

MEDICATION GUIDE

Levetiracetam Oral Solution USP (lee' ve' ra' se lam)

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

What is the most important information I should know about levetiracetam oral solution?

Like other antiepileptic drugs, levetiracetam oral solution may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

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

Do not stop levetiracetam oral solution without first talking to a healthcare provider. Stopping levetiracetam oral solution suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus).

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

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

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

What is levetiracetam oral solution? Levetiracetam oral solution is a prescription medicine taken by mouth that is used to treat partial-onset seizures in people 1 month of age and older.

Levetiracetam oral solution is a prescription medicine taken by mouth that is used with other medicines to treat:

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

It is not known if levetiracetam oral solution is safe or effective in children under:

- 1 month of age to treat partial-onset seizures
- 12 years of age to treat myoclonic seizures

6 years of age to treat primary generalized tonic-clonic seizures

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

Who should not take levetiracetam oral solution?

Do not take levetiracetam oral solution if you are allergic to levetiracetam.

What should I tell my healthcare provider before starting levetiracetam oral solution?

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

- have or have had depression, mood problems or suicidal thoughts or behavior.
- have kidney problems.
- are pregnant or planning to become pregnant. It is not known if levetiracetam oral solution will harm your unborn baby. You and your healthcare provider will have to decide if you should take levetiracetam oral solution while you are pregnant. If you become pregnant while taking levetiracetam oral solution, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334 or go to <http://www.aedpregnancyregistry.org>. The purpose of this registry is to collect information about the safety of levetiracetam oral solution and other antiepileptic medicine during pregnancy.

are breastfeeding or plan to breastfeed. Levetiracetam can pass into your breast milk. It is not known if the levetiracetam that passes into your breast milk can harm your baby. Talk to your doctor about the best way to feed your baby while you receive levetiracetam oral solution.

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

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

How should I take levetiracetam oral solution?

Take levetiracetam oral solution exactly as your healthcare provider tells you to take it.

Your healthcare provider will tell you how much levetiracetam oral solution to take and when to take it. Levetiracetam oral solution is usually taken 2 times each day.

Size: 400 x 600 mm
Book Folding: 40 x 40 mm
Spec.: 40 GSM Bible paper front & back side printing.
Color : Single (Pantone Black C)
Barcode position and orientation will be changed based on folding size
Note: 2D Barcode to be overprinting at supplier end & it contains our item code, supplier serial number.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEVETIRACETAM ORAL SOLUTION safely and effectively. See full prescribing information for LEVETIRACETAM ORAL SOLUTION.

LEVETIRACETAM oral solution

Initial U.S. Approval: 1999

Indications and Usage (1.1) **RECENT MAJOR CHANGES** 10/2019
Dosage and Administration (2.2, 2.6) 10/2019

INDICATIONS AND USAGE
Levetiracetam oral solution is indicated for the treatment of partial-onset seizures in patients 1 month of age and older (1.1)

Levetiracetam oral solution is indicated as adjunctive therapy for the treatment of:

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

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

Partial-Onset Seizures (monotherapy or adjunctive therapy)

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

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1 INDICATIONS AND USAGE

1.1 Partial-Onset Seizures

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

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy
Levetiracetam oral solution is indicated as adjunctive therapy for the treatment of myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy.

1.3 Primary Generalized Tonic-Clonic Seizures
Levetiracetam oral solution is indicated as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions
Levetiracetam oral solution is given orally with or without food. The levetiracetam oral solution dosing regimen depends on the indication, age group, dosage form (tablets or oral solution), and renal function. Prescribe the oral solution for pediatric patients with body weight <20 kg. Prescribe the oral solution or tablets for pediatric patients with body weight above 20 kg.

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

2.2 Dosing for Partial-Onset Seizures
The recommended dosing for monotherapy and adjunctive therapy is the same, as outlined below.

Adults 16 Years of Age and Older
Initiate treatment with a daily dose of 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.

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 every 2 weeks by increments 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.

Levetiracetam Oral Solution Weight-Based Dosing Calculation For Pediatric Patients
The following calculation should be used to determine the appropriate daily dose of oral solution for pediatric patients:

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

2.3 Dosing for Myoclonic Seizures in Patients 12 Years of Age and Older with Juvenile Myoclonic Epilepsy
Initiate treatment with a dose of 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.

2.4 Dosing for Primary Generalized Tonic-Clonic Seizures
Adults 16 Years of Age 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 6 to <16 Years of Age
Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg twice daily). The effectiveness of doses lower than 60 mg/kg/day has not been adequately studied. Patients with body weight <20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution (see Dosage and Administration (2.1)).

2.5 Dosage Adjustments in Adult Patients with Renal Impairment
Levetiracetam oral solution 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 (CL_{CR}) in mL/min must first be calculated using the following formula:

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

Then CL_{CR} is adjusted for body surface area (BSA) as follows:

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

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

| Group | Creatinine Clearance (mL/min) (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 ^a | Every 24 hours ^a |

^aFollowing dialysis, a 250 to 500 mg supplemental dose is recommended.

