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

ELEPSIA™ XR (levetiracetam) extended-release tablets, for oral use
Initial U.S. Approval: 1999

---------- INDICATIONS AND USAGE ----------
ELEPSIA XR is indicated for adjunctive therapy in the treatment of partial onset seizures in patients ≥12 years of age with epilepsy (1)

---------- DOSAGE AND ADMINISTRATION ----------
- ELEPSIA XR is administered once daily; treatment should be initiated with a dose of 1,000 mg once daily; the dosage may be adjusted in increments of 1,000 mg every 2 weeks, to a maximum recommended dose of 3,000 mg once daily (2.1)
- ELEPSIA XR should be taken whole; do not split or cut tablets (2.1)
- Not recommended for use in patients with moderate or severe renal impairment; the maximum recommended dose in patients with mild renal impairment is 2,000 mg (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Extended-release tablets, 1,000 mg, 1,500 mg (3)

---------- CONTRAINDICATIONS ----------
None (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Psychiatric Reactions: Monitor patients for behavioral abnormalities including psychotic symptoms, irritability, and aggressive behavior (5.1)
- Suicidal Behavior and Ideation: Monitor patients for new or worsening depression, suicidal thoughts/behavior, and/or unusual changes in mood or behavior (5.2)
- Somnolence and Fatigue: Monitor patients for these symptoms and advise patients not to drive or operate machinery until they have gained sufficient experience on ELEPSIA XR (5.3)
- Withdrawal Seizures: ELEPSIA XR must be withdrawn gradually (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥5% greater in ELEPSIA XR-treated patients than on placebo) include somnolence and irritability (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy: Plasma levels of levetiracetam may be decreased during pregnancy and need to be monitored closely. Based on animal data, may cause fetal harm (5.8, 8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ELEPSIA XR is indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥12 years of age with epilepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

ELEPSIA XR is administered once daily.

Treatment should be initiated with a dose of 1,000 mg once daily. The once daily dosage may be adjusted in increments of 1,000 mg every 2 weeks to a maximum recommended once daily dose of 3,000 mg.

ELEPSIA XR should be taken whole; do not split or cut tablets.

2.2 Dosage in Patients with Renal Impairment

ELEPSIA XR is not recommended for patients with moderate or severe renal impairment. Recommended doses and adjustment for patients with mild renal impairment are shown in Table 1. In order to calculate the dose recommended for patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min must first be calculated using the following formula:

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

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

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

Table 1: Dosing Adjustment Regimen For Adult Patients With Impaired Renal Function

Group	Creatinine Clearance ($mL/min/1.73m^2$)	Dosage (mg)	Frequency
Normal	greater than 80	1,000 to 3,000	Every 24 hours
Mild	50 to 80	1,000 to 2,000	Every 24 hours

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets:

- 1,000 mg: oval biconvex, coated, blue and white to off-white, bilayer tablet with drilled portal on blue layer; imprinted with "574" with black ink on one side and plain on the other side.
- 1,500 mg: oval biconvex, coated, blue and white to off-white, bilayer tablet with drilled portal on blue layer; imprinted with "575" with black ink on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Psychiatric Reactions

Patients taking ELEPSIA XR should be monitored for behavioral abnormalities.

Levetiracetam Extended-Release Tablets

A total of 6.5% of patients treated with levetiracetam extended-release tablets experienced non-psychotic behavioral disorders (reported as irritability and aggression), compared to no patient on placebo. Irritability was reported in 6.5% of patients treated with levetiracetam extended-release tablets. Aggression was reported in 1.3% of patients treated with levetiracetam extended-release tablets.

No patient discontinued treatment or had a dose reduction as a result of these adverse reactions.

There is considerably less controlled clinical trial experience with levetiracetam extended-release tablets than with immediate-release levetiracetam tablets, and some adverse reactions observed with immediate-release levetiracetam tablets may not have been detected in levetiracetam extended-release tablets clinical trials because of limited number of patients. These adverse reactions may however occur in patients receiving ELEPSIA XR.

Immediate-Release Levetiracetam Tablets

A total of 13.3% of adult patients and 37.6% of pediatric patients (4 to 16 years of age) treated with immediate-release levetiracetam tablets experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder), compared to 6.2% and 18.6% of adult and pediatric patients on placebo. A randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of immediate-release levetiracetam tablets as adjunctive therapy in pediatric patients (4 to 16 years of age). An exploratory analysis suggested a worsening in aggressive behavior in patients treated with immediate-release levetiracetam tablets in that study *[see Use in Specific Populations (8.4)]*.

