

Paper Size: H 50 cm x W 48 cm

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use ROWEEPRA safely and effectively. See full prescribing information for ROWEEPRA.**

**ROWEEPRA (levetiracetam) tablets, for oral use Initial U.S. Approval: 1999**

### INDICATIONS AND USAGE

ROWEEPRA is indicated for adjunctive therapy in the treatment of:

- Partial onset seizures in patients one month of age and older with epilepsy (1.1)
  - 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)
- DOSE AND ADMINISTRATION**-----
- Use the oral solution for pediatric patients with body weight  $\leq$  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

- 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 1,500 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 1,500 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 1,500 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)

### DOSE AND ADMINISTRATION

- 250 mg, 500 mg, 750 mg, and 1,000 mg film-coated, scored tablets (3)

### CONTRAINDICATIONS

None (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 ROWEEPRA (5.3)
- Withdrawal Seizures: ROWEEPRA must be gradually withdrawn (5.6)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq$  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 OWP Pharmaceuticals at 1-800-273-6729 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 (5.9, 8.1)

### See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2016

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### FULL PRESCRIBING INFORMATION

#### INDICATIONS AND USAGE

##### Partial Onset Seizures

ROWEEPRA is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy.

##### Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

ROWEEPRA is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.

##### Primary Generalized Tonic-Clonic Seizures

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

#### DOSE AND ADMINISTRATION

##### Important Administration Instructions

ROWEEPRA is given orally with or without food. The ROWEEPRA 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  $\leq$  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).

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

##### Dosing for Partial Onset Seizures

###### Adults 16 Years and Older

Initiate treatment with a daily dose of 1,000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1,000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3,000 mg. There is no evidence that doses greater than 3,000 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. The effectiveness of lower doses has not been studied.

###### 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 3,000 mg/day.

For ROWEEPRA 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 1,500 mg (750 mg twice daily).

For ROWEEPRA tablet dosing in pediatric patients weighing more than 40 kg, initiate treatment with a daily dose of 1,000 mg/day given as twice daily dosing (500 mg twice daily). Increase the daily dose every 2 weeks by increments of 1,000 mg/day to a maximum recommended daily dose of 3,000 mg (1,500 mg twice daily).

###### Levetiracetam Oral Solution, USP 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:

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

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

Initiate treatment with a dose of 1,000 mg/day, given as twice-daily dosing (500 mg twice daily). Increase the dosage by 1,000 mg/day every 2 weeks to the recommended daily dose of 3,000 mg. The effectiveness of doses lower than 3,000 mg/day has not been studied.

##### Dosing for Primary Generalized Tonic-Clonic Seizures

###### Adults 16 Years and Older

Initiate treatment with a dose of 1,000 mg/day, given as twice-daily dosing (500 mg twice daily). Increase dosage by 1,000 mg/day every 2 weeks to the recommended daily dose of 3,000 mg. The effectiveness of doses lower than

3,000 mg/day has not been adequately studied.

###### Pediatric Patients Ages 6 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). The effectiveness of doses lower than 60 mg/kg/day has not been adequately studied. Patients with body weight  $\leq$  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

ROWEEPRA 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:

$$\text{CLcr} = \frac{140 - \text{age (years)}}{72} \times \text{weight (kg)} \times \begin{cases} 1 & \text{for males} \\ 0.85 & \text{for females} \end{cases}$$

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

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

CLcr (mL/min/1.73m<sup>2</sup>) = ----- x 1.73

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

Group	Creatinine Clearance (mL/min/1.73m <sup>2</sup> )	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 <sup>1</sup>	Every 24 hours <sup>1</sup>

<sup>1</sup> Following dialysis, a 250 to 500 mg supplemental dose is recommended.

#### 3 DOSE FORMS AND STRENGTHS

ROWEEPRA 250 mg tablets are blue to light blue, oval, film-coated tablets, bisect debossed with logo "TL" and "622" on one side. The other side is blank.

ROWEEPRA 500 mg tablets are yellow to light yellow, oval, film-coated tablets, bisect debossed with logo "OWP" and "500" on one side. The other side is blank.

ROWEEPRA 750 mg tablets are orange to light orange, oval, film-coated tablets, bisect debossed with logo "OWP" and "750" on one side. The other side is blank.

ROWEEPRA 1000 mg tablets are white, oval, film-coated tablets, bisect debossed with logo "OWP" and "1000" on one side. The other side is blank.

#### 4 CONTRAINDICATIONS

None.

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Behavioral Abnormalities and Psychotic Symptoms

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

##### Behavioral abnormalities

In clinical studies, 13% of adult levetiracetam-treated patients and 38% of pediatric levetiracetam-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 levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in levetiracetam-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 levetiracetam-treated patients compared to 0% of placebo-treated patients.

