AUROMEDICS Pharma LLC

Levetiracetam Injection, USP

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LEVETIRACETAM Injection, USP for Intravenous Use

Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2, 1.3)	10/2014
Dosage and Administration (2.1, 2.3, 2.6)	10/2014
Warnings and Precautions (5.1, 5.2, 5.7)	10/2014
Warnings and Precautions, Hematologic Abnormalities (5.6)	03/2015

INDICATIONS AND USAGE

Levetiracetam injection, USP is indicated for adjunctive therapy, as an alternative when oral administration is temporarily not feasible, in the treatment of:

- Partial onset seizures in patients 1 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)

DOSAGE AND ADMINISTRATION

Levetiracetam injection is for intravenous use only (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 (2.1)
- 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 (2.1)
- 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 (2.1)
- Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to a recommended dose of 1500 mg twice daily (2.1)

Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older

- 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.2)

Primary Generalized Tonic Clonic Seizures

- 6 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 (2.3)
- Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.3)

Switching From or To Oral Levetiracetam

When switching from oral levetiracetam, the initial total daily dosage/frequency of levetiracetam injection should be equivalent to those of oral levetiracetam.

At the end of the intravenous treatment period, the patient may be switched to levetiracetam oral administration at the equivalent daily dosage and frequency (2.4, 2.5)

See full prescribing information for preparation and administration instructions (2.6) and dosage adjustment in adult patients with renal impairment (2.7)

DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/5 mL (100 mg/mL) single use vial (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)
- Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam (5.2)
- Withdrawal Seizures: Levetiracetam must be gradually withdrawn. (5.5)

ADVERSE REACTIONS

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

- Adults: 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 AuroMedics Pharma LLC at 1 866 850 2876 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 (5.8, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Partial Onset Seizures

Levetiracetam injection, USP is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy. Levetiracetam injection, USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Levetiracetam injection, USP 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. Levetiracetam injection, USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

1.3 Primary Generalized Tonic Clonic Seizures

Levetiracetam injection, USP 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. Levetiracetam injection, USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing for Partial Onset Seizures

Adults 16 Years and Older

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

Pediatric Patients

1 Month to < 6 Months

Initiate treatment with a daily dose of 14 mg/kg in 2 divided doses (7 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 14 mg/kg to the recommended daily dose of 42 mg/kg (21 mg/kg twice daily). In the clinical trial, the mean daily dose was 35 mg/kg in this age group. 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 3000 mg/day.

2.2 Dosing for Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

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

2.3 Dosing for Primary Generalized Tonic Clonic Seizures

Adults 16 Years and Older

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

Pediatric Patients 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 (10 mg/kg twice daily) 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.

2.4 Switching from Oral Dosing

When switching from oral levetiracetam, the initial total daily intravenous dosage of levetiracetam injection should be equivalent to the total daily dosage and frequency of oral levetiracetam.

2.5 Switching to Oral Dosing

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

2.6 Preparation and Administration Instructions

Levetiracetam injection is for intravenous use only and should be diluted in 100 mL of a compatible diluent prior to administration. If a smaller volume is required (e.g. pediatric patients), the amount of diluent should be calculated to not exceed a maximum levetiracetam concentration of 15 mg per mL of diluted solution. Consideration should also be given to the total daily fluid intake of the patient. Levetiracetam injection should be administered as a 15 minute IV infusion. One vial of levetiracetam injection contains 500 mg levetiracetam (500 mg/5 mL).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Product with particulate matter or discoloration should not be used.

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

Adults

See Table 1 for the recommended preparation and administration of levetiracetam injection for adults to achieve a dose of 500 mg, 1000 mg, or 1500 mg.

Table 1: Preparation and Administration of Levetiracetam Injection for Adults

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

For example, to prepare a 1000 mg dose, dilute 10 mL of levetiracetam injection in 100 mL of a compatible diluent and administer intravenously as a 15 minute infusion.

Pediatric Patients

When using levetiracetam injection for pediatric patients, dosing is weight based (mg per kg).

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

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

2.7 Dosage Adjustments in Adult Patients with Renal Impairment

Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults with renal impairment are shown in Table 2. Information is unavailable for dosage adjustments in pediatric patients with renal impairment. In order to calculate the dose recommended for adult patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CLcr) in mL/min must first be calculated using the following formula:

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

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

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

Table 2: Dosage Adjustment Regimen for Adult Patients with Renal Impairment

Group	Creatinine Clearance (mL/min/1.73 m²)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 hours
Mild	50 to 80	500 to 1,000	Every 12 hours
Moderate	30 to 50	250 to 750	Every 12 hours
Severe	< 30	250 to 500	Every 12 hours
ESRD patients using dialysis		500 to 1,000[1]	Every 24 hours[1]

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

2.8 Compatibility and Stability

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

Diluents

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

Other Antiepileptic Drugs

Lorazepam
Diazepam
Valproate sodium

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

3 DOSAGE FORMS AND STRENGTHS

One vial of levetiracetam injection contains 500 mg levetiracetam (500 mg/5 mL (100 mg/mL)).

4 CONTRAINDICATIONS

None.

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 using an oral formulation of levetiracetam, 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 an oral formulation 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 using an oral formulation of levetiracetam, 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 an oral formulation 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.

5.2 Somnolence and Fatigue

Levetiracetam may cause somnolence and fatigue. Patients should be monitored for somnolence and fatigue, and be 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 clinical studies using an oral formulation of levetiracetam in adult patients with 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 3000 mg/day. In a study in which there was no titration, about 45% of patients receiving levetiracetam 4000 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 using an oral formulation of levetiracetam in adult patients with 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 studies were comparable to those of the adult partial onset seizure studies.

5.3 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 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.

5.4 Coordination Difficulties

Levetiracetam may cause coordination difficulties.

In controlled clinical studies using an oral formulation of levetiracetam in adult patients with partial onset seizures, 3.4% of levetiracetam treated patients experienced coordination difficulties, (reported as 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 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 signs and symptoms of coordination difficulties 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.

5.5 Withdrawal Seizures

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

5.6 Hematologic Abnormalities

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

Partial Onset Seizures

Adults

In controlled clinical studies using an oral formulation of levetiracetam in adult patients with partial onset seizures, minor but statistically significant decreases compared to placebo in total mean RBC (0.03 x 10^6/mm^3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam treated patients.

A total of 3.2% of levetiracetam treated and 1.8% of placebo treated patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC, and 2.4% of levetiracetam treated and 1.4% of placebo treated patients had at least one possibly significant (≤1 x 10^9/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

In a controlled study in pediatric patients age 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 10^9/L and 0.3 x 10^9/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 treated patients (statistically significant).

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% on levetiracetam versus 4.2% on placebo). No patient was discontinued because of low WBC or neutrophil count.

In a randomized, double blind, placebo controlled study to assess the neurocognitive and behavioral effects of an oral formulation of levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age), 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 (≥10% or ≥0.7X10^9/L).

5.7 Increase in Blood Pressure

In a randomized, placebo controlled study in patients 1 month to <4 years of age using an oral formulation of levetiracetam, a significantly higher risk of increased diastolic blood pressure was observed in the levetiracetam treated patients (17%), compared to 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.

