LEVERTIRACETAM Tablets USP

For oral use

Initial U.S. Approval: 1999

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INDICATIONS AND USAGE

Levetiracetam tablets USP are indicated for the treatment of:

• Partial-onset seizures in patients 1 month of age and older
• Myoclonic seizures in patients 12 years and older with juvenile myoclonic epilepsy
• Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy

RECENT MAJOR CHANGES

In August 2019, Levetiracetam tablets received new warnings and precautions information regarding psychiatric symptoms, particularly suicidal ideation, increased aggression and irritability, and behavioral changes, which can occur at any time during treatment. The labeling has been updated to include: 

- Signs and symptoms of serious dermatological reactions
- Signs and symptoms of serious hepatic reactions

Use the oral solution for pediatric patients with body weight ≥10 kg.

For pediatric patients, use weight-based dosing for the oral solution with a calibrated measuring device (not a household measuring device) to ensure the correct dosage.

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DOSAGE AND ADMINISTRATION

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceutical Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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FULL PRESCRIBING INFORMATION: CONTENTS*

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• Partial-onset seizures in patients 1 month of age and older
• Myoclonic seizures in patients 12 years and older with juvenile myoclonic epilepsy
• Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy

Use the oral solution for pediatric patients with body weight ≥10 kg.

For pediatric patients, use weight-based dosing for the oral solution with a calibrated measuring device (not a household measuring device) to ensure the correct dosage.
2.1 Important Administration Instructions

Levetiracetam tablets USP are given orally with or without food. The levetiracetam dosing regimen depends on the indication, age group, dosage form (tablets), and renal function.

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

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

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

2.2 Dosing for Partial Onset Seizures

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

Adults 16 Years of Age and Older

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

Pediatric Patients

1 Month to <6 Months:

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

6 Months to <4 Years:

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose in 2 weeks by an increment of 20 mg/kg to the recommended daily dose of 50 mg/kg (25 mg/kg twice daily). If a patient cannot tolerate a daily dose of 50 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 47 mg/kg in this age group.

4 Years to <16 Years:

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

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

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

Levetiracetam Oral Solution Weight-Based Dosing Calculation For Pediatric Patients

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

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

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

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

2.4 Dosing for Primary Generalized Tonic-Clonic Seizures

Adults 16 Years of Age and Older

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

Pediatric Patients 6 to <16 Years of Age

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

2.5 Dosage Adjustments in Adults with Renal Impairment

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

\[
\text{CLcr} = \frac{140 - \text{age} (\text{years}) \times \text{weight} (\text{kg})}{\text{blood urea nitrogen (BUN) (mg/dL)} \times 72 \times \text{serum creatinine} (\text{mg/dL})}
\]
The finding of increased risk with AEDs of varying mechanisms of action and across a range of clinical trials suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for antiepileptic drugs in the pooled analysis.

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients</th>
<th>Drug Patients</th>
<th>Relative Risk</th>
<th>Incidence of Events in Drug Patients</th>
<th>Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events Per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1000 Patients</td>
<td>1000 Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Antiepileptic drugs (AEDs), including levetiracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with AED for any indication should be monitored for psychiatric signs and symptoms.

5.4 Psychotic Symptoms

In clinical studies, patients taking levetiracetam for any indication were more likely to experience psychotic symptoms compared to patients taking placebo for any indication. The most common psychotic symptoms reported in levetiracetam-treated patients were paranoid thoughts (4%) and thought disturbance (5%). Other psychotic symptoms reported in levetiracetam-treated patients included delusions, hallucinations, and catatonic behavior. In placebo-treated patients, the most common psychotic symptoms reported were delusions, hallucinations, and catatonic behavior. The incidence of psychotic symptoms was similar across age groups treated with levetiracetam and placebo.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine Clearance (mL/min/1.73 m²)</th>
<th>Dosage (mg)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;80</td>
<td>500 to 1,500</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Mild</td>
<td>50 to 80</td>
<td>500 to 1,000</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Moderate</td>
<td>30 to 50</td>
<td>250 to 750</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>250 to 500</td>
<td>Every 12 hours</td>
</tr>
</tbody>
</table>

* Following dialysis, a 250 to 500 mg supplemental dose is recommended.