In clinical studies, 1.7% of adult levetiracetam-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 levetiracetam-treated patients and in 0.5% of placebo-treated patients. Overall, 11% of levetiracetam-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 levetiracetam-treated adult patients, 2% of levetiracetam-treated pediatric patients 4 to 16 years of age, and 17% of levetiracetam-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 levetiracetam in pediatric patients 4 to 16 years of age, 1.6% of levetiracetam-treated patients experienced paranoia, compared to 0% of placebo-treated patients. In the same study, 3.1% of levetiracetam-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%) levetiracetam-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.

##### Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including ROWEEPRA, 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.

##### Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 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 ROWEEPRA 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.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

##### Somnolence and Fatigue

ROWEEPRA 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 levetiracetam 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 levetiracetam-treated patients reported somnolence, compared to 8% of placebo-treated patients. There was no clear dose response up to 3,000 mg/day. In a study with these patients, 45% of patients receiving 1,000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of levetiracetam-treated patients, compared to 0% in the placebo group. About 3% of levetiracetam-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo-treated patients. In 1.4% of levetiracetam-treated patients and 0.9% of placebo-treated patients, the dose was reduced, while 0.3% of the levetiracetam-treated patients were hospitalized due to somnolence.

**Asthenia**

In controlled clinical studies of adult patients with epilepsy experiencing partial onset seizures, 15% of levetiracetam-treated patients reported asthenia, compared to 9% of placebo-treated patients. Treatment was discontinued due to asthenia in 0.8% of levetiracetam-treated patients as compared to 0.5% of placebo-treated patients. In 0.5% of levetiracetam-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.

##### 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 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 rechallenges with levetiracetam has also been reported. Levetiracetam 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.

##### Coordination Difficulties

ROWEEPRA may cause coordination difficulties.

In controlled clinical studies in adult patients with partial onset seizure studies, 3.4% of adult levetiracetam-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 levetiracetam treatment due to ataxia, compared to 0% of placebo-treated patients. In 0.7% of levetiracetam-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to coordination difficulties, while one of the levetiracetam-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 levetiracetam to gauge whether it could adversely affect their ability to drive or operate machinery.

##### Withdrawal Seizures

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

##### Hematologic Abnormalities

ROWEEPRA can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in red blood cell (RBC) counts, hemoglobin, and hematocrit, and increases in eosinophil counts. Decreased white blood cell (WBC) and neutrophil counts also occurred in clinical trials. Cases of agranulocytosis have been reported in the postmarketing setting.

##### Partial Onset Seizures

**Adults**

Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 10<sup>12</sup>/mm<sup>3</sup>), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam-treated patients in controlled trials.

A total of 3.2% of levetiracetam-treated and 1.8% of placebo-treated patients had at least one possibly significant ( $\leq$  2.8 x 10<sup>12</sup>/L) decreased WBC, and 2.4% of levetiracetam-treated and 1.4% of placebo-treated patients had at least one possibly significant ( $\leq$  1.0 x 10<sup>9</sup>/L) decreased neutrophil count. Of the levetiracetam-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 levetiracetam-treated patients as compared to placebo. The mean decreases from baseline in the levetiracetam-treated group were -0.4 x 10<sup>12</sup>/L and -0.3 x 10<sup>9</sup>/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in levetiracetam-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

In the controlled trial, more levetiracetam-treated patients had a possibly clinically significant abnormally low WBC value (3% of levetiracetam-treated patients versus 0% of placebo-treated patients), however, there was no apparent difference between treatment groups with respect to neutrophil count (5% of levetiracetam-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 levetiracetam-treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant ( $\geq$ 10% or  $\geq$ 0.7X10<sup>9</sup>/L).

##### 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 levetiracetam-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 levetiracetam 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.

##### 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.

##### ADVERSE REACTIONS

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

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Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ROWEEPRA, 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

The safety and effectiveness of levetiracetam in the adjunctive treatment of partial onset seizures in pediatric patients age 1 month to 16 years old with epilepsy have been established [see *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 levetiracetam as adjunctive 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 levetiracetam as adjunctive therapy in 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)].

A 3-month, randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of levetiracetam as adjunctive therapy in 98 (levetiracetam 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 Letter-R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no substantial 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 levetiracetam-treated patients in aggressive behavior, one of the eight syndrome scores [see *Warnings and Precautions* (5.1)]. Studies of levetiracetam in juvenile rats (dosing from 4g through day 52 of age) and dogs (dosing from week 3 through week 7 of age) at doses of up to 1,800 mg/kg/day (approximately 7.4 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m<sup>2</sup> basis) did not indicate a potential for age-specific toxicity.

#### 8.5 Geriatric Use

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 levetiracetam 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 levetiracetam received in the clinical development program was 6,000 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 levetiracetam overdoses in postmarketing use.

##### 10.2 Management of Overdose

There is no specific antidote for overdose with levetiracetam. 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 levetiracetam.

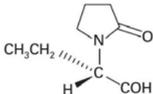
##### 10.3 Hemodialysis

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

ROWEEPRA is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow), 750 mg (orange), and 1,000 mg (white) tablets for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-[S]- $\alpha$ -ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>O, and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:



Levetiracetam, USP 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.)