5.8 Seizure Control During Pregnancy

Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

6 ADVERSE REACTIONS

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

- Behavioral Abnormalities and Psychotic Symptoms *[see Warnings and Precautions (5.1)]*
- Somnolence and Fatigue *[see Warnings and Precautions (5.2)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.3)]*
- Coordination Difficulties *[see Warnings and Precautions (5.4)]*
- Hematologic Abnormalities *[see Warnings and Precautions (5.6)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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

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

Partial Onset Seizures

Adults

In controlled clinical studies using levetiracetam tablets in adults with partial onset seizures, the most common adverse reactions in adult patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, asthenia, infection, and dizziness. Of the most common adverse reactions in adults experiencing partial onset seizures, asthenia, somnolence, and dizziness occurred predominantly during the first 4 weeks of treatment with levetiracetam.

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

Table3: Adverse Reactions* in Pooled Placebo Controlled, Add On Studies in Adults Experiencing Partial Onset Seizures

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

* Adverse reactions occurred in at least 1% of levetiracetam treated patients and occurred more frequently than placebo treated patients

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

Table4: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Pooled Placebo Controlled Studies in Adults Experiencing Partial Onset Seizures

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

Pediatric Patients 4 Years to <16 Years

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

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

Table5: Adverse Reactions* in Pooled Placebo Controlled, Add On Studies in Pediatric Patients Ages 4 to 16 Years Experiencing Partial Onset Seizures

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

* Adverse reactions occurred in at least 2% of pediatric levetiracetam treated patients and occurred more frequently than placebo treated patients

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

Pediatric Patients 1 Month to <4 Years

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

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

Table6: Adverse Reactions* in a Placebo Controlled, Add On Study in Pediatric Patients Ages 1 Month to <4 Years Experiencing Partial Onset Seizures

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

* Adverse reactions occurred in at least 5% of levetiracetam treated patients and occurred more frequently than placebo treated patients

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

Myoclonic Seizures

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

In the controlled clinical study using levetiracetam tablets in patients with myoclonic seizures, the most common adverse reactions in patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, neck pain, and pharyngitis.

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

Table7: Adverse Reactions* in a Placebo Controlled, Add On Study in Patients 12 Years of Age and Older with Myoclonic Seizures

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

* Adverse reactions occurred in at least 5% of levetiracetam treated patients and occurred more frequently than placebo treated patients

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

Table 8: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Patients with Juvenile Myoclonic Epilepsy

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

Primary Generalized Tonic Clonic Seizures

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

In the controlled clinical study that included patients 4 years of age and older with PGTC seizures, the most common adverse reaction in patients receiving levetiracetam oral formulation in combination with other AEDs, for events with rates greater than placebo was nasopharyngitis.

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

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

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

* Adverse reactions occurred in at least 5% of levetiracetam treated patients and occurred more frequently than placebo treated patients

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

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

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

Comparison of Gender, Age and Race

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

6.2 Postmarketing Experience

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

The following adverse reactions have been reported in patients receiving levetiracetam worldwide. The listing is alphabetized: abnormal liver function test, choreoathetosis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, muscular weakness, pancreatitis,

pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, and weight loss. Alopecia has been reported with levetiracetam use; recovery was observed in majority of cases where levetiracetam was discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Levetiracetam blood levels may decrease during pregnancy [*see Warnings and Precautions (5.8)*].

Teratogenic Effects

Pregnancy Category C

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

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

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

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

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

Pregnancy Registry

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from levetiracetam, 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 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 (2.6)*].

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 years to 16 years, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no substantive differences were observed between the placebo and drug treated groups in the median change from baseline in this battery, the study was not adequate to assess formal statistical non inferiority of the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/6 18), a standardized validated tool used to assess a child's competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL/6 18 indicated, on average, a worsening in 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 day 4 through day 52 of age) and dogs (dosing from week 3 through week 7 of age) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m^2 basis) did not indicate a potential for age specific toxicity.

8.5 Geriatric Use

There were 347 subjects in clinical studies of levetiracetam that were 65 years old 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)*]. Dosage adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis [*see Dosage and Administration (2.7)*].

10 OVERDOSAGE

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

The highest known dose of oral levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma were observed with 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.

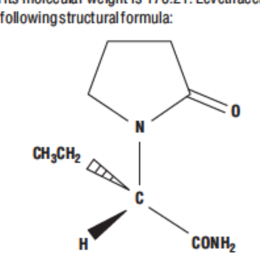
10.3 Hemodialysis

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

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

The chemical name of levetiracetam, a single enantiomer, is ( ) (S) α ethyl 2 oxo 1 pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:



Levetiracetam USP is a white to off white crystalline powder. It is very soluble in water (104 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.)

Levetiracetam injection, USP contains 100 mg of levetiracetam per mL. It is supplied in single use 5 mL vials containing 500 mg levetiracetam, water for injection, 45 mg sodium chloride, and buffered at approximately pH 5.5 with glacial acetic acid and 8.2 mg sodium acetate trihydrate. Levetiracetam injection, USP must be diluted prior to intravenous infusion [*see Dosage and Administration (2.6)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

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

12.2 Pharmacodynamics

Effects on QTc Interval

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

12.3 Pharmacokinetics

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

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

Overview

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

Distribution

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

Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

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

Elimination

Levetiracetam plasma half life in adults is 7 ± 1 hour and is unaffected by either dose, route of administration or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment [*see Dosage and Administration (2.6) and Use in Specific Populations (8.6)*].

Specific Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61 to 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

- Intravenous Formulation

  A population pharmacokinetic analysis for the intravenous formulation was conducted in 49 pediatric patients (1 month to < 16 years of age) weighing 3 to 79 kg. Patients received levetiracetam as a 15 minute IV infusion at doses between 14 mg/kg/day and 60 mg/kg/day twice daily. Plasma concentrations and model derived steady state exposure $AUC_{(0-12)}$ were within the range of the exposure observed in pediatric patients receiving equivalent doses of the oral solution.

- Oral Formulations

  Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6 to 12 years) after single oral dose (20 mg/kg) of the immediate release formulation of levetiracetam. 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 of the immediate release formulation of levetiracetam. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses, with a T_{max} of about 1 hour and a $t_{1/2}$ of 5 hours across all dosing levels. The pharmacokinetics of levetiracetam in pediatric patients 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 pediatric patients with epilepsy (1 month to < 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. Levetiracetam half life in pediatric patients 1 month to < 4 years with epilepsy was shorter (5.3 h) than in adults (7.2 h), and apparent clearance (1.5 mL/min/kg) was faster than in 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_{max} and AUC were 20% higher in women (N 11) compared to men (N 12). However, clearances adjusted for body weight were comparable.

Race

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

Renal Impairment

The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr 50 to 80 mL/min), 50% in the moderate group (CLcr 30 to 50 mL/min) and 60% in the severe renal impairment group (CLcr <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr >80 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure [*see Dosage and Administration (2.7)*].