A total of 1.7% of adult patients treated with immediate-release levetiracetam tablets discontinued treatment due to behavioral adverse events, compared to 0.2% of patients on placebo. The treatment dose was reduced in 0.8% of adult patients treated with immediate-release levetiracetam tablets, compared to 0.5% of patients on placebo. Overall, 10.9% of pediatric patients treated with immediate-release levetiracetam tablets experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6.2% of pediatric patients on placebo.

One percent of adult patients and 2% of pediatric patients (4 to 16 years of age) treated with immediate-release levetiracetam tablets experienced psychotic symptoms, compared to 0.2% and 2%, respectively, in adult and pediatric patients on placebo. In the controlled study that assessed the neurocognitive and behavioral effects of immediate-release levetiracetam tablets in pediatric patients 4 to 16 years of age, 1 (1.6%) patient treated with levetiracetam experienced paranoia, compared to no patients on placebo. There were 2 (3.1%) patients treated with immediate-release levetiracetam tablets who experienced confusional state, compared to no patients on placebo *[see Use in Specific Populations (8.4)]*.

Two (0.3%) adult patients treated with immediate-release levetiracetam tablets were hospitalized, and their treatment was discontinued due to psychosis. In both patients, the psychosis event 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 pediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

5.2 Suicidal Behavior and Ideation

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

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Risk By Indication For Antiepileptic Drugs In The Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

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

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

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

5.3 Somnolence and Fatigue

Patients should be monitored for somnolence and fatigue, and be advised not to drive or operate machinery until they have gained sufficient experience on levetiracetam extended-release tablets to gauge whether it adversely

affects their ability to drive or operate machinery. In clinical trials of immediate-release levetiracetam tablets, somnolence and asthenia occurred most frequently within the first 4 weeks of treatment.

Levetiracetam Extended-Release Tablets

In the levetiracetam extended-release tablets double-blind, controlled trial in patients experiencing partial onset seizures, 7.8% of patients treated with levetiracetam extended-release tablets experienced somnolence compared to 2.5% of patients on placebo.

No patient discontinued treatment or had a dose reduction as a result of these adverse reactions.

There is considerably less controlled clinical trial experience with levetiracetam extended-release tablets than with immediate-release levetiracetam tablets, and some adverse reactions observed with immediate-release levetiracetam tablets may not have been detected in levetiracetam extended-release tablets clinical trials because of limited number of patients. These adverse reactions may however occur in patients receiving ELEPSIA XR.

Immediate-Release Levetiracetam Tablets

In general, the incidences of somnolence and fatigue in the pediatric partial onset seizure studies were comparable to those of the adult partial onset seizure studies.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.8% of patients treated with immediate-release levetiracetam tablets reported somnolence, compared to 8.4% of patients on placebo. There was no clear dose response up to 3,000 mg/day. In a study in which there was no titration, about 45% of patients receiving 4,000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of patients treated with immediate-release levetiracetam tablets, compared to no patients on placebo. About 3% of patients treated with immediate-release levetiracetam tablets discontinued treatment due to somnolence, compared to 0.7% of patients on placebo. The dose was reduced due to somnolence in 1.4% of patients treated with immediate-release levetiracetam tablets and in 0.9% of patients on placebo, while 0.3% of the patients treated with immediate-release levetiracetam tablets were hospitalized due to somnolence.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.7% of patients treated with immediate-release levetiracetam tablets reported asthenia, compared to 9.1% of patients on placebo. Treatment was discontinued due to asthenia in 0.8% of patients treated with immediate-release levetiracetam tablets, compared to 0.5% of patients on placebo. The dose was reduced due to asthenia in 0.5% of patients treated with immediate-release levetiracetam tablets and in 0.2% of patients on placebo.

5.4 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults 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 extended-release tablets 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.

5.5 Coordination Difficulties

Patients should be monitored for coordination difficulties and advised not to drive or operate machinery until they have gained sufficient experience on levetiracetam extended-release tablets to gauge whether it could adversely affect their ability to drive or operate machinery.

A total of 3.4% of adult patients treated with immediate-release levetiracetam tablets experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination), compared to 1.6% of patients on placebo. A total of 0.4% of patients in controlled trials discontinued immediate-release levetiracetam tablets treatment due to ataxia, compared to no patients on placebo. In 0.7% of patients treated with immediate-release levetiracetam tablets and in 0.2% of patients on placebo, the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of preexisting ataxia. These events occurred most frequently within the first 4 weeks of treatment.