ROWEEPRA tablets contain the labeled amount of levetiracetam, USP. Inactive ingredients: colloidal silicon dioxide, corn starch, hypromellose, lactose monohydrate, magnesium stearate, povidone, titanium dioxide, triacetin 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

#### 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 brief 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  $\mu$ M 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 SV2A is not fully 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 levetiracetam on QTc: prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of levetiracetam (1,000 mg or 5,000 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

###### 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<sub>max</sub> by 20% and delays T<sub>max</sub> by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5,000 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, ucbl057 (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  $\pm$  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 ucbl057 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 (ucbl057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a T<sub>max</sub> of about 1 hour and a t<sub>1/2</sub> 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.

###### Gender

Levetiracetam C<sub>max</sub> 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 (CL<sub>r</sub> = 50-80 mL/min), 50% in the moderate group (CL<sub>r</sub> = 30-50 mL/min) and 60% in the severe renal impairment group (CL<sub>r</sub> <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 (CL<sub>r</sub> >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<sub>max</sub> 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

Levetiracetam (3,000 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

Levetiracetam (1,500 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, ucbl057.

###### Other Antiepileptic Drugs

Potential drug interactions between levetiracetam 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

Levetiracetam (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

Levetiracetam (1,000 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

Levetiracetam (1,000 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 1,000 mg twice daily. C<sub>max</sub> of the metabolite, ucbl057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucbl057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucbl057. The effect of levetiracetam 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 1,800 mg/kg/day. The highest dose is 6 times the maximum recommended daily human dose (MRHD) of 3,000 mg on a mg/m<sup>2</sup> 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 4,000 mg/kg/day, lowered to 3,000 mg/kg/day after 45 weeks due to intolerance) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3,000 mg/kg/day) is approximately 5 times the MRHD on a mg/m<sup>2</sup> 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 (ucbl057) 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 1,800 mg/kg/day (6 times the maximum recommended human dose on a mg/m<sup>2</sup> or systemic exposure [AUC] basis).

#### 14 CLINICAL STUDIES

##### 14.1 Partial Onset Seizures

###### Effectiveness in Partial Onset Seizures in Adults with Epilepsy

The effectiveness of levetiracetam 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 with or without secondary generalization. The tablet formulation was used in all of these studies. In these studies, 904 patients were randomized to placebo, 1,000 mg, 2,000 mg, or 3,000 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 levetiracetam 1,000 mg/day (N=97), levetiracetam 3,000 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  $\geq$ 50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Study 1 are displayed in Table 10.

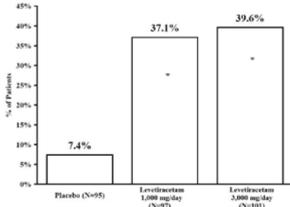
**Table 10: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 1**

	Placebo (N=95)	Levetiracetam 1,000 mg/day (N=97)	Levetiracetam 3,000 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  $\geq$ 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 ( $\geq$ 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 levetiracetam 1,000 mg/day (N=106), levetiracetam 2,000 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  $\geq$ 50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Period A are displayed in Table 11.

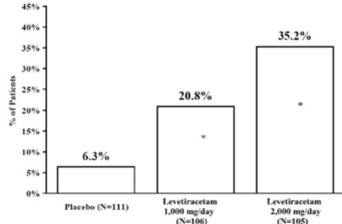
**Table 11: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 2: Period A**

	Placebo (N=111)	Levetiracetam 1,000 mg/day (N=106)	Levetiracetam 2,000 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  $\geq$ 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 ( $\geq$ 50% Reduction from Baseline) in Study 2: Period A**



\*statistically significant versus placebo

The comparison of levetiracetam 2,000 mg/day to levetiracetam 1,000 mg/day for responder rate was statistically significant (P=0.02). Analysis of the trial as a crossover yielded similar results.

###### Study 3

Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing levetiracetam 3,000 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  $\geq$ 50% reduction from baseline in partial onset seizure frequency). Table 12 displays the results of the analysis of Study 3.

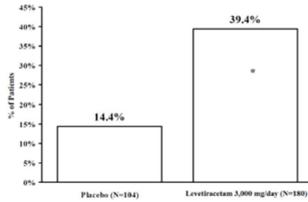
**Table 12: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 3**

	Placebo (N=104)	Levetiracetam 3,000 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  $\geq$ 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 ( $\geq$ 50% Reduction from Baseline) in Study 3**



\*statistically significant versus placebo

###### Effectiveness in Partial Onset Seizures in Pediatric Patients 4 Years to 16 Years with Epilepsy

The effectiveness of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) 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 levetiracetam or placebo. The enrolled population included 198 patients (levetiracetam 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, levetiracetam 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  $\geq$  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)	Levetiracetam (N=101)
Percent reduction in partial seizure frequency over placebo	–	26.8%*