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, 6, 6)

DOSE FORMS AND STRENGTHS
100 mg/mL solution (3)

CONTRAINDICATIONS
Known hypersensitivity to levetiracetam; angioedema and anaphylaxis have occurred (4, 5, 4)

WARNINGS AND PRECAUTIONS
Behavioral abnormalities including psychotic symptoms, suicidal ideation, irritability, and aggressive behavior have been observed; monitor patients for psychiatric signs and symptoms (5.1)

Suicidal Behavior and Ideation: Monitor patients for new or worsening depression, suicidal thoughts/behavior, and/or unusual changes in mood or behavior (5.2)

Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam (5.3)

Serious Dermatological Reactions: Discontinue levetiracetam at the first sign of rash unless clearly not drug related (5.5)

Coordination Difficulties: Monitor for ataxia, abnormal gait, and incoordination. Advise patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam (5.6)

Withdrawal Seizures: Levetiracetam must be gradually withdrawn (5.7)

ADVERSE REACTIONS
Most common adverse reactions (incidence >5% more than placebo) include:

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

To report SUSPECTED ADVERSE REACTIONS, contact Helsco Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Pregnancy: Plasma levels of levetiracetam may be decreased and therefore need to be monitored closely during pregnancy. Based on animal data, may cause fetal harm (5.10, 8, 1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 01/2020

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2.6 Discontinuation of Levetiracetam Oral Solution
Avoid abrupt withdrawal from levetiracetam oral solution in order to reduce the risk of increased seizure frequency and status epilepticus (see Warnings and Precautions (5.7)).

3 DOSAGE FORMS AND STRENGTHS
Levetiracetam oral solution USP, 100 mg/mL is a clear, colorless, grape-flavored liquid.

4 CONTRAINDICATIONS
Levetiracetam oral solution is contraindicated in patients with a hypersensitivity to levetiracetam. Reactions have included anaphylaxis and angioedema (see Warnings and Precautions (4, 5)).

5 WARNINGS AND PRECAUTIONS
5.1 Behavioral Abnormalities and Psychotic Symptoms
Levetiracetam may cause behavioral abnormalities and psychotic symptoms. Patients treated with levetiracetam 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 (aggression, agitation, anger, anxiety, apathy, depression, depression, emotional lability, hostility, hyperexcitability, 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 with placebo in 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.

5.2 Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including levetiracetam, 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 is supported by 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 (6 to 100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

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

| Indication | Placebo Patients with Events Per 1,000 Patients | Drugs 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 | 1.9 | 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 levetiracetam or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.3 Somnolence and Fatigue
Levetiracetam may cause somnolence and fatigue. Patients should be monitored for these signs and clinical signs and advise patients 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 where there was no titration, about 45% of patients receiving 4,000 mg/day reported somnolence. The somnolence was considered serious in 0.5% 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.

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

5.5 Serious Dermatological Reactions
Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients treated with levetiracetam. The median time to onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of therapy. Recurrence of serious skin reactions following rechallenge 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.

5.6 Coordination Difficulties
Levetiracetam 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

these reactions are reported voluntarily from a population of uncertain size. It is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

Levetiracetam blood levels may decrease during pregnancy (See *Warnings and Precautions* (5.10)).

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

Data

Human Data

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

Animal Data

When levetiracetam (0, 400, 1,200, or 3,600 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, reduced fetal weights and increased incidence of fetal skeletal variations were observed at the highest dose (3,600 mg/kg/day) in 14 pregnant rats. The no-effect dose for levetiracetam was 400 mg/kg/day. At doses similar to human therapeutic doses (1,200 mg/kg/day) is approximately 4 times the maximum recommended human dose (MRHD) of 3,000 mg on a body surface area (mg/m²) basis.

Oral administration of levetiracetam (0, 200, 600, or 1,800 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and incidence of fetal skeletal variations at the mid and high dose and decreased fetal weights and increased incidence of fetal malformations at the high dose, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m² basis. Oral administration of levetiracetam (0, 70, 350, or 1,800 mg/kg/day) to female rats throughout pregnancy and lactation led to an increased incidence of fetal skeletal variations, reduced fetal body weight, and increased pre- and postnatal mortality. The no-effect dose for adverse effects on pre- and postnatal development was 70 mg/kg/day (5 times the MRHD on a mg/m² basis).

Oral administration of levetiracetam to rats during the latter part of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1,800 mg/kg/day (5 times the MRHD on a mg/m² basis).

8.2 Lactation

Risk Summary

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

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

8.3 Pediatric Use

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

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

The safety and effectiveness of levetiracetam as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established (See *Warnings and Precautions* (5.1)).

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

A 3-month, randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of levetiracetam as adjunctive therapy in 98 levetiracetam-N=44, placebo-N=34 pediatric patients, ages 4 to 16 years old, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter-R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no statistically differences were observed between the placebo and drug treatment 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) 1.0, a standardized tool used to assess a child's competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL-1.0 indicated on average a worsening in levetiracetam-treated patients in aggressive behavior, one of the eight syndrome scores (See *Warnings and Precautions* (5.1)).