Hepatic Impairment

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

Drug Interactions

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

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

Phenytoin

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

Valproate

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

Other Antiepileptic Drugs

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

Warfarin

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

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of 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 1800 mg/kg/day. The highest dose is 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a mg/m^2 basis.

Mutagenesis

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

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1800 mg/kg/day (6 times the maximum recommended human dose on a mg/m^2 or systemic exposure [AUC] basis).

14 CLINICAL STUDIES

All clinical studies supporting the efficacy of levetiracetam utilized oral formulations. The finding of efficacy of levetiracetam injection is based on the results of studies using an oral formulation of levetiracetam, and on the demonstration of comparable bioavailability of the oral and parenteral formulations [*see Pharmacokinetics (12.3)*].

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

Study 1

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

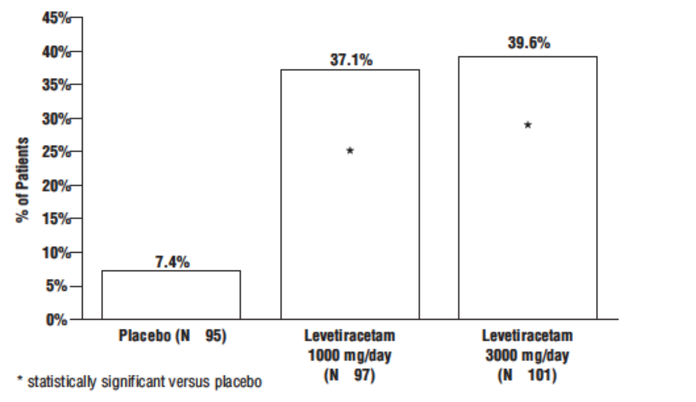
Table 10: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 1

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

* statistically significant versus placebo

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

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



* statistically significant versus placebo

Study 2

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

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

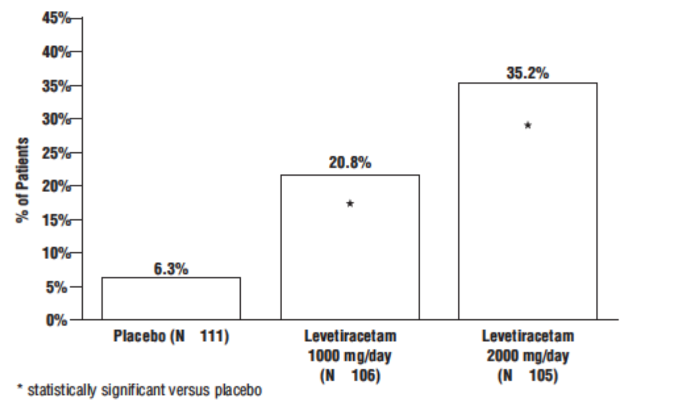
Table 11: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 2: Period A

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

* statistically significant versus placebo

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

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



* statistically significant versus placebo

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

Study 3

Study 3 was a double blind, placebo controlled, parallel group study conducted at 47 centers in Europe comparing levetiracetam 3000 mg/day (N 180) and placebo (N 104) in patients with refractory partial onset seizures, with or without secondary generalization, receiving only one concomitant AED. Study drug was given in two divided doses. After a prospective baseline period of 12 weeks, patients were randomized to one of two treatment groups described above. The 16 week treatment period consisted of a 4 week titration period, followed by a 12 week fixed dose evaluation period, during which concomitant AED doses were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly seizure frequency relative to placebo over the entire randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). Table 12 displays the results of the analysis of Study 3.

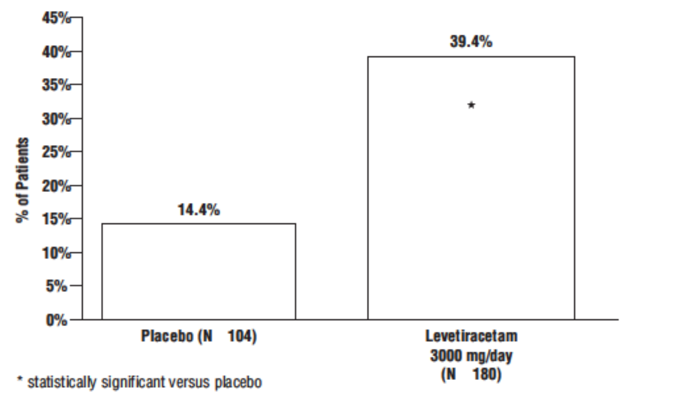
Table 12: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 3

	Placebo (N 104)	Levetiracetam 3000 mg/day (N 180)
Percent reduction in partial seizure frequency over placebo		23%*

* statistically significant versus placebo

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

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



* statistically significant versus placebo

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

Study 4 was a multicenter, randomized double blind, placebo controlled study, in pediatric patients 4 to 16 years of age with partial seizures uncontrolled by standard antiepileptic drugs (AEDs). Study 4 was conducted at 60 sites in North America. The study consisted of an 8 week baseline period and 4 week titration period followed by a 10 week evaluation period. Eligible patients who still experienced, on a stable dose of 1 to 2 AEDs, 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. 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 efficacy was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire 14 week randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency per week). The enrolled population included 198 patients (levetiracetam N 101, placebo N 97) with refractory partial onset seizures, whether or not secondarily generalized. Table 13 displays the results of Study 4.

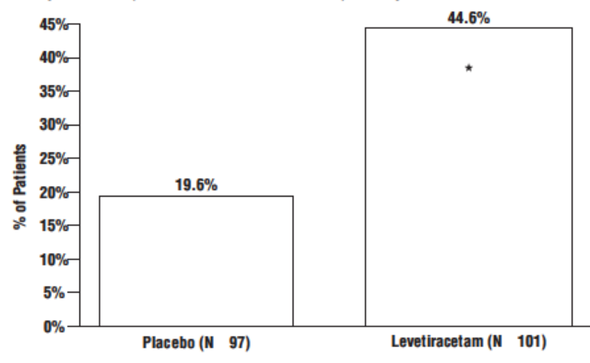
Table 13: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 4

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

* statistically significant versus placebo

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

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

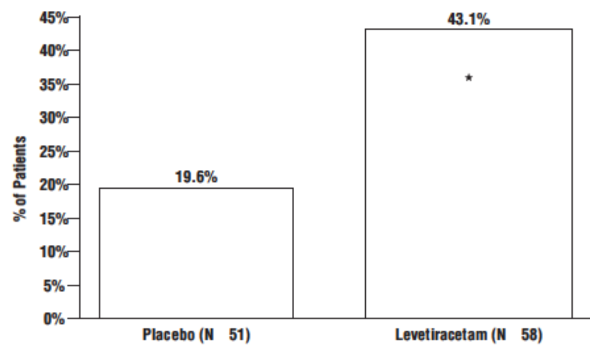


* statistically significant versus placebo

Effectiveness in Partial Onset Seizures in Pediatric Patients 1 Month to <4 Years with Epilepsy