5.5 Discontinuation of Levetiracetam Tablets

Avoid abrupt withdrawal from Levetiracetam Tablets in order to reduce the risk of increased seizure frequency and status epilepticus [see WARNINGS AND PRECAUTIONS (5.7)].
In a randomized, placebo-controlled study in patients 1 month to <4 years of age, a significantly higher treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that.

In the controlled cognitive and neuropsychological safety study, 5 patients (8.6%) in the levetiracetam-treated patients discontinued treatment due to low WBC or neutrophil counts. No patients, however, there was no apparent difference between treatment groups with respect to abnormally low WBC value (3% of levetiracetam-treated patients versus 0% of placebo-treated patients).

The mean decreases from baseline in the levetiracetam-treated group

Pediatric Patients 4 Years to < 16 Years:

Partial - Onset Seizures

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

Somnia

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 15% of levetiracetam-treated patients reported somnolence, compared to 8% of placebo-treated patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of 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.

Anxiety

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

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

Anaphylaxis and Angioedema

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

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 4 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.

Coordination Difficulties

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

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

Withdrawal Seizures

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

Hematologic Abnormalities

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

Partial - Onset Seizures

Adults:

Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 10^6/mm^3), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam-treated patients in controlled trials.

A total of 3.2% of levetiracetam-treated and 1.8% of placebo-treated patients had at least one possibly significant (≤1.0 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 (≤2.8 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:

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 patients (statistically significant).

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

In the controlled cognitive and neuropsychological safety study, 5 patients (0.8%) in the levetiracetam-treated group and 2 patients (0.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant (≥10% or ≥20 x 10^9/L).

5.9 Increase in Blood Pressure

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

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

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

6 ADVERSE REACTIONS
The following adverse reactions are discussed in more details in other sections of labeling:
- Behavior Abnormalities and Psychotic Symptoms [see WARNINGS AND PRECAUTIONS (5.1)]
- Suicidal Behavior and Ideation [see WARNINGS AND PRECAUTIONS (5.2)]
- Somnolence and Fatigue [see WARNINGS AND PRECAUTIONS (5.3)]
- Amphotiasis and Angioedema [see WARNINGS AND PRECAUTIONS (5.4)]
- Serious Dermatological Reactions [see WARNINGS AND PRECAUTIONS (5.5)]
- Coordination Difficulties [see WARNINGS AND PRECAUTIONS (5.6)]
- Hematologic Abnormalities [see WARNINGS AND PRECAUTIONS (5.8)]
- Increase in Blood Pressure [see WARNINGS AND PRECAUTIONS (5.9)]

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

Partial - Onset Seizures

Adults
In controlled clinical studies in adults with partial - onset seizures, [see CLINICAL STUDIES (14.3)], the most common adverse reactions in 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 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Levetiracetam (N=769)</th>
<th>Placebo (N=439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>15 (2%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Infection</td>
<td>13 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>7 (1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Aesthesia</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hostility</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Faresness</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

In controlled adult clinical studies, 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Levetiracetam (N=769)</th>
<th>Placebo (N=439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>15 (2%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Infection</td>
<td>13 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>7 (1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Aesthesia</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hostility</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Faresness</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Pediatric Patients: 4 Years to <16 Years:

The adverse reaction data presented below was obtained from a pooled analysis of two controlled pediatric clinical studies in pediatric patients 4 to 16 years of age with partial onset seizures. The most common adverse reactions in pediatric patients receiving 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Levetiracetam (N=165)</th>
<th>Placebo (N=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19 (12%)</td>
<td>15 (10%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15 (12%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (12%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (10%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (8%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Aggression</td>
<td>10 (8%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (6%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>9 (6%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>9 (6%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>8 (5%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Abnormal Behavior</td>
<td>7 (5%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (5%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>7 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>7 (5%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>6 (4%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (3%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>4 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>4 (3%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Head Injury</td>
<td>4 (3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
In the placebo-controlled study, 5% of patients receiving levetiracetam and 8% receiving placebo experienced 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.