Coordination difficulties were not observed in the levetiracetam extended-release tablets controlled trial. There is considerably less controlled clinical trial experience with levetiracetam extended-release tablets than with immediate-release levetiracetam tablets, and some adverse reactions observed with immediate-release levetiracetam tablets may not have been detected in levetiracetam extended-release tablets clinical trials because of limited number of patients. These adverse reactions may however occur in patients receiving ELEPSIA XR.

5.6 Withdrawal Seizures

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

5.7 Hematologic Abnormalities

Although there were no obvious hematologic abnormalities observed in the levetiracetam extended-release tablets controlled study, there is considerably less controlled clinical trial experience with levetiracetam extended-release tablets than with immediate-release levetiracetam tablets, and some adverse reactions observed with immediate-release levetiracetam tablets may not have been detected in levetiracetam extended-release tablets clinical trials because of limited number of patients. These adverse reactions may however occur in patients receiving ELEPSIA XR.

In controlled trials, a minor but statistically significant decrease (compared to placebo) in total mean RBC count ($0.03 \times 10^6/mm^3$), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), was seen in adult patients treated with immediate-release levetiracetam tablets. A total of 3.2% of adult patients treated with immediate-release levetiracetam tablets, and 1.8% of patients on placebo had at least one possibly significant ($\leq 2.8 \times 10^9$/L) decreased WBC, and 2.4% of patients treated with immediate-release levetiracetam tablets vs. 1.4% of patients on placebo had at least one possibly significant ($\leq 1.0 \times 10^9$/L) decreased neutrophil count. Of the patients treated with immediate-release levetiracetam tablets 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.

In pediatric patients (4 to <16 years of age), statistically significant decreases in WBC and neutrophil counts were seen in patients treated with immediate-release levetiracetam tablets, as compared to placebo. The mean decreases from baseline in the immediate-release levetiracetam tablets group were -0.4×10^9/L and -0.3×10^9/L, respectively, whereas there were small increases in the placebo group. A significant increase in mean relative lymphocyte counts was observed in 1.7% of patients treated with immediate-release levetiracetam tablets compared to a decrease of 4% in patients on placebo.

In the controlled pediatric trial, a possibly clinically significant abnormal low WBC value was observed in 3% of patients treated with immediate-release levetiracetam tablets, compared to no patients on placebo. However, there was no apparent difference between treatment groups with respect to neutrophil count. No patient was discontinued secondary to low WBC or neutrophil counts.

In the controlled pediatric cognitive and neuropsychological safety study, two subjects (6.1%) in the placebo group and 5 subjects (8.6%) in the immediate-release levetiracetam tablets-treated group had high eosinophil count values that were possibly clinically significant (≥10% or ≥0.7X10^9/L).

5.8 Seizure Control During Pregnancy

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

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Psychiatric Reactions *[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)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.4)]*
- Coordination Difficulties *[see Warnings and Precautions (5.5)]*
- Withdrawal Seizures *[see Warnings and Precautions (5.6)]*
- Hematologic Abnormalities *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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

The prescriber should be aware that the adverse reaction incidence figures in the following table, obtained when levetiracetam extended-release tablets were added to concurrent AED therapy, cannot be used to predict the frequency of adverse reactions in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical trials. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse reaction incidences in the population studied.

Levetiracetam Extended-Release Tablets

In the controlled clinical study using levetiracetam extended-release tablets in patients with partial onset seizures (Study 1), the most frequently reported adverse reactions in patients receiving levetiracetam extended-release tablets in combination with other AEDs, for events with rates greater than placebo, were irritability and somnolence.

Table 3 lists adverse reactions that occurred in at least 5% of epilepsy patients treated with levetiracetam extended-release tablets participating in the placebo-controlled study (Study 1) and were numerically more common than in patients treated with placebo. In this study, either levetiracetam extended-release tablets or placebo was added to concurrent AED therapy.