Study 5 was a multicenter, randomized double blind, placebo controlled study, in pediatric patients 1 month to less than 4 years of age with partial seizures, uncontrolled by standard epileptic drugs (AEDs). Study 5 was conducted at 62 sites in North America, South America, and Europe. Study 5 consisted of a 5 day evaluation period, which included a 1 day titration period followed by a 4 day maintenance period. Eligible patients who experienced, on a stable dose of 1 to 2 AEDs, at least 2 partial onset seizures during the 48 hour baseline video EEG were randomized to receive either levetiracetam or placebo. Randomization was stratified by age range as follows: 1 month to less than 6 months of age (N 4 treated with levetiracetam), 6 months to less than 1 year of age (N 8 treated with levetiracetam), 1 year to less than 2 years of age (N 20 treated with levetiracetam), and 2 years to less than 4 years of age (N 28 treated with levetiracetam). Levetiracetam dosing was determined by age and weight as follows: children 1 month to less than 6 months old were randomized to a target dose of 40 mg/kg/day, and children 6 months to less than 4 years old were randomized to a target dose of 50 mg/kg/day. The primary measure of efficacy was the responder rate (percent of patients with ≥ 50% reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48 hour video EEG performed during the last two days of the 4 day maintenance period. The enrolled population included 116 patients (levetiracetam N 60, placebo N 56) with refractory partial onset seizures, whether or not secondarily generalized. A total of 109 patients were included in the efficacy analysis. A statistically significant difference between levetiracetam and placebo was observed in Study 5 (see Figure 5). The treatment effect associated with levetiracetam was consistent across age groups.

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



* statistically significant versus placebo

14.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Study 6 was a multicenter, randomized, double blind, placebo controlled study in patients 12 years of age and older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures. Study 6 was conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 antiepileptic drug (AED) experiencing one or more myoclonic seizures per day for at least 8 days during the prospective 8 week baseline period were randomized to either levetiracetam or placebo (levetiracetam N 60, placebo N 60). Patients were titrated over 4 weeks to a target dose of 3000 mg/day and treated at a stable dose of 3000 mg/day over 12 weeks (evaluation period). Study drug was given in 2 divided doses. The primary measure of efficacy was the proportion of patients with at least 50% reduction in the number of days per week with one or more myoclonic seizures during the treatment period (titration + evaluation periods) as compared to baseline. Table 14 displays the results for the 113 patients with JME in this study. Of 120 patients enrolled, 113 had a diagnosis of confirmed or suspected JME. The results of Study 6 are displayed in Table 14.

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

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

* statistically significant versus placebo

14.3 Primary Generalized Tonic Clonic Seizures

Effectiveness in Primary Generalized Tonic Clonic Seizures in Patients ≥6 years of age

Study 7 was a multicenter, randomized, double blind, placebo controlled study in patients 6 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic clonic (PGTC) seizures. Study 7 was conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 antiepileptic drugs (AEDs) experiencing at least 3 PGTC seizures during the 8 week combined baseline period (at least one PGTC seizure during the 4 weeks prior to the prospective baseline period and at least one PGTC seizure during the 4 week prospective baseline period) were randomized to either levetiracetam or placebo. The 8 week combined baseline period is referred to as "baseline" in the remainder of this section. Patients were titrated over 4 weeks to a target dose of 3000 mg/day for adults or a pediatric target dose of 60 mg/kg/day and treated at a stable dose of 3000 mg/day (or 60 mg/kg/day for children) over 20 weeks (evaluation period). Study drug was given in 2 equally divided doses per day. The primary measure of efficacy was the percent reduction from baseline in weekly PGTC seizure frequency for levetiracetam and placebo treatment groups over the treatment period (titration + evaluation periods). The population included 164 patients (levetiracetam N 80, placebo N 84) with idiopathic generalized epilepsy (predominately juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening) experiencing primary generalized tonic clonic seizures. Each of these syndromes of idiopathic generalized epilepsy was well represented in this patient population.

There was a statistically significant decrease from baseline in PGTC frequency in the levetiracetam treated patients compared to the placebo treated patients in Study 7 (see Table 15).

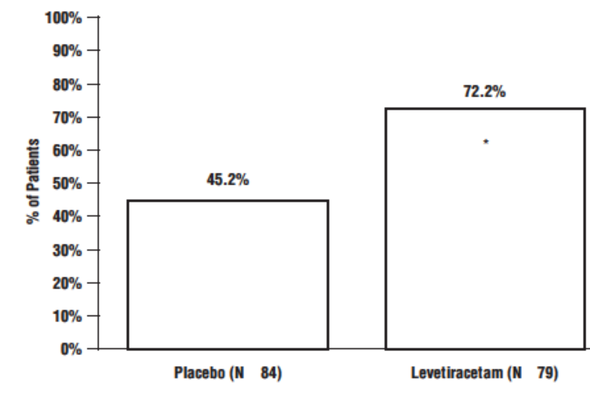
Table 15: Median Percent Reduction from Baseline in PGTC Seizure Frequency per Week in Study 7

	Placebo (N 84)	Levetiracetam (N 78)
Percentage reduction in PGTC seizure frequency	44.6%	77.6%*

* statistically significant versus placebo

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

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



* statistically significant versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Levetiracetam injection USP, 500 mg/5 mL (100 mg/mL) is a clear, colorless, sterile solution.

Single Use 5 mL Vials in a carton of 10 vials NDC 55150 177 05

16.2 Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Suicidal Behavior and Ideation

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

Psychiatric Reactions and Changes in Behavior

Advise patients and their caregivers that levetiracetam may cause changes in behavior (e.g., aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms.

Effects on Driving or Operating Machinery

Inform patients that levetiracetam may cause dizziness and somnolence. Inform 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.

Dermatological Adverse Reactions

Advise patients that serious dermatological adverse reactions have occurred in patients treated with levetiracetam and instruct them to call their physician immediately if a rash develops.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during levetiracetam therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1 888 233 2334 [*see Use In Specific Populations (8.1)*].

Manufactured for:
AuroMedics Pharma LLC
6 Wheeling Road
Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
IDA, Pashamylaram 502307
India

P1505345

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

LEVETIRACETAM Injection, USP for Intravenous Use
Initial U.S. Approval: 1999

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

Indications and Usage (1.1, 1.2, 1.3)	10/2014
Dosage and Administration (2.1, 2.3, 2.6)	10/2014
Warnings and Precautions (5.1, 5.2, 5.7)	10/2014
Warnings and Precautions, Hematologic Abnormalities (5.6)	03/2015

----------INDICATIONS AND USAGE----------
Levetiracetam injection, USP is indicated for adjunctive therapy, as an alternative when oral administration is temporarily not feas ble, in the treatment of:

- Partial onset seizures in patients 1 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)

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

Levetiracetam injection is for intravenous use only (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 (2.1)
- 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 (2.1)
- 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 (2.1)
- Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to a recommended dose of 1500 mg twice daily (2.1)

Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older

- 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.2)

Primary Generalized Tonic-Clonic Seizures

- 6 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 (2.3)
- Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.3)

Switching From or To Oral Levetiracetam

When switching from oral levetiracetam, the initial total daily dosage/frequency of levetiracetam injection should be equivalent to those of oral levetiracetam.