**Primary Generalized Tonic-Clonic Seizures**

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

In the controlled clinical study in patients 12 years of age and older with myoclonic seizures, [see CLINICAL STUDIES (14.2)], the most common adverse reactions in patients receiving 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 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Levetiracetam (N=60) %</th>
<th>Placebo (N=60) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Irritability</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Influenza</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Vertigo</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

In the placebo-controlled study, 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Levetiracetam (N=60) %</th>
<th>Placebo (N=56) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnesia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypersomnolence</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Irritability</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Primary Generalized Tonic-Clonic Seizures**

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

In the controlled clinical study that included patients 4 years of age and older with PGTC seizures, [see CLINICAL STUDIES (14.3)], the most common adverse reaction in patients receiving levetiracetam 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Levetiracetam (N=79) %</th>
<th>Placebo (N=84) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Irritability</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mood swings</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

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 marketed levetiracetam worldwide. The listing is alphabetized abnormal liver function test, acute kidney injury, anaphylaxis, angioedema, agranulocytosis, aseptic meningitis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hypersensitivity, 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

Pregnancy Exposure Registry

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

Risk Summary

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

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Consideration

Levetiracetam blood levels may decrease during pregnancy (see WARNINGS AND PRECAUTIONS (5.1)).

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

Data

Human Data

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

Animal Data

When levetiracetam (0, 400, 1200, or 3600 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, reduced fetal weights and increased incidence of fetal skeletal variations were observed at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rats (1200 mg/kg/day) is approximately 4 times the maximum recommended human dose (MRHD) of 3600 mg on a body surface area (mg/m²) basis.

Oral administration of levetiracetam (0, 200, 600, or 1800 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and incidences of fetal skeletal abnormalities at various gestational ages:in the mid- and high-dose and decreased fetal weights and increased incidence of fetal malformations at the high dose, which associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m² basis.

Oral administration of levetiracetam (0, 70, 350, or 1800 mg/kg/day) to pregnant rats during the period of organogenesis increased incidence of fetal skeletal variations, reduced fetal body weight, and decreased growth in offspring at the mid and high dose and decreased fetal weights and increased incidence of fetal malformations at the high dose, which associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m² basis.

8.2 Lactation

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

8.4 Pediatric Use

The safety and effectiveness of levetiracetam for the treatment of partial-onset seizures in patients 1 month to 18 years of age have been established (see CLINICAL STUDIES (14.1)). The dosing recommendation for these pediatric patients varies according to age group and is weight-based (see PHARMACOKINETICS (12.3) and CLINICAL STUDIES (14.1)).

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

The safety and effectiveness of levetiracetam as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established (see CLINICAL STUDIES (14.3)).

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

A 3-month, randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of levetiracetam adjunctive therapy in 98 (levetiracetam N=64, placebo N=34) pediatric patients, ages 4 to 16 years old, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the 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) to 18), a standardized validated tool used to assess a child’s competencies and behavioral/emotional problems, was also assessed in this study. Analysis of the CBCL to 18 indicated no average worsening in levetiracetam-treated patients in aggressive behavior, one of the eight syndrome scores, (see
100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect absorption following oral administration in fasting subjects. The oral bioavailability of levetiracetam tablets is approximately 15%.

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration.

12.3 Pharmacokinetics

The effect of levetiracetam on QTc prolongation was evaluated in a randomized, double-blind, placebo-controlled study in healthy volunteers. Levetiracetam did not cause significant prolongation of QTc interval compared to placebo. The largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of QTc prolongation in this study.

12.2 Pharmacodynamics

Effects on QTc Interval

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

Absorption and Distribution

Absorption of levetiracetam is rapid, with peak plasma concentration occurring in about an hour following oral administration in fasting subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect absorption following oral administration in fasting subjects. The oral bioavailability of levetiracetam tablets is approximately 15%.

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affect the extent of absorption of levetiracetam but it decreases CL\text{total} by 20% and delays T\text{max} by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500 to 5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

**Metabolism**

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

**Elimination**

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 ml/min/kg and the renal clearance is 0.6 ml/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 ml/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment [see USE IN SPECIFIC POPULATIONS (8.6) and DOSAGE AND ADMINISTRATION (2.5)].

