 15% of patients receiving KEPPRA and 12% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. Table 5 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 5: Adverse Reactions That Most Commonly Resulted In Discontinuation Or Dose Reduction That Occurred More Frequently In KEPPRA-Treated Patients In Placebo-Controlled Studies In Adult Patients Experiencing Partial Onset Seizures

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

Myoclonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from that seen in patients with partial 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 using KEPPRA tablets in patients with myoclonic seizures, the most frequently reported adverse reactions in patients using KEPPRA in combination with other AEDs, for events with rates greater than placebo, were somnolence, neck pain, and pharyngitis.

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Table 6 lists adverse reactions that occurred in at least 5% of juvenile myoclonic epilepsy patients experiencing myoclonic seizures treated with KEPPRA tablets and were numerically more common than in patients treated with placebo. In this study, either KEPPRA or placebo was added to concurrent AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 6: Incidence (%) Of Adverse Reactions In A Placebo-Controlled, Add-On Study In Patients With Myoclonic Seizures By Body System (Adverse Reactions Occurred In At Least 5% Of KEPPRA-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ Adverse Reaction	**KEPPRA (N=60) %**	**Placebo (N=60) %**
Ear and labyrinth disorders		
Vertigo	5	3
Infections and infestations		
Pharyngitis	7	0
Influenza	5	2
Musculoskeletal and connective tissue disorders		
Neck pain	8	2
Nervous system disorders		
Somnolence	12	2
Psychiatric disorders		
Depression	5	2

In the placebo-controlled study using KEPPRA tablets, 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 7.

Table 7: Adverse Reactions That Resulted In Discontinuation Or Dose Reduction That Occurred More Frequently In KEPPRA-Treated Patients In The 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 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 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 primary generalized tonic-clonic (PGTC) seizures, the most frequently reported adverse reaction associated with the use of KEPPRA in combination with other AEDs, for events with rates greater than placebo was nasopharyngitis.

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Table 8 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. Adverse reactions were usually mild to moderate in intensity.

Table 8: Incidence (%) Of Adverse Reactions In A Placebo-Controlled, Add-On Study In Patients 4 Years Of Age And Older With PGTC Seizures By MedDRA System Organ Class (Adverse Reactions Occurred In At Least 5% Of KEPPRA-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ Adverse Reaction	**KEPPRA (N=79) %**	**Placebo (N=84) %**
Gastrointestinal disorders		
Diarrhea	8	7
General disorders and administration site conditions		
Fatigue	10	8
Infections and infestations		
Nasopharyngitis	14	5
Psychiatric disorders		
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 5 and 7).

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

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 experience reports 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.

In addition to the adverse reactions listed above [*see Adverse Reactions (6.1)*], the following adverse events have been reported in patients receiving marketed KEPPRA worldwide. The listing is alphabetized: abnormal liver function test, choreoathetosis, dyskinesia, erythema multiforme, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), thrombocytopenia, and weight loss. Alopecia has been reported with KEPPRA use; recovery was observed in majority of cases where KEPPRA was discontinued.

7 DRUG INTERACTIONS

No significant pharmacokinetic interactions were observed between levetiracetam or its major metabolite and concomitant medications via human liver cytochrome P450 isoforms, epoxide hydrolase, UDP-glucuronidation enzymes, P-glycoprotein, or renal tubular secretion [*see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

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8.1 Pregnancy

Keppra levels may decrease during pregnancy [*see Warnings and Precautions (5.7)*].

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. KEPPRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of levetiracetam to female rats throughout pregnancy and lactation led to increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Oral administration of levetiracetam to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day.

When levetiracetam was administered orally to pregnant rats during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study.

Treatment of rats during the last third 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).

Pregnancy Registries

To provide information regarding the effects of in utero exposure to KEPPRA, physicians are advised to recommend that pregnant patients taking KEPPRA enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by the patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes associated with pregnant women being treated with all UCB antiepileptic drugs, including KEPPRA. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling 1-888-537-7734 (toll free).

8.2 Labor and Delivery

The effect of KEPPRA on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from KEPPRA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of KEPPRA injection in patients below the age of 16 years have not been established.

8.5 Geriatric Use

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There were 347 subjects in clinical studies of levetiracetam 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 Use in Patients with Impaired Renal Function

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance [*see Clinical Pharmacology (12.3)*]. Dosage adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis [*see Dosage and Administration (2.6)*].