Table 3: Incidence (%) Of Adverse Reactions In The Placebo-Controlled, Add-On Study By Body System (Adverse Reactions Occurred In At Least 5% Of Levetiracetam Extended-Release Tablets-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/Adverse Reaction	Levetiracetam Extended-Release Tablets (N=77) %	Placebo (N=79) %
Gastrointestinal Disorders		
Nausea	5	3
Infections and Infestations		
Influenza	8	4
Nasopharyngitis	7	5
Nervous System Disorders		
Somnolence	8	3
Dizziness	5	3
Psychiatric Disorders		
Irritability	7	0

Discontinuation or Dose Reduction in the Levetiracetam Extended-Release Tablets Controlled Clinical Study

In the controlled clinical study using levetiracetam extended-release tablets, 5.2% of patients receiving levetiracetam extended-release tablets and 2.5% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions that resulted in discontinuation and that occurred more frequently in levetiracetam extended-release tablets-treated patients than in placebo-treated patients were asthenia, epilepsy, mouth ulceration, rash and respiratory failure. Each of these adverse reactions led to discontinuation in a levetiracetam extended-release tablets-treated patient and no placebo-treated patients.

Table 4 lists the adverse reactions seen in the controlled studies of immediate-release levetiracetam tablets in adult patients experiencing partial onset seizures. Although the pattern of adverse reactions in the levetiracetam extended-release tablets study seems somewhat different from that seen in partial onset seizure controlled studies for immediate-release levetiracetam tablets, this is possibly due to the much smaller number of patients in this study compared to the immediate-release tablet studies. The adverse reactions for levetiracetam extended-release tablets are expected to be similar to those seen with immediate-release levetiracetam tablets.

Immediate-Release Levetiracetam Tablets

Adults

In controlled clinical studies of immediate-release levetiracetam tablets as adjunctive therapy to other AEDs in adults with partial onset seizures, the most frequently reported adverse reactions, for events with rates greater than placebo, were somnolence, asthenia, infection and dizziness.

Table 4 lists adverse reactions that occurred in at least 1% of adult epilepsy patients treated with immediate-release levetiracetam tablets participating in placebo-controlled studies and were numerically more common than in patients treated with placebo. In these studies, either immediate-release levetiracetam tablets or placebo was added to concurrent AED therapy.

Table 4: Incidence (%) Of Adverse Reactions In Placebo-Controlled, Add-On Studies In Adults Experiencing Partial Onset Seizures By Body System (Adverse Reactions Occurred In At Least 1% Of Immediate-Release Levetiracetam Tablets-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ Adverse Reaction	Immediate-Release Levetiracetam Tablets (N=769) %	Placebo (N=439) %
Body as a Whole		
Asthenia	15	9

Headache	14	13
Infection	13	8
Pain	7	6
Digestive System		
Anorexia	3	2
Nervous System		
Somnolence	15	8
Dizziness	9	4
Depression	4	2
Nervousness	4	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Hostility	2	1
Paresthesia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Diplopia	2	1

Pediatric Patients 4 Years to <16 Years
In a pooled analysis of two controlled pediatric clinical studies in children 4 to 16 years of age with partial onset seizures, the adverse reactions most frequently reported with the use of immediate-release levetiracetam tablets in combination with other AEDs, and with greater frequency than in patients on placebo, were fatigue, aggression, nasal congestion, decreased appetite, and irritability.

Table 5 lists adverse reactions that occurred in at least 2% of pediatric patients treated with immediate-release levetiracetam tablets and were more common than in pediatric patients on placebo. In these studies, either immediate-release levetiracetam tablets or placebo was added to concurrent AED therapy.

Table 5: Incidence (%) Of Adverse Reactions In Pooled Placebo-Controlled, Add-On Studies In Pediatric Patients Ages 4 to 16 Years Experiencing Partial Onset Seizures By Body System (Adverse Reactions Occurred In At Least 2% Of Patients Treated With Immediate-Release Levetiracetam Tablets And Occurred More Frequently Than Patients on Placebo)

Body System/ Adverse Reaction	**Immediate-Release Levetiracetam Tablets (N=165) %**	**Placebo (N=131) %**
Ear and Labyrinth Disorders		
Ear Pain	2	1
Eye Disorders		
Conjunctivitis	2	0
Gastrointestinal Disorders		
Vomiting	15	12
Upper Abdominal Pain	9	8
Diarrhea	6	5
Constipation	3	1

General Disorders and Administration Site Conditions		
Fatigue	11	5
Infections and Infestations		
Nasopharyngitis	15	12
Influenza	3	1
Gastroenteritis	2	0
Rhinitis	2	0
Injury, Poisoning and Procedural Complications		
Head Injury	4	0
Contusion	3	1
Fall	3	2
Joint Sprain	2	1
Metabolism and Nutrition Disorders		
Decreased Appetite	8	2
Anorexia	4	3
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	2	0
Neck Pain	2	1
Nervous System		
Headache	19	15
Somnolence	13	9
Dizziness	7	5
Lethargy	6	2
Sedation	2	1
Psychiatric Disorders		
Aggression	10	5
Abnormal Behavior	7	4
Irritability	7	1
Insomnia	5	3
Agitation	4	1
Depression	3	1
Altered Mood	3	1
Affect Lability	2	1
Anxiety	2	1
Confusional State	2	0
Mood Swings	2	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	9	5
Nasal Congestion	9	2
Pharyngolaryngeal Pain	7	4

In controlled pediatric clinical studies in patients 4 to 16 years of age, 7% of patients treated with immediate-release levetiracetam tablets and 9% of patients on placebo discontinued as a result of an adverse event.