**Specific Populations**

**Elderly:**

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61 to 88 years) with creatinine clearance ranging from 30 to 74 ml/min. Following oral administration of twice-daily dosing for 36 days, total body clearance decreased by 30% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

**Pediatric Patients:**

Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 2 to 12 years) after single dose (20 mg/kg). The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher in adults. A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4 to 12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam in infants (2.5 to 22.5 kg) and children (22.5 to 100 kg) demonstrated rapid absorption of levetiracetam at all doses with a T\text{max} of about 1 hour and a t\text{1/2} of 3 hours across the three dosing levels. The pharmacokinetics of levetiracetam in children was linear between 20 to 200 mg/kg/day. The potential interaction of levetiracetam with other AEDs was also evaluated in these patients. Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate or lamotrigine. However, there was about a 22% increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED (e.g., carbamazepine).

Following single dose administration (20 mg/kg) of a 10% oral solution to children with epilepsy (1 month to <4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 mL/min/kg) than for adults (0.96 mL/min/kg). Population pharmacokinetic analysis showed that body weight was significantly correlated to the clearance of levetiracetam in pediatric patients; clearance increased with an increase in body weight.

**Pregnancy:**

Levetiracetam levels may decrease during pregnancy. [see WARNINGS AND PRECAUTIONS (5.10) and USE IN SPECIFIC POPULATIONS (8.1)].

**Gender:**

Levetiracetam C\text{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 Caucasian (N=12) and Asian (N=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

**Renal Impairment:**

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

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CL\text{cr} =70 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure [see DOSAGE AND ADMINISTRATION (2.5)].

**Hepatic Impairment:**

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normals, 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\text{max} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isozymes, 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.

**Phenotype:**

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 was also 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 hormone and
progestrone levels, indicating that impairment of contraceptive efficacy is unlikely. Co-administration 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 at a 0.25 mg dose every day. Co-administration 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. Co-administration 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. Cmax 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. Plasma exposure (AUC) at the highest dose was approximately 6 times that in humans at the maximum recommended daily human dose (MRHD) of 3000 mg. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4800 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to immeasurability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a body surface area (mg/m²) basis.

**Mutagenesis**
Levetiracetam was negative in vitro (Ames, chromosomal aberration in mammalian cells) and in vivo (mouse micronucleus) assays. The major human metabolite of levetiracetam (ucb L057) was negative in vitro (Ames, 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, which were associated with plasma exposures (AUC) up to approximately 6 times that in humans at the MRHD.

### 14 CLINICAL STUDIES

#### 14.1 Partial Onset Seizures

**Effectiveness in Partial-Onset Seizures in Adults**
The effectiveness of levetiracetam for the treatment of partial-onset seizures in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial-onset seizures with or without secondary generalization. The tablet formulation was used in all these studies. In these studies, 904 patients were randomized to placebo, 1000 mg, 2000 mg, or 3000 mg/day. Patients enrolled in Study 1 or Study 2 had refractory partial-onset seizures for at least 2 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 more than 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). Patients were randomized to one of the three treatment groups described above. 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>
<thead>
<tr>
<th></th>
<th>Placebo (N=95)</th>
<th>Levetiracetam 1000 mg/day (N=97)</th>
<th>Levetiracetam 3000 mg/day (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td></td>
<td>26.1%±22.3%</td>
<td>30.1%±25.4%</td>
</tr>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>26.1%*</td>
<td>30.1%*</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th></th>
<th>Placebo (N=111)</th>
<th>Levetiracetam 1000 mg/day (N=106)</th>
<th>Levetiracetam 2000 mg/day (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>17.1%*</td>
<td>21.4%*</td>
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</table>

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 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>
<thead>
<tr>
<th></th>
<th>Placebo (N=104)</th>
<th>Levetiracetam 3000 mg/day (N=180)</th>
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</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>23.0%*</td>
</tr>
</tbody>
</table>