10 OVERDOSAGE

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

The highest known dose of oral 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.

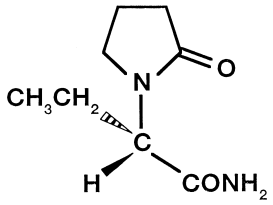
10.3 Hemodialysis

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 injection is an antiepileptic drug available as a clear, colorless, sterile solution (100 mg/mL) for intravenous administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ 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

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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 injection contains 100 mg of levetiracetam per mL. It is supplied in single-use 5 mL vials containing 500 mg levetiracetam, water for injection, 45 mg sodium chloride, and buffered at approximately pH 5.5 with glacial acetic acid and 8.2 mg sodium acetate trihydrate. KEPPRA injection must be diluted prior to intravenous infusion [*see Dosage and Administration (2.1)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepines, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, *in vitro* studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells.

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 synaptic vesicle protein 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

Equivalent doses of intravenous (IV) levetiracetam and oral levetiracetam result in equivalent C_{max}, C_{min}, and total systemic exposure to levetiracetam when the IV levetiracetam is administered as a 15 minute infusion.

The pharmacokinetics of levetiracetam have been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment.

Overview

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Levetiracetam is rapidly and almost completely absorbed after oral administration. Levetiracetam injection and tablets are bioequivalent. The pharmacokinetics of levetiracetam are linear and time-invariant, with low intra- and inter-subject variability. Levetiracetam is not significantly protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renally excreted. Plasma half-life of levetiracetam across studies is approximately 6-8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Distribution

The equivalence of levetiracetam injection and the oral formulation was demonstrated in a bioavailability study of 17 healthy volunteers. In this study, levetiracetam 1500 mg was diluted in 100 mL 0.9% sterile saline solution and was infused over 15 minutes. The selected infusion rate provided plasma concentrations of levetiracetam at the end of the infusion period similar to those achieved at T_{max} after an equivalent oral dose. It is demonstrated that levetiracetam 1500 mg intravenous infusion is equivalent to levetiracetam 3 x 500 mg oral tablets. The time independent pharmacokinetic profile of levetiracetam was demonstrated following 1500 mg intravenous infusion for 4 days with BID dosing. The $AUC_{(0-12)}$ at steady-state was equivalent to AUC_{inf} following an equivalent single dose.

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, route of administration 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 impaired renal function [*see Use in Specific Populations (8.6) and Dosage and Administration (2.6)*].

Special 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
Safety and effectiveness of KEPPRA injection in patients below the age of 16 years have not been established.

Pregnancy
Keppra levels may decrease during pregnancy.

Gender

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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 >80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis [*see Dosage and Administration (2.6)*].

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.

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

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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. The highest dose is 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. 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 mg/m^2 basis.

Mutagenesis

Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay.

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 (6 times the maximum recommended human dose on a mg/m^2 or systemic exposure [AUC] basis).

14 CLINICAL STUDIES

All efficacy trials utilized oral formulations. The recommendation for the parenteral formulation is based upon these studies as well as the demonstration of comparable bioavailability of the oral and the parenteral formulation [*see Pharmacokinetics (12.3)*].

In the following studies, statistical significance versus placebo indicates a p value <0.05.

14.1 Partial Onset Seizures

Effectiveness in Partial Onset Seizures in Adults with Epilepsy

The effectiveness of KEPPRA as adjunctive therapy (added to other antiepileptic drugs) in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial onset seizures

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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 9.

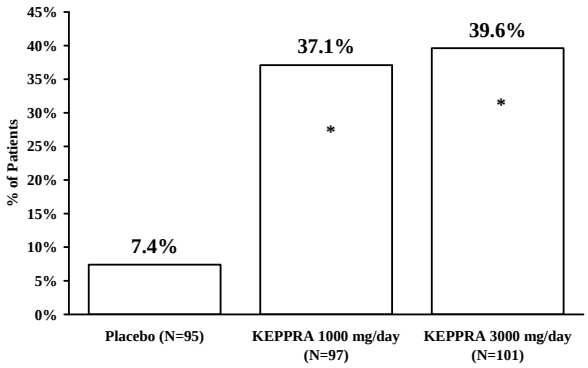
Table 9: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures In Study 1

	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.