In addition, the following adverse reactions were seen in other well-controlled studies of immediate-release levetiracetam tablets: balance disorder, disturbance in attention, eczema, hyperkinesia, memory impairment, myalgia, personality disorders, pruritus, and vision blurred.

Comparison of Gender, Age and Race
There are insufficient data for levetiracetam extended-release tablets to support a statement regarding the distribution of adverse experience reports by gender, age and race.

6.2 Postmarketing Experience

In addition to the adverse reactions listed above for immediate-release levetiracetam tablets [*see Adverse Reactions (6.1)*], the following adverse reactions have been identified during post-approval use of immediate-release levetiracetam tablets. 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 listing is alphabetized: abnormal liver function test, choreoathetosis, dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, leukopenia, muscular weakness, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, and weight loss. Alopecia has been reported with immediate-release levetiracetam tablets use; recovery was observed in majority of cases where immediate-release levetiracetam tablets were discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Oral administration of levetiracetam to female rats throughout pregnancy and lactation led to increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (equivalent to the maximum recommended human dose of 3,000 mg [MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1,800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Oral administration of levetiracetam to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1,800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1,800 mg/kg/day.

When levetiracetam was administered orally to pregnant rats during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3,600 mg/kg/day (12 times the MRHD). 1,200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study.

Treatment of rats with levetiracetam during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at oral doses of up to 1,800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

Pregnancy Registry
To provide information regarding the effects of in utero exposure to ELEPSIA XR, physicians are advised to recommend that pregnant patients taking ELEPSIA XR enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry. This can be done by calling the toll free number 1-888-233-2334, and must be

done by the patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from levetiracetam extended-release tablets, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients 12 years of age and older has been established based on pharmacokinetic data in adults and adolescents using levetiracetam extended-release tablets and efficacy and safety data in controlled pediatric studies using immediate-release levetiracetam tablets *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

Safety and effectiveness of levetiracetam extended-release tablets in patients below the age of 12 years have not been established.

A 3-month, randomized, double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of immediate-release levetiracetam tablets as adjunctive therapy in 98 pediatric patients with inadequately controlled partial seizures, ages 4 to 16 years (levetiracetam N=64; placebo N=34). The target dose of immediate-release levetiracetam tablets was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter-R Attention and Memory (AM) Battery, which assesses various aspects of a child's memory and attention. Although no substantive differences were observed between the placebo-and levetiracetam-treated groups in the median change from baseline in this battery, the study was not adequate to assess formal statistical non-inferiority between the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/6-18), a standardized validated tool used to assess a child’s competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL/6-18 indicated a worsening in aggressive behavior, one of the eight syndrome scores, in patients treated with levetiracetam [*see Warnings and Precautions (5.1)*].

Studies of levetiracetam in juvenile rats (dosing from day 4 through day 52 of age) and dogs (dosing from week 3 through week 7 of age) at doses of up to 1,800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m^2 basis) did not indicate a potential for age-specific toxicity.

8.5 Geriatric Use

There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of levetiracetam extended-release tablets in these patients. It is expected that the safety of levetiracetam extended-release tablets in elderly patients 65 and over would be comparable to the safety observed in clinical studies of immediate-release levetiracetam tablets.

There were 347 subjects in clinical studies of immediate-release levetiracetam, that were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of immediate-release levetiracetam tablets 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

The effect of levetiracetam extended-release tablets on renally impaired patients was not assessed in the controlled study. However, it is expected that the effect on ELEPSIA XR-treated patients would be similar to the effect seen in controlled studies of immediate-release levetiracetam tablets. Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance [*see Clinical Pharmacology (12.3)]*. ELEPSIA XR is not recommended in patients with moderate or severe renal impairment. Dose adjustment is recommended for patients with mild renal impairment [*see Dosage and Administration (2.1)*].