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

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

*statistically significant versus placebo

**Effectiveness in Partial-Onset Seizures in Pediatric Patients 4 to 16 Years of Age**
The effectiveness of levetiracetam as adjunctive therapy for the treatment of partial-onset seizures in pediatric patients was established in one multicenter, randomized double-blind, placebo-controlled study (Study 4), conducted at 60 sites in North America, in pediatric patients 4 to 16 years of age with partial seizures uncontrolled by standard antiepileptic drugs (AEDs). Eligible patients on a stable dose of 1 to 2 AEDs, who still experienced at least 4 partial onset seizures during the 4 weeks prior to screening, as well as at least 4 partial-onset seizures in each of the two 4-week baseline periods, were randomized to receive either levetiracetam or placebo. The enrolled population included 198 patients (levetiracetam N=101, placebo N=97) with refractory partial-onset seizures, whether or not secondarily generalized. The study consisted of an 8-week baseline period and 4-week titration period followed by a 10-week evaluation period. Dosing was initiated at a dose of 20 mg/kg/day in two divided doses. During the treatment period, levetiracetam doses were adjusted in 20 mg/kg/day increments, at 2-week intervals to the target dose of 60 mg/kg/day. The primary measure of effectiveness was a between-group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire 14-week randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from baseline in partial-onset seizure frequency per week). Table 13 displays the results of this study.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=97)</th>
<th>Levetiracetam (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent reduction in partial seizure frequency over placebo</td>
<td>-</td>
<td>26.8%*</td>
</tr>
</tbody>
</table>

The percentage of patients (y-axis) who achieved ≥50% reduction in weekly seizure rates from
Effectiveness in Partial-Onset Seizures in Pediatric Patients 1 Month to < 4 Years of Age

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

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

The effectiveness of levetiracetam as adjunctive therapy in patients 12 years of age and older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 6), conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 antiepileptic drug (AED) experiencing one or more myoclonic seizures per day for at least 8 days during the prospective 8-week baseline period were randomized to either 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 effectiveness was the proportion of patients with at least 50% reduction in the number of days per week with one or more myoclonic seizures during the treatment period (titration + evaluation periods) as compared to baseline. Of the 120 patients enrolled, 113 had a diagnosis of confirmed or suspected JME. Table 14 displays the results for the 113 patients with JME in this study.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=59)</th>
<th>Levetiracetam (N=58)</th>
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</thead>
<tbody>
<tr>
<td>Percentage of responders</td>
<td>23.7%</td>
<td>60.4%*</td>
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</table>

Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

Primary Generalized Tonic-Clonic Seizures

The effectiveness of levetiracetam as adjunctive therapy in patients 6 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic (PGTC) seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 7), conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 antiepileptic drugs (AEDs) experiencing at least 3 PGTC seizures during the 8-week combined baseline period (at least one PGTC seizure during the 4 weeks prior to the prospective baseline period) 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.
weeks (evaluation period). Study drug was given in 2 equally divided doses per day. The primary measure of effectiveness was the percent reduction from baseline in weekly PGTC seizure frequency for 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.

<table>
<thead>
<tr>
<th>Placebo (N=84)</th>
<th>Levetiracetam (N=78)</th>
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<tbody>
<tr>
<td>Percent reduction in PGTC seizure frequency</td>
<td>44.6%</td>
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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 tablets USP, 250 mg are blue coloured, oblong-shaped, biconvex, film-coated tablets debossed with “L” and “U” on either side of the breakline on one side and “X01” on the other side. They are supplied as follows:

- NDC 68180-112-09 Bottles of 90’s
- NDC 68180-112-16 Bottles of 120’s
- NDC 68180-112-02 Bottles of 500’s

Levetiracetam tablets USP, 500 mg are yellow coloured, oblong-shaped, biconvex, film-coated tablets debossed with “L” and “U” on either side of the breakline on one side and “X02” on the other side. They are supplied as follows:

- NDC 68180-113-09 Bottles of 90’s
- NDC 68180-113-16 Bottles of 120’s
- NDC 68180-113-02 Bottles of 500’s

Levetiracetam tablets USP, 750 mg are orange coloured, oblong-shaped, biconvex, film-coated tablets debossed with “L” and “U” on either side of the breakline on one side and “X03” on the other side. They are supplied as follows:

- NDC 68180-114-09 Bottles of 90’s
- NDC 68180-114-16 Bottles of 120’s
- NDC 68180-114-02 Bottles of 500’s

Levetiracetam tablets USP, 1000 mg are white to off-white coloured, oblong-shaped, biconvex, film-coated tablets debossed with “L” and “U” on either side of the breakline on one side and “X04” on the other side. They are supplied as follows:

- NDC 68180-115-07 Bottles of 60’s
- NDC 68180-115-02 Bottles of 500’s

### 16.2 Storage

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

Pharmacist: Dispense in a tight, light-resistant container with child-resistant closure along with medication guide provided separately.