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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 10.

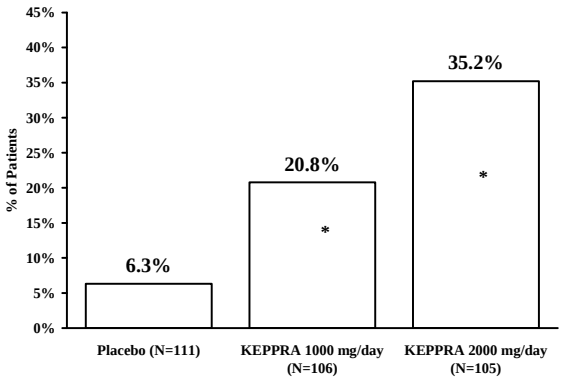
Table 10: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures In Study 2: Period A

	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 11 displays the results of the analysis of Study 3.

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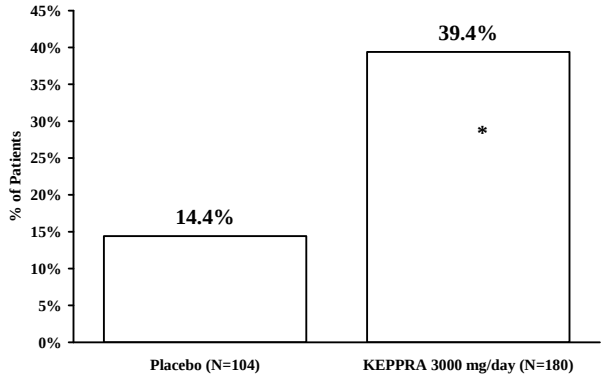
Table 11: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures In Study 3

	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

14.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Effectiveness in Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy (JME)

The effectiveness of KEPPRA as adjunctive therapy (added to other antiepileptic drugs) in patients with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures was established in one multicenter, randomized, double-blind, placebo-controlled study, conducted at 37 sites in 14 countries. Of the 120 patients enrolled, 113 had a diagnosis of confirmed or suspected JME. 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. Table 12 displays the results for the 113 patients with JME in this study.

Table 12: Responder Rate (≥50% Reduction From Baseline) In Myoclonic Seizure Days Per Week For Patients With JME

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

* statistically significant versus placebo

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14.3 Primary Generalized Tonic-Clonic Seizures

The effectiveness of KEPPRA as adjunctive therapy (added to other antiepileptic drugs) in patients with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic (PGTC) seizures was established in one multicenter, randomized, double-blind, placebo-controlled study, 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. 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. 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). There was a statistically significant decrease from baseline in PGTC frequency in the KEPPRA-treated patients compared to the placebo-treated patients.

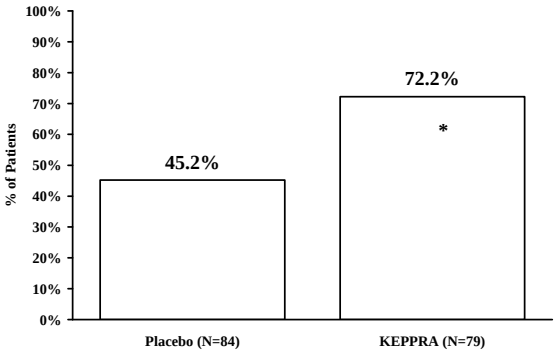
Table 13: Median Percent Reduction From Baseline In PGTC Seizure Frequency Per Week

	Placebo (N=84)	KEPPRA (N=78)
Percentage 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 4.

Figure 4: Responder Rate (≥50% Reduction From Baseline) In PGTC Seizure Frequency Per Week



* statistically significant versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

KEPPRA (levetiracetam) 500 mg/5 mL injection is a clear, colorless, sterile solution. It is supplied in single-use 5 mL vials, available in cartons of 10 vials (NDC 50474-002-63).

16.2 Storage

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

17 PATIENT COUNSELING INFORMATION

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.

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 in rare cases, psychotic symptoms have occurred.

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.

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.

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. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334. Additionally, inform patients they can enroll in the UCB AED Pregnancy Registry and they or their healthcare provider can call 1-888-537-7734 (toll free) [*see Use In Specific Populations (8.1)*].

KEPPRA injection manufactured for
UCB, Inc.
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