10 OVERDOSAGE

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

The signs and symptoms for levetiracetam extended-release tablets overdose are expected to be similar to those seen with immediate-release levetiracetam tablets.

The highest known dose of oral immediate-release levetiracetam tablets received in the clinical development program was 6,000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with immediate-release levetiracetam tablets overdoses in postmarketing use.

10.2 Management of Overdose

There is no specific antidote for overdose with levetiracetam extended-release tablets. 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 extended-release tablets.

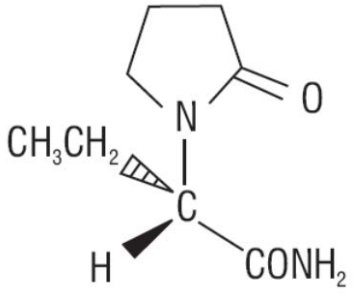
10.3 Hemodialysis

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

ELEPSIA XR contains levetiracetam, an antiepileptic drug, as extended-release tablets for oral administration.

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



Levetiracetam, USP is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.

Each extended-release tablet contains 1,000 mg or 1,500 mg of levetiracetam. Inactive ingredients: povidone, hypromellose, amino methacrylate copolymer, colloidal silicon dioxide, magnesium stearate, talc, silicified microcrystalline cellulose, crospovidone, sodium lauryl sulfate, FD&C Blue #1 aluminum lake, ethylcellulose, dibutyl sebacate, triethyl citrate, polysorbate 20, polyvinyl alcohol, polyethylene glycol, and polysorbate 80. The imprinting ink contains shellac glaze, iron oxide black, N-butyl alcohol, propylene glycol, and ammonium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

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

findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

12.2 Pharmacodynamics

Effects on QTc Interval

The effects of levetiracetam extended-release tablets on QTc prolongation is expected to be the same as that of immediate-release levetiracetam tablets. The effect of immediate-release levetiracetam tablets on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of immediate-release levetiracetam tablets (1,000 mg or 5,000 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of significant QTc prolongation in this study.

12.3 Pharmacokinetics

Overview

Bioavailability of levetiracetam extended-release tablets is similar to that of the immediate-release levetiracetam tablets. The pharmacokinetics (AUC and C_{max}) were shown to be dose proportional after single dose administration of 1,000 mg, 2,000 mg, and 3,000 mg extended-release levetiracetam. Plasma half-life of extended-release levetiracetam is approximately 7 hours. ELEPSIA XR 1,500 mg tablets are bioequivalent to Keppra XR (levetiracetam) extended release tablets (2 tablets of 750 mg) in both fasted and fed states.

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

Absorption and Distribution

Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release levetiracetam than with immediate-release tablets. After multiple dose levetiracetam extended-release tablets intake, extent of exposure (AUC_{0-24}) was similar to extent of exposure after multiple dose immediate-release tablets intake. C_{max} and C_{min} were lower by 17% and 26% after multiple dose levetiracetam extended-release tablets intake in comparison to multiple dose immediate-release tablets intake. Intake of a high fat, high calorie breakfast before the administration of levetiracetam extended-release tablets resulted in a longer median time to peak. The median time to peak (T_{max}) was 3 to 4.5 hours longer in the fed state. There was no effect on peak plasma concentration however; the extent of exposure (AUC) was 21 to 25% higher.

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 impaired renal function [*see Use in Specific Populations (8.6) and Dosage and Administration (2.1)*].

Special Populations

Elderly

There are insufficient pharmacokinetic data to specifically address the use of extended-release levetiracetam in the elderly population.

Pharmacokinetics of immediate-release levetiracetam were evaluated in 16 elderly subjects (age 61 to 88 years) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pediatric Patients

An open label, multicenter, parallel-group, two-arm study was conducted to evaluate the pharmacokinetics of extended-release levetiracetam in pediatric patients (13 to 16 years old) and in adults (18 to 55 years old) with epilepsy. Levetiracetam extended-release tablets (1,000 mg to 3,000 mg) were administered once daily with a minimum of 4 days and a maximum of 7 days of treatment to 12 pediatric patients and 13 adults in the study. Dose-normalized steady-state exposure parameters, C_{max} and AUC, were comparable between pediatric and adult patients.

Pregnancy

Levetiracetam extended-release tablets levels may decrease during pregnancy.

Gender

When given in a single dose, extended-release levetiracetam C_{max} was 21 to 30% higher and AUC was 8 to 18% higher in women (N=12) compared to men (N=12). However, clearances adjusted for body weight were comparable. Similar results were observed in a multiple dose study.