## 17 PATIENT COUNSELING INFORMATION

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

### Psychiatric Reactions and Changes in Behavior

Advise patients that levetiracetam may cause changes in behavior (e.g. aggression, agitation, anger, anxiety, depression, hostility, and irritability) and psychiatric symptoms [see WARNINGS AND PRECAUTIONS (5.1)].

### Suicidal Behavior and Ideation

Advise 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, suicidal tendencies, or unusual changes in mood or behavior; or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their caregivers, and/or families to immediately report behaviors of concern to a healthcare provider [see WARNINGS AND PRECAUTIONS (5.2)].

### Effects on Driving or Operating Machinery

Inform patients that 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 [see WARNINGS AND PRECAUTIONS (5.3)].

### Anaphylaxis and Angioedema

Advise patients to discontinue levetiracetam and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema [see WARNINGS AND PRECAUTIONS (5.4)].

### Dermatological Adverse Reactions

Advising the patient to read the FDA-approved patient labeling (Medication Guide).
Take levetiracetam tablets exactly as prescribed.

How should I take levetiracetam tablets?

Swallow the tablets whole. Do not chew or crush tablets.

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

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

Call your healthcare provider between visits as needed, especially if you are worried about any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.

Do not start a new medicine without first talking to your healthcare provider. 

A healthcare provider will tell you how much levetiracetam tablets to take and when to take it. Levetiracetam tablets are usually taken twice a day.

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

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

Take levetiracetam tablets exactly as prescribed. 

Your healthcare provider will tell you how much levetiracetam tablets to take and when to take it. Levetiracetam tablets are usually taken twice a day.

Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.

Take levetiracetam tablets with or without food.

Swallow the tablets whole. Do not chew or crush tablets. Ask your healthcare provider for levetiracetam oral solution if you cannot swallow tablets.

If you take too much levetiracetam tablets, call your local Poison Control Center or go to the nearest emergency room immediately.
emergency room right away.

What should I avoid while taking levetiracetam tablets?

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

What are the possible side effects of levetiracetam tablets?

can cause serious side effects including:

- See “What is the most important information I should know about levetiracetam tablets?”

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

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

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

- sleepiness
- infection
- weakness
- dizziness

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

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

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of levetiracetam tablets. For more information, ask your healthcare provider or pharmacist.

How should I store Levetiracetam tablets?

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

Keep Levetiracetam tablets and all medicines out of the reach of children.

General information about safe and effective use of Levetiracetam Tablets.

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

What are the ingredients of levetiracetam tablets?

Leveretiracetam tablets

active ingredient: levetiracetam

For 250 mg, 500 mg and 750 mg strengths:

Inactive ingredients: colloidal silicon dioxide, corn starch, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, titanium dioxide, and additional agents listed below:

250 mg tablets:
- FD & C Blue No. 2/indigo carmine Aluminum Lake

500 mg tablets:
- Yellow Iron Oxide

750 mg tablets:
- FD & C Blue No. 2/indigo carmine Aluminum Lake, FD & C Yellow No. 6/sunset yellow PCE Aluminum Lake, iron oxide red

For 1000 mg strength:

Inactive ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc and titanium dioxide.

Leveretiracetam tablets do not contain lactose or gluten.

This Medication Guide has been approved by the US Food and Drug Administration.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States.

MADE IN INDIA.