At the end of the intravenous treatment period, the patient may be switched to levetiracetam oral administration at the equivalent daily dosage and frequency (2.4, 2.5)

See full prescribing information for preparation and administration instructions (2.6) and dosage adjustment in adult patients with renal impairment (2.7)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 500 mg/5 mL (100 mg/mL) single-use vial (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)
- Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam (5.2)
- Withdrawal Seizures: Levetiracetam must be gradually withdrawn. (5.5)

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

- Adults: 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 AuroMedics Pharma LLC at 1-866-850-2876 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 (5.8, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Partial Onset Seizures

Levetiracetam injection, USP is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy. Levetiracetam injection, USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Levetiracetam injection, USP 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. Levetiracetam injection, USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

1.3 Primary Generalized Tonic-Clonic Seizures

Levetiracetam injection, USP 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. Levetiracetam injection, USP is for intravenous use only as an alternative for patients when oral administration is temporarily not feasible.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing for Partial Onset Seizures

Adults 16 Years and Older

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

Pediatric Patients

1 Month to < 6 Months

Initiate treatment with a daily dose of 14 mg/kg in 2 divided doses (7 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 14 mg/kg to the recommended daily dose of 42 mg/kg (21 mg/kg twice daily). In the clinical trial, the mean daily dose was 35 mg/kg in this age group. 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 3000 mg/day.

2.2 Dosing for Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

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

2.3 Dosing for Primary Generalized Tonic-Clonic Seizures

Adults 16 Years and Older

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

Pediatric Patients 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 (10 mg/kg twice daily) 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.

2.4 Switching from Oral Dosing

When switching from oral levetiracetam, the initial total daily intravenous dosage of levetiracetam injection should be equivalent to the total daily dosage and frequency of oral levetiracetam.

2.5 Switching to Oral Dosing

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

2.6 Preparation and Administration Instructions

Levetiracetam injection is for intravenous use only and should be diluted in 100 mL of a compatible diluent prior to administration. If a smaller volume is required (e.g. pediatric patients), the amount of diluent should be calculated to not exceed a maximum levetiracetam concentration of 15 mg per mL of diluted solution. Consideration should also be given to the total daily fluid intake of the patient. Levetiracetam injection should be administered as a 15-minute IV infusion. One vial of levetiracetam injection contains 500 mg levetiracetam (500 mg/5 mL).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Product with particulate matter or discoloration should not be used.

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

Adults

See Table 1 for the recommended preparation and administration of levetiracetam injection for adults to achieve a dose of 500 mg, 1000 mg, or 1500 mg.

Table 1: Preparation and Administration of Levetiracetam Injection for Adults

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

For example, to prepare a 1000 mg dose, dilute 10 mL of levetiracetam injection in 100 mL of a compatible diluent and administer intravenously as a 15-minute infusion.

Pediatric Patients

When using levetiracetam injection for pediatric patients, dosing is weight-based (mg per kg).

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

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

2.7 Dosage Adjustments in Adult Patients with Renal Impairment

Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults with renal impairment are shown in Table 2.

Information is unavailable for dosage adjustments in pediatric patients with renal impairment. In order to calculate the dose recommended for adult patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CLcr) in mL/min must first be calculated using the following formula:

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

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

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

Table 2: Dosage Adjustment Regimen for Adult Patients with Renal Impairment

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

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

2.8 Compatibility and Stability

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

Diluents

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

Other Antiepileptic Drugs

Lorazepam
Diazepam
Valproate sodium

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

3 DOSAGE FORMS AND STRENGTHS

One vial of levetiracetam injection contains 500 mg levetiracetam (500 mg/5 mL (100 mg/mL)).

4 CONTRAINDICATIONS

None.

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 using an oral formulation of levetiracetam, 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 an oral formulation 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 using an oral formulation of levetiracetam, 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 an oral formulation 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.

5.2 Somnolence and Fatigue

Levetiracetam may cause somnolence and fatigue. Patients should be monitored for somnolence and fatigue, and be 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 clinical studies using an oral formulation of levetiracetam in adult patients with 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 3000 mg/day. In a study in which there was no titration, about 45% of patients receiving levetiracetam 4000 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 using an oral formulation of levetiracetam in adult patients with 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 studies were comparable to those of the adult partial onset seizure studies.

5.3 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 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.

5.4 Coordination Difficulties

Levetiracetam may cause coordination difficulties.

In controlled clinical studies using an oral formulation of levetiracetam in adult patients with partial onset seizures, 3.4% of levetiracetam-treated patients experienced coordination difficulties, (reported as 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 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 signs and symptoms of coordination difficulties 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.

5.5 Withdrawal Seizures

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

5.6 Hematologic Abnormalities

Levetiracetam can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in red blood cells count (RBC), hemoglobin, and hematocrit, and increases in eosinophil counts. Decreased white blood cells count (WBC) and

neutrophil counts also occurred in clinical trials. Cases of agranulocytosis have been reported in the postmarketing setting.

Partial Onset Seizures

Adults

In controlled clinical studies using an oral formulation of levetiracetam in adult patients with partial onset seizures, minor but statistically significant decreases compared to placebo in total mean RBC (0.03 x 10^6/mm^3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam-treated patients.

A total of 3.2% of levetiracetam-treated and 1.8% of placebo-treated patients had at least one possibly significant (≤2.8 x 10^9/L) decreased WBC, and 2.4% of levetiracetam-treated and 1.4% of placebo-treated patients had at least one possibly significant (≤1 x 10^9/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

In a controlled study in pediatric patients age 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 × 10^9/L and -0.3 × 10^9/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in levetiracetam-treated patients, compared to a decrease of 4% in placebo-treated patients (statistically significant).

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% on levetiracetam versus 4.2% on placebo). No patient was discontinued because of low WBC or neutrophil count.

In a randomized, double-blind, placebo-controlled study to assess the neurocognitive and behavioral effects of an oral formulation of levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age), 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 (≥10% or ≥0.7X10^9/L).

5.7 Increase in Blood Pressure

In a randomized, placebo-controlled study in patients 1 month to <4 years of age using an oral formulation of levetiracetam, a significantly higher risk of increased diastolic blood pressure was observed in the levetiracetam-treated patients (17%), compared to 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.

5.8 Seizure Control During Pregnancy

Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

6 ADVERSE REACTIONS

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

- Behavioral Abnormalities and Psychotic Symptoms *[see Warnings and Precautions (5.1)]*
- Somnolence and Fatigue *[see Warnings and Precautions (5.2)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.3)]*
- Coordination Difficulties *[see Warnings and Precautions (5.4)]*
- Hematologic Abnormalities *[see Warnings and Precautions (5.6)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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

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

Partial Onset Seizures

Adults

In controlled clinical studies using levetiracetam tablets in adults with partial onset seizures, the most common adverse reactions in adult patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, asthenia, infection, and dizziness. Of the most common adverse reactions in adults experiencing partial onset seizures,

asthenia, somnolence, and dizziness occurred predominantly during the first 4 weeks of treatment with levetiracetam.

