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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LEVETIRACETAM tablets, for oral use Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions (5.6) 3/2024

INDICATIONS AND USAGE

Levetiracetam tablets are indicated for the treatment of partial-onset seizures in patients 1 month of age and older (1.1)

Levetiracetam tablets are indicated for adjunctive therapy for the treatment of: Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy (1.2) Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy (1.3)

DOSAGE AND ADMINISTRATION

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

Partial-Onset Seizures (monotherapy or adjunctive therapy)

- 4 Month to < 6 Months: 7 mg/kg twice daily; increase by 7 mg/kg twice daily every 2 weeks to recommended dose of 21 mg/kg twice daily (2.2)
6 Months to < 4 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 25 mg/kg twice daily (2.2)
4 Years to < 16 Years: 10 mg/kg twice daily; increase by 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily (2.2)
Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to a recommended dose of 1500 mg twice daily (2.2)

Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older
500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.3)

Primary Generalized Tonic-Clonic Seizures

- 6 Years to < 16 Years: 10 mg/kg twice daily; increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily (2.4)
Adults 16 Years and Older: 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.4)

Adult Patients with Impaired Renal Function

- Dose adjustment is recommended, based on the patient's estimated creatinine clearance (2.5, 8.6)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Partial-Onset Seizures
Levetiracetam tablets are indicated for the treatment of partial-onset seizures in patients 1 month of age and older.

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions
Levetiracetam tablets are given orally with or without food. The levetiracetam dosing regimen depends on the indication, age group, dosing form (tablets or oral solution), and renal function.

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

When using the oral solution 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 every 2 weeks by an increment 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 50 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 47 mg/kg. The maximum daily dose was 3000 mg/day.

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.

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:

Total daily dose (mL/day) = (Daily dose (mg/kg/day) x patient weight (kg)) / 100 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 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.

2.4 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 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 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 Adult Patients 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, the 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:

CLcr = (140-age (years)) x weight (kg) / 72 x serum creatinine (mg/dL) x 0.85 for female patients

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

CLcr (mL/min/1.73m²) = CLcr (mL/min) / BSA subject (m²) x 1.73

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

Table with 5 columns: Group, Creatinine Clearance (mL/min/1.73m²), Dosage (mg), Frequency, and Duration. Rows include Normal, Mild, Moderate, Severe, and ESRD patients using dialysis.

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

DOSAGE FORMS AND STRENGTHS

- 250 mg, 500 mg, 750 mg, and 1000 mg film-coated, scored tablets (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Behavioral abnormalities including psychotic symptoms, suicidal ideation, irritability, and aggressive behavior have been observed; monitor patients for psychiatric signs and symptoms (5.1)
Suicidal Behavior and Ideation: Monitor patients for new or worsening depression, suicidal thoughts/behavior, or unusual changes in mood or behavior (5.2)
Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam (5.3)
Serious Dermatological Reactions: Discontinue levetiracetam at the first sign of rash unless clearly not drug related (5.5)
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multorgan Hypersensitivity: Discontinue if no alternative etiology (5.6)
Coordination Difficulties: Monitor for ataxia, abnormal gait, and incoordination. Advise patients not to drive or operate machinery until they have gained experience on levetiracetam (5.7)
Withdrawal Seizures: Levetiracetam must be gradually withdrawn (5.8)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5% more than placebo) include: Adult patients: somnolence, asthenia, infection and dizziness (6.1) Pediatric patients: fatigue, aggression, nasal congestion, decreased appetite, and irritability (6.1)

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

USE IN SPECIFIC POPULATIONS

Pregnancy: Plasma levels of levetiracetam may be decreased and therefore need to be monitored closely during pregnancy. Based on animal data, may cause fetal harm (5.11, 8.1)

PATIENT COUNSELING INFORMATION AND Medication Guide.

Revised: 04/2024

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2.6 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 (5.8)).

3 DOSAGE FORMS AND STRENGTHS

Levetiracetam tablets: 250 mg are white colored, oblong shaped, scored, film coated tablets debossed with 'H' on one side and '87' on other side. Levetiracetam tablets USP, 500 mg are yellow colored, oblong shaped, scored, film coated tablets debossed with 'H' on one side and '98' on other side.