Race

Formal pharmacokinetic studies of the effects of race have not been conducted with extended-release or immediate-release levetiracetam. Cross study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of immediate-release 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 effect of levetiracetam extended-release tablets on renally impaired patients was not assessed in the controlled study. However, it is expected that the effect on ELEPSIA XR-treated patients would be similar to that seen in controlled studies of immediate-release levetiracetam tablets.

The disposition of immediate-release 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 (CL_{cr} >80 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4- hour hemodialysis procedure.

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

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

Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening with immediate-release levetiracetam tablets in the placebo-controlled clinical studies in epilepsy patients. The potential for drug interactions for levetiracetam extended-release tablets is expected to be essentially the same as that with immediate-release levetiracetam tablets.

Phenytoin
Immediate-release levetiracetam tablets (3,000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate
Immediate-release levetiracetam tablets (1,500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

Other Antiepileptic Drugs
Potential drug interactions between immediate-release levetiracetam tablets 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.

Oral Contraceptives
Immediate-release levetiracetam tablets (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

Immediate-release levetiracetam tablets (1,000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin
Immediate-release levetiracetam tablets (1,000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid
Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1,000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of immediate-release levetiracetam tablets on probenecid was not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1,800 mg/kg/day. The highest dose is 6 times the maximum recommended daily human dose (MRHD) of 3,000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4,000 mg/kg/day, lowered to 3,000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3,000 mg/kg/day) is approximately 5 times the MRHD on a mg/m^2 basis.

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

Impairment of Fertility
No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1,800 mg/kg/day (6 times the maximum recommended human dose on a mg/m^2 or systemic exposure [AUC] basis).

14 CLINICAL STUDIES

The effectiveness of levetiracetam extended-release tablets as adjunctive therapy in partial onset seizures in adults was established in one multicenter, randomized, double-blind, placebo-controlled clinical study in patients who had refractory partial onset seizures with or without secondary generalization. This was supported by the demonstration of efficacy of immediate-release levetiracetam tablets (see below) in partial seizures in three multicenter, randomized, double-blind, placebo-controlled clinical studies in adults, as well as a demonstration of comparable bioavailability between the extended-release and immediate-release formulations *[see Clinical Pharmacology (12.3)]* in adults. The effectiveness for levetiracetam extended-release tablets as adjunctive therapy in partial onset seizures in pediatric patients, 12 years of age and older, was based upon a

single pharmacokinetic study showing comparable pharmacokinetics of levetiracetam extended-release tablets in adults and adolescents *[see Clinical Pharmacology (12.3)]*. All studies are described below.

14.1 Levetiracetam Extended-Release Tablets in Adults

The effectiveness of levetiracetam extended-release tablets as adjunctive therapy (added to other antiepileptic drugs) was established in one multicenter, randomized, double-blind, placebo-controlled clinical study across 7 countries in patients who had refractory partial onset seizures with or without secondary generalization (Study 1).

Study 1

Patients enrolled in Study 1 had at least eight partial seizures with or without secondary generalization during the 8-week baseline period and at least two partial seizures in each 4-week interval of the baseline period. Patients were taking a stable dose regimen of at least one AED, and could take a maximum of three AEDs. After a prospective baseline period of 8 weeks, 158 patients were randomized to placebo (N=79) or 1,000 mg (two 500 mg tablets) of levetiracetam extended-release tablets (N=79), given once daily over a 12-week treatment period.

The primary efficacy endpoint in Study 1 was the percent reduction over placebo in mean weekly frequency of partial onset seizures. The median percent reduction in weekly partial onset seizure frequency from baseline over the treatment period was 46% in the levetiracetam extended-release tablets 1,000 mg treatment group (N=74) and 33% in the placebo group (N=78). The estimated percent reduction over placebo in weekly partial onset seizure frequency over the treatment period was 14% (statistically significant).

The relationship between the effectiveness of the same daily dose of levetiracetam extended-release tablets and immediate-release levetiracetam tablets has not been studied and is unknown.

14.2 Immediate-release Levetiracetam Tablets in Adults

The effectiveness of immediate-release levetiracetam as adjunctive therapy (added to other antiepileptic drugs) in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial onset seizures with or without secondary generalization (Studies 2, 3, and 4). The tablet formulation was used in all three studies. In these studies, 904 patients were randomized to placebo, levetiracetam 1,000 mg, levetiracetam 2,000 mg, or levetiracetam 3,000 mg/day. Patients enrolled in Study 2 or Study 3 had refractory partial onset seizures for at least two years, and had taken two or more AEDs. Patients enrolled in Study 4 had refractory partial onset seizures for at least 1 year and had taken one AED. At the time of the study, patients were taking a stable dose regimen of at least one AED, 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 2

Study 2 was a double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States, comparing immediate-release levetiracetam 1,000 mg/day (N=97), immediate-release levetiracetam 3,000 mg/day (N=101), and placebo (N=95), given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, patients in Study 2 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 in Study 2 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 Study 2 are displayed in Table 6.