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

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

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

* Adverse reactions occurred in at least 1% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

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

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

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

Pediatric Patients 4 Years to <16 Years

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

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

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

	Levetiracetam (N = 165) %	Placebo (N = 131) %
Headache	19	15
Nasopharyngitis	15	12
Vomiting	15	12
Somnolence	13	9
Fatigue	11	5
Aggression	10	5
Abdominal Pain Upper	9	8
Cough	9	5
Nasal Congestion	9	2
Decreased Appetite	8	2
Abnormal Behavior	7	4
Dizziness	7	5
Irritability	7	1
Pharyngolaryngeal Pain	7	4
Diarrhea	6	2
Lethargy	6	5
Insomnia	5	3

	Levetiracetam (N = 165) %	Placebo (N = 131) %
Agitation	4	1
Anorexia	4	3
Head Injury	4	0
Constipation	3	1
Contusion	3	1
Depression	3	1
Fall	3	2
Influenza	3	1
Mood Altered	3	1
Affect Lability	2	1
Anxiety	2	1
Arthralgia	2	0
Confusional State	2	0
Conjunctivitis	2	0
Ear Pain	2	1
Gastroenteritis	2	0
Joint Sprain	2	1
Mood Swings	2	1
Neck Pain	2	1
Rhinitis	2	0
Sedation	2	1

* Adverse reactions occurred in at least 2% of pediatric levetiracetam-treated patients and occurred more frequently than placebo-treated patients

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

Pediatric Patients 1 Month to < 4 Years

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

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

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

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

* Adverse reactions occurred in at least 5% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

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

Myoclonic Seizures

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

In the controlled clinical study using levetiracetam tablets in patients with myoclonic seizures, the most common adverse reactions in patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, neck pain, and pharyngitis.

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

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

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

* Adverse reactions occurred in at least 5% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

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

Table 8: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Patients with Juvenile Myoclonic Epilepsy

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

Primary Generalized Tonic-Clonic Seizures

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

In the controlled clinical study that included patients 4 years of age and older with PGTC seizures, the most common adverse reaction in patients receiving levetiracetam oral formulation in combination with other AEDs, for events with rates greater than placebo was nasopharyngitis.

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

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

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

* Adverse reactions occurred in at least 5% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients

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

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

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

Comparison of Gender, Age and Race

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

6.2 Postmarketing Experience

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

The following adverse reactions have been reported in patients receiving levetiracetam worldwide. The listing is alphabetized: abnormal liver function test, choreoathetosis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, muscular weakness, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, and

weight loss. Alopecia has been reported with levetiracetam use; recovery was observed in majority of cases where levetiracetam was discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Levetiracetam blood levels may decrease during pregnancy [*see Warnings and Precautions (5.8)*].

Teratogenic Effects

Pregnancy Category C

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

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

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

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

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

Pregnancy Registry

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from levetiracetam, 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 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 (2.6)*].

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 years to 16 years, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter-R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no substantive differences were observed between the placebo and drug treated groups in the median change from baseline in this battery, the study was not adequate to assess formal statistical non-inferiority of the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/6-18), a standardized validated tool used to assess a child's competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL/6-18 indicated, on average, a worsening in 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 day 4 through day 52 of age) and dogs (dosing from week 3 through week 7 of age) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m^2 basis) did not indicate a potential for age-specific toxicity.

8.5 Geriatric Use

There were 347 subjects in clinical studies of levetiracetam that were 65 years old 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)*]. Dosage adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis [*see Dosage and Administration (2.7)*].

10 OVERDOSAGE

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

The highest known dose of oral levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma were observed with 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.

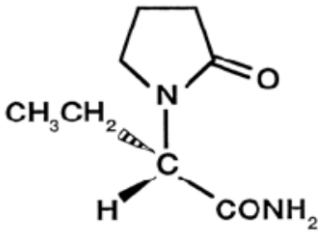
10.3 Hemodialysis

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

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

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:



Levetiracetam USP is a white to off-white crystalline powder. It is very soluble in water (104 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.)

Levetiracetam injection, USP contains 100 mg of levetiracetam per mL. It is supplied in single-use 5 mL vials containing 500 mg levetiracetam, water for injection, 45 mg sodium chloride, and buffered at approximately pH 5.5 with glacial acetic acid and 8.2 mg sodium acetate trihydrate. Levetiracetam injection, USP must be diluted prior to intravenous infusion [*see Dosage and Administration (2.6)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial

seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

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

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

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

12.2 Pharmacodynamics

Effects on QTc Interval

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

12.3 Pharmacokinetics

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

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

Overview

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

Distribution

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

Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

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

Elimination

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

metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment [*see Dosage and Administration (2.6) and Use in Specific Populations (8.6)*].

Specific Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61 to 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

- Intravenous Formulation

  A population pharmacokinetic analysis for the intravenous formulation was conducted in 49 pediatric patients (1 month to < 16 years of age) weighing 3 to 79 kg. Patients received levetiracetam as a 15-minute IV infusion at doses between 14 mg/kg/day and 60 mg/kg/day twice daily. Plasma concentrations and model derived steady-state exposure $AUC_{(0-12)}$ were within the range of the exposure observed in pediatric patients receiving equivalent doses of the oral solution.

- Oral Formulations

  Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6 to 12 years) after single oral dose (20 mg/kg) of the immediate release formulation of levetiracetam. 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 of the immediate release formulation of levetiracetam. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses, with a T_{max} of about 1 hour and a $t_{1/2}$ of 5 hours across all dosing levels. The pharmacokinetics of levetiracetam in pediatric patients 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 pediatric patients with epilepsy (1 month to < 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. Levetiracetam half-life in pediatric patients 1 month to < 4 years with epilepsy was shorter (5.3 h) than in adults (7.2 h), and apparent clearance (1.5 mL/min/kg) was faster than in 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_{max} and AUC were 20% higher in women (N = 11) compared to men (N = 12). However, clearances adjusted for body weight were comparable.

Race

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

Renal Impairment

The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr = 50 to 80 mL/min), 50% in the moderate group (CLcr = 30 to 50 mL/min) and 60% in the severe renal impairment group (CLcr <30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr >80 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure [*see Dosage and Administration (2.7)*].

Hepatic Impairment

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal

clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

Drug Interactions

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

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

Phenytoin

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

Valproate

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

Other Antiepileptic Drugs

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

Warfarin

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

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of 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 1800 mg/kg/day. The highest dose is 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a mg/m^2 basis.

Mutagenesis

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

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1800 mg/kg/day (6 times the maximum recommended human dose on a mg/m^2 or systemic exposure [AUC] basis).

14 CLINICAL STUDIES

All clinical studies supporting the efficacy of levetiracetam utilized oral formulations. The finding of efficacy of levetiracetam injection is based on the results of studies using an oral formulation of levetiracetam, and on the demonstration of comparable bioavailability of the oral and parenteral formulations [*see Pharmacokinetics (12.3)*].