Levetiracetam tablets USP, 750 mg are orange colored, oblong shaped, scored, film coated tablets debossed with 'H' on one side and '90' on other side. Levetiracetam tablets USP, 1000 mg are white colored, oblong shaped, scored, film coated tablets debossed with 'H' on one side and '91' on other side.

4 CONTRAINDICATIONS

Levetiracetam tablets are contraindicated in patients with a hypersensitivity to levetiracetam. Reactions have included anaphylaxis and angioedema. (See Warnings and Precautions (5.4)).

5 WARNINGS AND PRECAUTIONS

5.1 Behavioral Abnormalities and Psychotic Symptoms

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

Behavioral abnormalities

In clinical studies, 13% of adult levetiracetam-treated patients and 38% of pediatric levetiracetam-treated patients (4 to 16 years of age) compared to 6% and 19% of adult and pediatric placebo-treated patients, experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, irritability, nervousness, neurosis, and personality changes) (see Clinical Studies (14.1)).

A randomized double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in levetiracetam-treated patients on aggressive behavior (one of eight behavior dimensions) as measured in a standardized and systematic way using a validated instrument, the Achenbach Child Behavior Checklist (CBCL) (5.18).

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, 17% 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 patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6% of placebo-treated patients.

Psychotic symptoms

In clinical studies, 1% of levetiracetam-treated adult patients, 2% of levetiracetam-treated pediatric patients 4 to 16 years of age, and 17% of levetiracetam-treated pediatric patients 6 to < 16 years of age experienced psychotic symptoms, compared to 0.2%, 2%, and 5% in the corresponding age groups treated with placebo. In a controlled study that assessed the neurocognitive and behavioral effects of levetiracetam in pediatric patients 4 to 16 years of age, 1.6% of levetiracetam-treated patients experienced paranoia, compared to 0% of placebo-treated patients in the same study. 3.1% of levetiracetam-treated patients experienced confusional state, compared to 0% of placebo-treated patients (see Use in Specific Populations (8.1)).

In clinical studies, two (0.3%) levetiracetam-treated adult patients were hospitalized and their treatment was discontinued due to psychosis. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. There was no difference between drug and placebo-treated patients in the incidence of the pediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

5.2 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including levetiracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI [1.2, 2.7]) of suicidal thoughts or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,865 AED-treated patients was 43%, compared to 24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thoughts or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included patients who were not being treated for depression, 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 all evaluated AEDs.

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

Table with 5 columns: Indication, Placebo Patients with Events Per 1000 Patients, Drug Patients with Events Per 1000 Patients, Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients, Risk Difference: Additional Drug Patients/Events Per 1000 Patients. Rows include Epilepsy, Psychiatric, Other, and Total.

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

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

5.3 Somnolence and Fatigue

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

Somnolence

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 15% of levetiracetam-treated patients reported somnolence, compared to 8% of placebo-treated patients. There was no clear dose response up to 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.

Asthenia

In controlled clinical studies of adult patients with epilepsy experiencing partial-onset seizures, 15% of levetiracetam-treated patients reported asthenia, compared to 9% of placebo-treated patients. Treatment was discontinued due to asthenia in 0.8% of levetiracetam-treated patients as compared to 0.5% of placebo-treated patients. In 0.5% of levetiracetam-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to asthenia.

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

5.4 Anaphylaxis and Angioedema

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

5.5 Serious Dermatological Reactions

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

5.6 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including levetiracetam. These events can be fatal or life-threatening, particularly if diagnosis and treatment do not occur as early as possible. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes with a positive direct Coombs' test. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not listed here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Levetiracetam should be discontinued if an alternative etiology for the signs or symptoms cannot be established. (See Contraindications (4)).

5.7 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. In the levetiracetam-treated patients who were 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.

5.8 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.