Juvenile Animal Toxicity Data

Studies of levetiracetam in juvenile rats (dosed on postnatal days 4 through 52) and dogs (dosed from postnatal weeks 3 through 7) at doses of up to 1,800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m² basis) did not demonstrate adverse effects on postnatal development.

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 Overdose 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, ataxia, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdose 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.

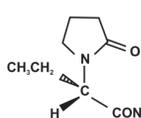
10.3 Hemodialysis

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

Levetiracetam is an antiepileptic drug available as a clear, colorless, grape-flavored liquid (100 mg/mL) for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (1S)-2-ethyl-2-oxo-1-pyrrolidine acetonamide. Its molecular formula is C₁₀H₁₆N₂O₂ 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 (1,040 mg/mL). It is freely soluble in chloroform (653 mg/mL) and in methanol (536 mg/mL), soluble in ethanol (165 mg/mL), sparingly soluble in acetone (57 mg/mL), and practically insoluble in n-hexane. (Solubility limits are expressed as mg/mL solvent.)

Levetiracetam oral solution, USP contains 100 mg of levetiracetam, USP per mL. Inactive ingredients: acesulfame potassium, artificial grape flavor, citric acid monohydrate, glycerin, glyoxylic acid ammonium, methyl parabens, methylparaben, purified water, and sodium citrate dihydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiepileptic 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

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

Absorption and Distribution

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in healthy subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500 to 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, *ucb* 1057 (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 hydrolyzation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 86% 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* 1057 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 to 88 years) with creatinine clearance ranging from 20 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 to 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 to 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 at 1, 2, and 3 times the therapeutic dose (1, 2, and 3 times the MRHD) demonstrated rapid absorption of levetiracetam at all doses with a T_{max} of about 1 hour and a t_{1/2} of 5 hours across the three dosing levels. The pharmacokinetics of levetiracetam were similar 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 in 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 hr) than for adults (7.2 hr) and apparent clearance was faster (1.5 mL/min/kg) than for adults (0.96 mL/min/kg). Population pharmacokinetic analysis showed that body weight was significantly correlated to the clearance of levetiracetam in pediatric patients; clearance increased with an increase in body weight.

Pregnancy

Levetiracetam levels may decrease during pregnancy (See *Warnings and Precautions* (5.10) and *Use in Specific Populations* (8.1)).

Gender

Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearance 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_{CR} = 50 to 80 mL/min), 50% in the moderate group (CL_{CR} = 30 to 50 mL/min) and 60% in the severe renal impairment group (CL_{CR} < 30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance. In acute (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CL_{CR} > 80 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure (See *Dosage and Administration* (2.5)).

Hepatic Impairment

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

Drug Interactions

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

Potential pharmacokinetic interactions of 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.

Phenoyl

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, *ucb* 1057.

Other Antiepileptic Drugs

Potential drug interactions between levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, valproic acid) were also assessed. The pharmacokinetics 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 oral contraceptive efficacy is not expected. 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 (EOG) 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_{max} of the metabolite, *ucb* 1057, 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* 1057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of *ucb* 1057. The effect of levetiracetam on probenecid was not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Rates were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300, and 1,800 mg/kg/day. Plasma exposure (AUC) at the highest dose was approximately 6 times that in humans at the maximum recommended daily human dose (MRHD) of 3,000 mg. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4,000 mg/kg/day, lowered to 2,000 mg/kg/day after 45 weeks due to intolerance) resulted in 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 body surface area (mg/m²) basis.

Mutagenesis

Levetiracetam was negative in *in vitro* (Ames, chromosomal aberration in mammalian cells) and *in vivo* (mouse micronucleus) assays. The major human metabolite of levetiracetam (*ucb* 1057) was negative in *in vitro* (Ames, mouse lymphoma) assays.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1,800 mg/kg/day, which were associated with plasma exposures (AUC) up to approximately 6 times that in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Partial-Onset Seizures

The effectiveness of levetiracetam in the treatment of partial-onset seizures in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial-onset seizures with or without secondary generalization. The tablet formulation was used in all these studies. In these studies, patients were randomized to placebo, levetiracetam 3,000 mg/day, or levetiracetam 1,000 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 3,000 mg/day (N=101) and placebo (N=97) 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) within the two treatment groups (x-axis) is presented in Figure 4.

responder rate (incidence of patients with ≥50% reduction from baseline in partial-onset seizure frequency). The results of the analysis of Study 1 are displayed in Table 10.

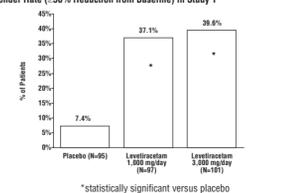
Table 10: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 1

| | Placebo (N=95) | 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 ≥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



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 ≥50% reduction from baseline in partial-onset seizure frequency). The results of the analysis of Period A are displayed in Table 11.

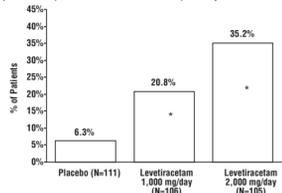
Table 11: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 2: Period A

| | 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 ≥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 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 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 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 ≥50%