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

Study 1

Study 1 was a double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States comparing levetiracetam 1000 mg/day (N = 97), levetiracetam 3000 mg/day (N = 101), and placebo (N = 95) given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, patients were randomized to one of the three treatment groups described above. The 18-week treatment period consisted of a 6-week titration period, followed

by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). The results of the analysis of Study 1 are displayed in Table 10.

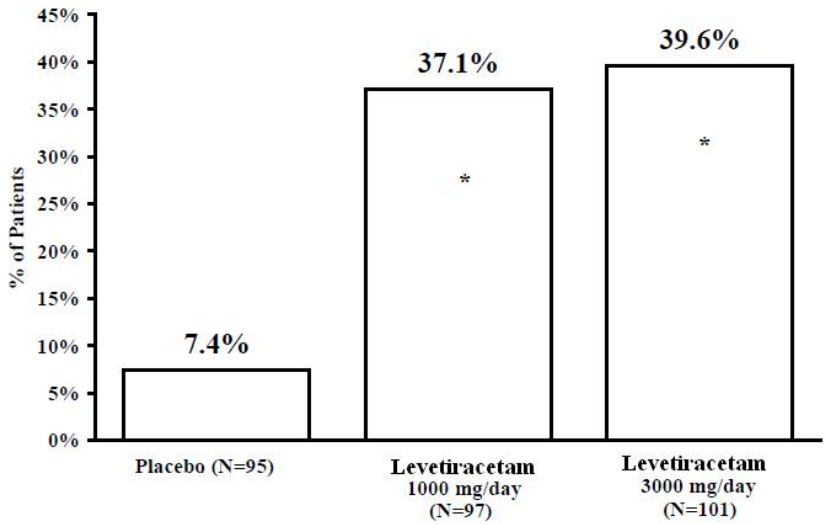
Table 10: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 1

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

* statistically significant versus placebo

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

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



* statistically significant versus placebo

Study 2

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

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

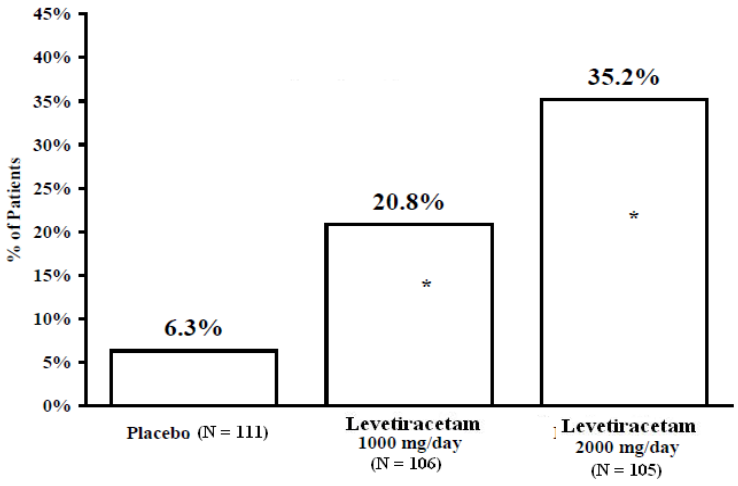
Table 11: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 2: Period A

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

* statistically significant versus placebo

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

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



* statistically significant versus placebo

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

Study 3

Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing levetiracetam 3000 mg/day (N = 180) and placebo (N = 104) in patients with refractory partial onset seizures, with or without secondary generalization, receiving only one concomitant AED. Study drug was given in two divided doses. After a prospective baseline period of 12 weeks, patients were randomized to one of two treatment groups described above. The 16-week treatment period consisted of a 4-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED doses were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly seizure frequency relative to placebo over the entire randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency). Table 12 displays the results of the analysis of Study 3.

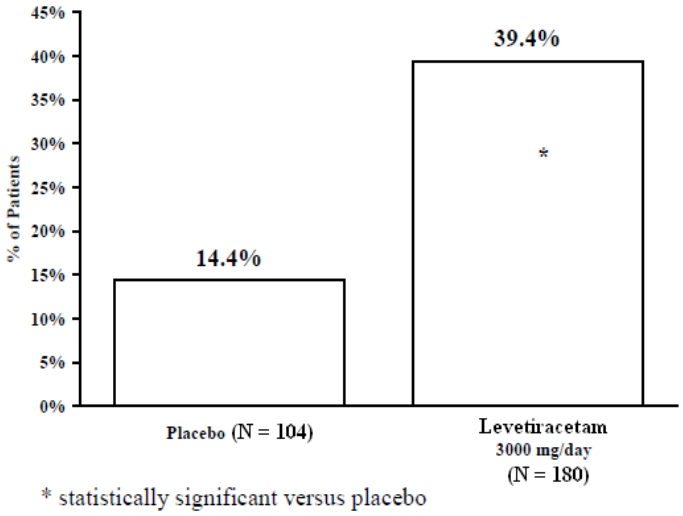
Table 12: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 3

	Placebo (N = 104)	**Levetiracetam 3000 mg/day (N = 180)**
Percent reduction in partial seizure frequency over placebo	–	23%*

* statistically significant versus placebo

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

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



* statistically significant versus placebo

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

Study 4 was a multicenter, randomized double-blind, placebo-controlled study, in pediatric patients 4 to 16 years of age with partial seizures uncontrolled by standard antiepileptic drugs (AEDs). Study 4 was conducted at 60 sites in North America. The study consisted of an 8-week baseline period and 4-week titration period followed by a 10-week evaluation period. Eligible patients who still experienced, on a stable dose of 1 to 2 AEDs, 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. 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 efficacy was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire 14-week randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency per week). The enrolled population included 198 patients (levetiracetam N = 101, placebo N = 97) with refractory partial onset seizures, whether or not secondarily generalized. Table 13 displays the results of Study 4.

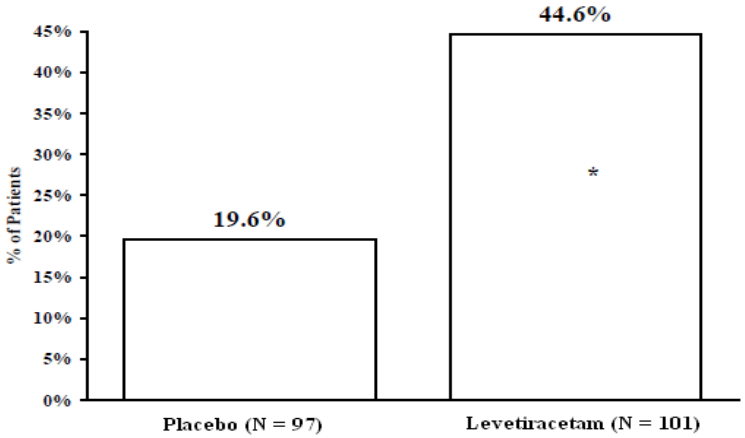
Table 13: Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 4