5.9 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 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 10¹²/mm³), 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 (≤ 2.8 x 10¹²/mm³ decreased WBC, and 2.4% of levetiracetam-treated and 1.4% of placebo-treated patients had at least one possibly significant (≤ 1.0 x 10¹²/mm³ decreased neutrophil count). Of the levetiracetam-treated patients with a 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 10¹²/mm³ and -0.3 x 10¹²/mm³, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in levetiracetam-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

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

In the controlled cognitive and neuropsychological safety study, 5 patients (8.6%) in the levetiracetam-treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant (≥ 10% or > 0.7 x 10⁹/L).

5.10 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.

5.11 Seizure Control During Pregnancy

Levetiracetam 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))
Anaphylaxis and Angioedema (See Warnings and Precautions (5.4))
Serious Dermatological Reactions (See Warnings and Precautions (5.5))
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multorgan Hypersensitivity (See Warnings and Precautions (5.6))
Coordination Difficulties (See Warnings and Preca

The listing is alphabetized: abnormal liver function test, acute kidney injury, anaphylaxis, angioedema, agranulocytosis, choroatretosis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hypomagnesemia, muscular weakness, obsessive-compulsive disorders (OCD), pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, weight loss, and worsening of seizures including in patients with SCN8A mutations. 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 exposure with levetiracetam in pregnant women has not identified a drug-associated risk of major birth defects or miscarriage, based on published literature, which includes data from pregnancy registries and reflects experience over two decades (see Human Data). In animal studies, levetiracetam produced developmental toxicity (increased embryofetal and offspring mortality, increased incidences of fetal structural abnormalities, decreased embryofetal and offspring growth, neurobehavioral alterations in offspring) at doses similar to human therapeutic doses (see Animal Data).
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Levetiracetam blood levels may decrease during pregnancy (see Warnings and Precautions (5.1)).

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

Data

Human Data

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

Animal Data

When levetiracetam (0, 400, 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 3000 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 incidence of fetal skeletal variations at the mid and high dose and decreased fetal weights and increased incidence of fetal malformations at the high dose, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m² basis.
Oral administration of levetiracetam (0, 70, 250, or 800 mg/kg/day) to female rats throughout pregnancy and lactation led to an increased incidence of fetal skeletal variations, reduced fetal body weight, and decreased growth in offspring at the mid and high doses and increased pup mortality and neurobehavioral alterations in offspring at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on pre- and post-natal development in rats (70 mg/kg/day) is less than the MRHD on a mg/m² basis.
Oral administration of levetiracetam to rats during the latter part of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m² basis).

2.2 Lactation

Levetiracetam is excreted in human milk. There are no data on the effects of levetiracetam on the breastfed infant, or the effects on milk production.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for levetiracetam and any potential adverse effects on the breastfed infant from levetiracetam or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of levetiracetam for the treatment of partial-onset seizures in patients 1 month to 16 years of age have been established (see Clinical Pharmacology (12.3) and Clinical Studies (14.1)). The dosing recommendation in these pediatric patients varies according to age group and is weight-based (see Dosage and Administration (2.2)).
The safety and effectiveness of levetiracetam as adjunctive therapy for the treatment of myoclonic seizures in adolescents 12 years of age and older with juvenile myoclonic epilepsy have been established (see Clinical Studies (14.2)).
The safety and effectiveness of levetiracetam as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients 6 years of age and older with idiopathic generalized epilepsy have been established (see Clinical Studies (14.3)).

Safety and effectiveness for the treatment of partial-onset seizures in pediatric patients below the age of 1 month; 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 as adjunctive therapy in 98 (levetiracetam N=44, placebo N=54) 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 memory non-inferiority of the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/4 to 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/4 to 18 indicated no overall differences in levetiracetam-treated patients in aggressive behavior, one of the eight syndrome scores (see Warnings and Precautions (5.1)).

Juvenile Animal Toxicity Data
Studies of levetiracetam in juvenile rats (dosed on postnatal days 4 through 52) and dogs (dosed from postnatal weeks 3 through 7) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m² basis) did not demonstrate adverse effects on postnatal development.

8.5 Geriatric Use

There were 347 subjects in clinical studies of levetiracetam that were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of levetiracetam 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

Levetiracetam clearance is decreased in patients with renal impairment and is correlated with creatinine clearance (see Clinical Pharmacology (12.3)). Dose adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis (see Dosage and Administration (2.5)).