Revised: January 2020

ID#: 263339
### Leviteracem Tablets USP

**Rx Only**

*****

#### Leviteracem Tablets USP

**Rx Only**

- **750 mg**
- **1000 mg**

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#### Leviteracem Tablets USP

**Rx Only**

- **1000 mg**

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### LEVITERACETAM

**leviteracem tablet, film coated**

#### Product Information

- **Product Type:** HUMAN PRESCRIPTION DRUG
- **Item Code (Source):** NDC:68180-112

#### Route of Administration

- **ORAL**

#### Active Ingredient/Active Moiety

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<th>Basis of Strength</th>
<th>Strength</th>
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</thead>
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<tr>
<td>LEVITERACETAM (UNII: 44YRR34555)</td>
<td>LEVITERACETAM</td>
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#### Inactive Ingredients

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<tr>
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<td>FD&amp;C BLUE NO. 2</td>
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<td>HYPROMELLOSE (6 MPA.S)</td>
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<td>MAGNESIUM STEARATE</td>
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#### Product Characteristics

- **Color:** BLUE (Blue)
- **Shape:** OVAL (Oblong-shaped, Biconvex, Film-Coated)
- **Size:** 15mm
- **Score:** 2 pieces

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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Marketing Information

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LEVETIRACETAM

levetiracetam tablet, film coated

Product Information

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<td>NDC:68180-113</td>
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Active Ingredient/Active Mixture

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<th>Ingredient Name</th>
<th>Basis of Strength</th>
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inactive ingredients

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Product Characteristics

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Packaging

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Marketing Information

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<th>Category</th>
<th>Application Number or Monograph Citation</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
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<tbody>
<tr>
<td>ANDA</td>
<td>ANDA078154</td>
<td>01/15/2009</td>
<td></td>
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</tbody>
</table>

LEVETIRACETAM

levetiracetam tablet, film coated

Product Information

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Item Code (Source)</th>
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</thead>
<tbody>
<tr>
<td>HUMAN PRESCRIPTION DRUG</td>
<td>NDC:68180-114</td>
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Active Ingredient/Active Mixture

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
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inactive ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
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</table>

Product Characteristics

<table>
<thead>
<tr>
<th>Color</th>
<th>Shape</th>
<th>Size</th>
<th>Flavor</th>
<th>Imprint Code</th>
</tr>
</thead>
</table>

Packaging

<table>
<thead>
<tr>
<th>Item Code</th>
<th>Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
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</table>

Marketing Information

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<tr>
<th>Category</th>
<th>Application Number or Monograph Citation</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
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<tr>
<td>ANDA</td>
<td>ANDA078154</td>
<td>01/15/2009</td>
<td></td>
</tr>
</tbody>
</table>
**LEVERTIRACETAM**
levetiracetam tablet, film coated

**Product Information**
- **Product Type**: HUMAN PRESCRIPTION DRUG
- **Route of Administration**: ORAL

**Active Ingredient/Active Mixture**
- **Ingredient Name**: LEVERTIRACETAM
- **Code (Source)**: NDC:68180-115-07

**Inactive Ingredients**
- **Ingredient Name**: CELLULOSE, MICROCRYSTALLINE (UNII: O01WK00X41)
- **Strenght**: 1000 mg

**Product Characteristics**
- **Color**: WHITE (White to off-white)
- **Shape**: OVAL (Oblong-shaped, Biconvex, Film-Coated)
- **Size**: 22mm
- **Flavor**: Imprint Code: L;U;X04

**Packaging**

<table>
<thead>
<tr>
<th># Item Code</th>
<th>Package Description</th>
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<th>Marketing End Date</th>
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<td>60 in 1 BOTTLE; Type 0: Not a Combination Product</td>
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<td>NDC:68180-115-02</td>
<td>500 in 1 BOTTLE; Type 0: Not a Combination Product</td>
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**Marketing Information**
- **Marketing Category**: ANDA
- **Application Number or Monograph Citation**: ANDA078154
- **Marketing Start Date**: 01/15/2009
- **Marketing End Date**: 01/15/2009

**Labeler** - Lupin Pharmaceuticals, Inc. (089153071)

**Registrant** - LUPIN LIMITED (675923163)

**Establishment**
- **Name**: LUPIN LIMITED
- **Address**: 67000032

**Establishment**
- **Name**: LUPIN LIMITED
- **Address**: 67500027

Revised: 1/2020

Lupin Pharmaceuticals, Inc.