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

*statistically significant versus placebo

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

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

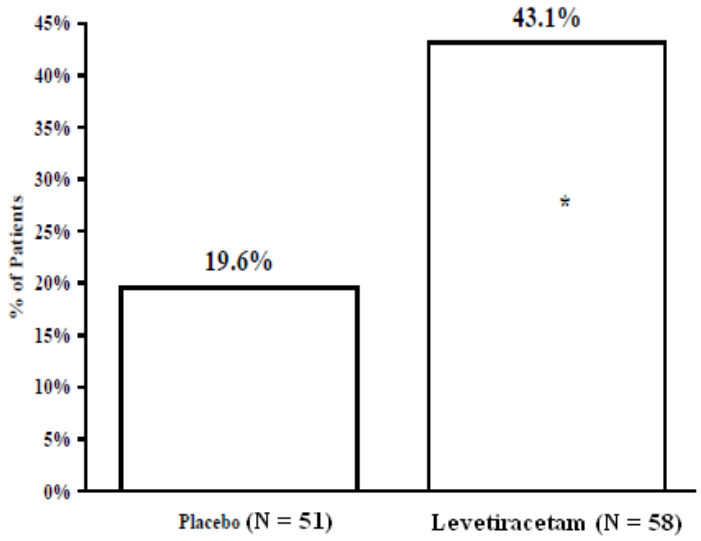


*statistically significant versus placebo

Effectiveness in Partial Onset Seizures in Pediatric Patients 1 Month to <4 Years with Epilepsy

Study 5 was a multicenter, randomized double-blind, placebo-controlled study, in pediatric patients 1 month to less than 4 years of age with partial seizures, uncontrolled by standard epileptic drugs (AEDs). Study 5 was conducted at 62 sites in North America, South America, and Europe. Study 5 consisted of a 5-day evaluation period, which included a 1-day titration period followed by a 4-day maintenance period. Eligible patients who experienced, on a stable dose of 1 to 2 AEDs, at least 2 partial onset seizures during the 48-hour baseline video EEG were randomized to receive either levetiracetam or placebo. Randomization was stratified by age range as follows: 1 month to less than 6 months of age (N = 4 treated with levetiracetam), 6 months to less than 1 year of age (N = 8 treated with levetiracetam), 1 year to less than 2 years of age (N = 20 treated with levetiracetam), and 2 years to less than 4 years of age (N = 28 treated with levetiracetam). Levetiracetam dosing was determined by age and weight as follows: children 1 month to less than 6 months old were randomized to a target dose of 40 mg/kg/day, and children 6 months to less than 4 years old were randomized to a target dose of 50 mg/kg/day. The primary measure of efficacy was the responder rate (percent of patients with ≥ 50% reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG performed during the last two days of the 4-day maintenance period. The enrolled population included 116 patients (levetiracetam N = 60, placebo N = 56) with refractory partial onset seizures, whether or not secondarily generalized. A total of 109 patients were included in the efficacy analysis. A statistically significant difference between levetiracetam and placebo was observed in Study 5 (see Figure 5). The treatment effect associated with levetiracetam was consistent across age groups.

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



*statistically significant versus placebo

14.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Study 6 was a multicenter, randomized, double-blind, placebo-controlled study in patients 12 years of age and older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures. Study 6 was conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 antiepileptic drug (AED) experiencing one or more myoclonic seizures per day for at least 8 days during the prospective 8-week baseline period were randomized to either levetiracetam or placebo (levetiracetam N = 60, placebo N = 60). Patients were titrated over 4 weeks to a target dose of 3000 mg/day and treated at a stable dose of 3000 mg/day over 12 weeks (evaluation period). Study drug was given in 2 divided doses. The primary measure of efficacy was the proportion of patients with at least 50% reduction in the number of days per week with one or more myoclonic seizures during the treatment period (titration + evaluation periods) as compared to baseline. Table 14 displays the results for the 113 patients with JME in this study. Of 120 patients enrolled, 113 had a diagnosis of confirmed or suspected JME. The results of Study 6 are displayed in Table 14.

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

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

* statistically significant versus placebo

14.3 Primary Generalized Tonic-Clonic Seizures

Effectiveness in Primary Generalized Tonic-Clonic Seizures in Patients ≥6 years of age

Study 7 was a multicenter, randomized, double-blind, placebo-controlled study in patients 6 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic (PGTC) seizures. Study 7 was conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 antiepileptic drugs (AEDs) experiencing at least 3 PGTC seizures during the 8-week combined baseline period (at least one PGTC seizure during the 4 weeks prior to the prospective baseline period and at least one PGTC seizure during the 4-week prospective baseline period) were randomized to either levetiracetam or placebo. The 8-week combined baseline period is referred to as “baseline” in the remainder of this section. Patients were titrated over 4 weeks to a target dose of 3000 mg/day for adults or a pediatric target dose of 60 mg/kg/day and treated at a stable dose of 3000 mg/day (or 60 mg/kg/day for children) over 20 weeks (evaluation period). Study drug was given in 2 equally divided doses per day. The primary measure of efficacy was the percent reduction from baseline in weekly PGTC seizure frequency for levetiracetam and placebo treatment groups over the treatment period (titration + evaluation periods). The population included 164 patients (levetiracetam N = 80, placebo N = 84) with idiopathic generalized epilepsy (predominately juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening) experiencing primary generalized tonic-clonic seizures. Each of these syndromes of idiopathic generalized epilepsy was well represented in this patient population.

There was a statistically significant decrease from baseline in PGTC frequency in the levetiracetam-treated patients compared to the placebo-treated patients in Study 7 (see Table 15).

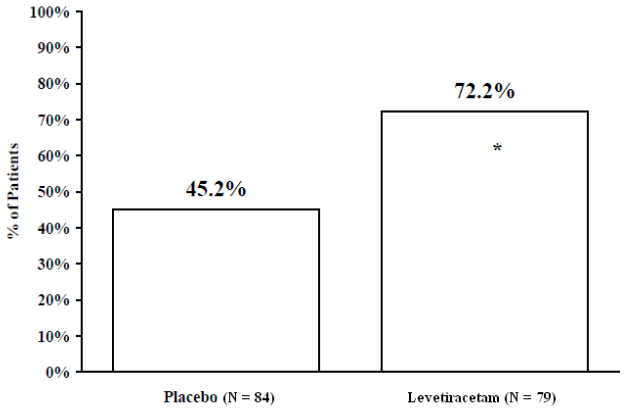
Table 15: Median Percent Reduction from Baseline in PGTC Seizure Frequency per Week in Study 7

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

* statistically significant versus placebo

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

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



* statistically significant versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Levetiracetam injection USP, 500 mg/5 mL (100 mg/mL) is a clear, colorless, sterile solution.

Single Use 5 mL Vials in a carton of 10 vials NDC 55150-177-05

16.2 Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Suicidal Behavior and Ideation

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

Psychiatric Reactions and Changes in Behavior

Advise patients and their caregivers that levetiracetam may cause changes in behavior (e.g., aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms.

Effects on Driving or Operating Machinery

Inform patients that levetiracetam may cause dizziness and somnolence. Inform 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.

Dermatological Adverse Reactions

Advise patients that serious dermatological adverse reactions have occurred in patients treated with levetiracetam and instruct them to call their physician immediately if a rash develops.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during levetiracetam therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [*see Use In Specific Populations (8.1)*].

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