10 OVERDOSAGE

10.1 Signs, Symptoms and Laboratory Findings of Acute Overdose in Humans
The highest known dose of levetiracetam received in the clinical development program was 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 managed with levetiracetam overdoses in postmarketing use.

10.2 Management of Overdose

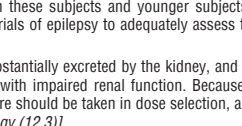
There is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs 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 is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow), 750 mg (orange), and 1000 mg (white) tablets for oral administration.
The chemical name of levetiracetam, a single enantiomer, is (-)-(+)-S)- α -ethyl-2-oxo-1-pyrrolidine acetonamide, its molecular formula is C₁₁H₁₆N₂O, and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:



Levetiracetam USP is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (1:400 mg/mL). It is freely soluble in chloroform (653 mg/mL) and in methanol (536 mg/mL), soluble in ethanol (165 mg/mL), and sparingly soluble in acetonitrile (57 mg/mL) and practically insoluble in n-hexane. (Solubility limits are expressed as mg/mL solvent.)
Levetiracetam tablets, USP contain the labeled amount of levetiracetam USP. Inactive ingredients: corn starch, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, povidone, talc and additional agents listed below.
250 mg tablets: opadry II blue FD&C blue #2/pindigo carmine aluminum lake, polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc
500 mg tablets: opadry II yellow (iron oxide yellow, polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc)
750 mg tablets: opadry II orange (FD&C yellow #6/ sunset yellow FCF aluminum lake, iron oxide red, polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc)
1000 mg tablets: opadry II white (polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc) USP Dissolution test is 4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

The pharmacokinetics of levetiracetam are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures.
Absorption and Distribution
Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of

absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{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. There are no statistically 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). It is not dependent on CYP and/or cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydrolyzation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 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 10 days, total body clearance decreased by 38% and renal clearance by 50% compared to younger subjects. This is most likely due to the decrease in renal function in these subjects.
Pediatric Patients
Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6 to 12 years) after single dose (20 mg/kg). The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults.
A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4 to 12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (*ucb* L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a *t*_{1/2} of approximately 1 hour and a *t*_{1/2} of 5 hours across the three dosing levels. The pharmacokinetics of levetiracetam in children was linear between 20 to 60 mg/kg/day. The potential interaction of levetiracetam with other AEDs was also evaluated in these patients. Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate or lamotrigine. However, there was about a 22% increase in apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED (e.g. carbamazepine).
Following single dose administration (20 mg/kg) of a 10% oral solution to children with epilepsy (1 month to < 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 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.

Pediatric Patients with Obesity

A population PK analysis of levetiracetam was conducted in 164 obese and non-obese pediatric patients 2 to < 18 years of age with median (range) weight 39.2 (11.3 to 134 kg) to evaluate the potential impact of obesity on plasma levetiracetam exposures. Obesity was defined as BMI ≥25th percentile for age and sex based on CDC 2000 growth chart recommendations. Simulations were conducted for obese and non-obese pediatric patients ages 4 to < 15 years.

• When the recommended tablet dose is administered to pediatric patients weighing < 40 kg, obese pediatric patients have 27% higher median C_{max} and 19% higher median C_{min} compared to non-obese patients.
• When the recommended tablet dose is administered to pediatric patients weighing ≥ 40 kg, obese pediatric patients have 10 to 11% lower median C_{max} and 2% lower median C_{min} compared to non-obese patients.
• When the recommended oral solution dose is administered to pediatric patients across the full weight range, obese pediatric patients have 25% higher median C_{max} and 41% higher median C_{min} compared to non-obese pediatric patients.

However, differences in exposures between obese and non-obese pediatric patients are not expected to be clinically meaningful because the recommended dose titration at initiation of levetiracetam therapy would establish an appropriate dose for each individual patient.
Pregnancy
Levetiracetam levels may decrease during pregnancy (see Warnings and Precautions (5.1)) and Use in Specific Populations (8.1)).
Gender
Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, 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=72) and Asians (N=12) showed no differences in pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Renal Impairment

The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CL_{CR} = 50 to 80 mL/min), 50% in the moderate group (CL_{CR} = 30 to 50 mL/min) and 60% in the severe renal impairment group (CL_{CR} < 30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.
In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (N=10). 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 B) 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 isoenzymes, 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, valproic acid, carbamazepine, 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 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 concentrations 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_{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 complete 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. Lifetime exposure (AUC) was the highest dose of 1800 mg/kg/day. Levetiracetam (3000 mg/day) and placebo (N=95) were administered to 94 patients who were randomized to placebo, 1000 mg, 2000 mg, or 3000 mg/kg/day, lowered to 3000 mg/kg/day after 46 weeks due to intertolerability) 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 *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 *in vitro* (Ames, mouse lymphoma) assays.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 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 three studies. In these studies, 904 patients were randomized to placebo, 1000 mg, 2000 mg, or 3000 mg/kg/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 oral 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 2000 mg/day (N=105), 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.

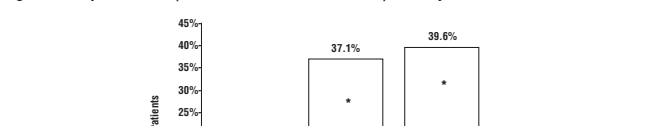
Table 10: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 1

| | 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.

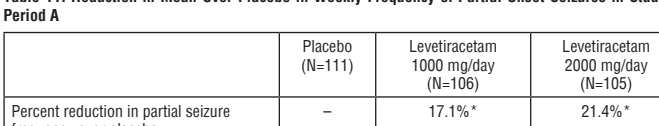
Table 11: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 2: Period A

| | 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 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.

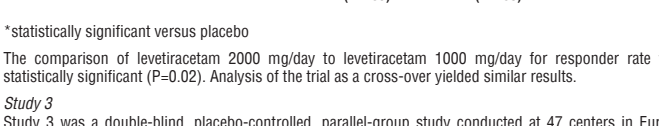
Table 12: Reduction in Mean Over Placebo in Weekly Frequency of Partial-Onset Seizures in Study 3

| | Placebo (N=104) | Levetiracetam 3000 mg/day (N=180) |
|---|-----------------|-----------------------------------|
| Percent reduction in partial seizure frequency over placebo | - | 23.0%* |

*statistically significant versus placebo

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

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



*statistically significant versus placebo

The effectiveness 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 | | |



| | | | | |
|----------------------|---|----------------------|---|-------------------|
| | | | | |
| Material Code | 2081647 | | | |
| Material Description | Printed prescribed information leaflet for levetiracetam tablets, USP 250mg/500mg/750mg/1000mg camber united states | | | |
| Market/ Country | USA | Customer | Camber | |
| Dimensions | Open Length (L) in mm | | Open Width (W) in mm | |
| | 385 | | 600 | |
| | Folded Length (L) in mm | | Folded Width (W) in mm | |
| | 33 | | 33 | |
| PIL Type | <input checked="" type="checkbox"/> Booklet/ <input type="checkbox"/> Pre-fold/ <input type="checkbox"/> Open form | Pharma Code | Front | Back |
| | | | 110 | 111 |
| Type of Paper | <input checked="" type="checkbox"/> Bible / <input type="checkbox"/> Maplitho | Grammage | <input type="checkbox"/> 31 GSM/ <input checked="" type="checkbox"/> 40 GSM/ <input type="checkbox"/> 60 GSM | |
| Barcode | <input type="checkbox"/> 1D / <input checked="" type="checkbox"/> 2D <input type="checkbox"/> NA | Non-Printing Colours | ■ Diecut | |
| Printing Colours(01) | Black | | | |
| If Any | Font Style: Headlines: Helvetica Condensed Bold 6pt Text matter: Helvetica Condensed Regular 6pt | | | |
| | Prepared By | Reviewed By | Reviewed By | Approved By |
| Department | Packaging Development | Regulatory Affairs | Production | Quality Assurance |
| Signature | | | | |
| Date | | | | |