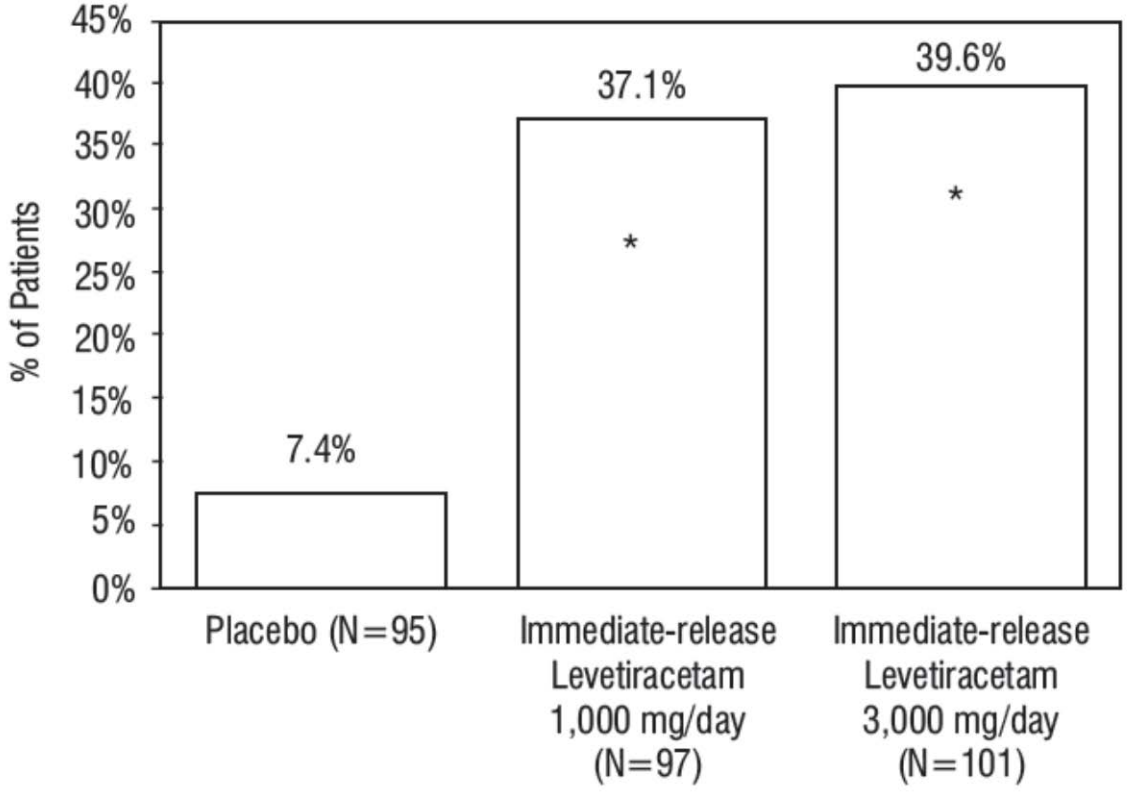
Table 6: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures In Study 2

	Placebo (N=95)	Immediate-release Levetiracetam 1,000 mg/day (N=97)	Immediate-release Levetiracetam 3,000 mg/day (N=101)
Percent reduction in partial seizure frequency over placebo	–	26.1%*	30.1%*

* statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction from baseline in weekly partial onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the three treatment groups (x-axis) in Study 2 is presented in Figure 1.

Figure 1: Responder Rate (≥50% Reduction From Baseline) In Study 2



* statistically significant versus placebo

Study 3

Study 3 was a double-blind, placebo-controlled, crossover study conducted at 62 centers in Europe, comparing immediate-release levetiracetam 1,000 mg/day (N=106), immediate-release levetiracetam 2,000 mg/day (N=105), and placebo (N=111), given in equally divided doses twice daily.

The first period of the study (Period A) was designed to be analyzed as a parallel-group study. After a prospective baseline period of up to 12 weeks, patients in Study 3 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 in Study 3 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 7.

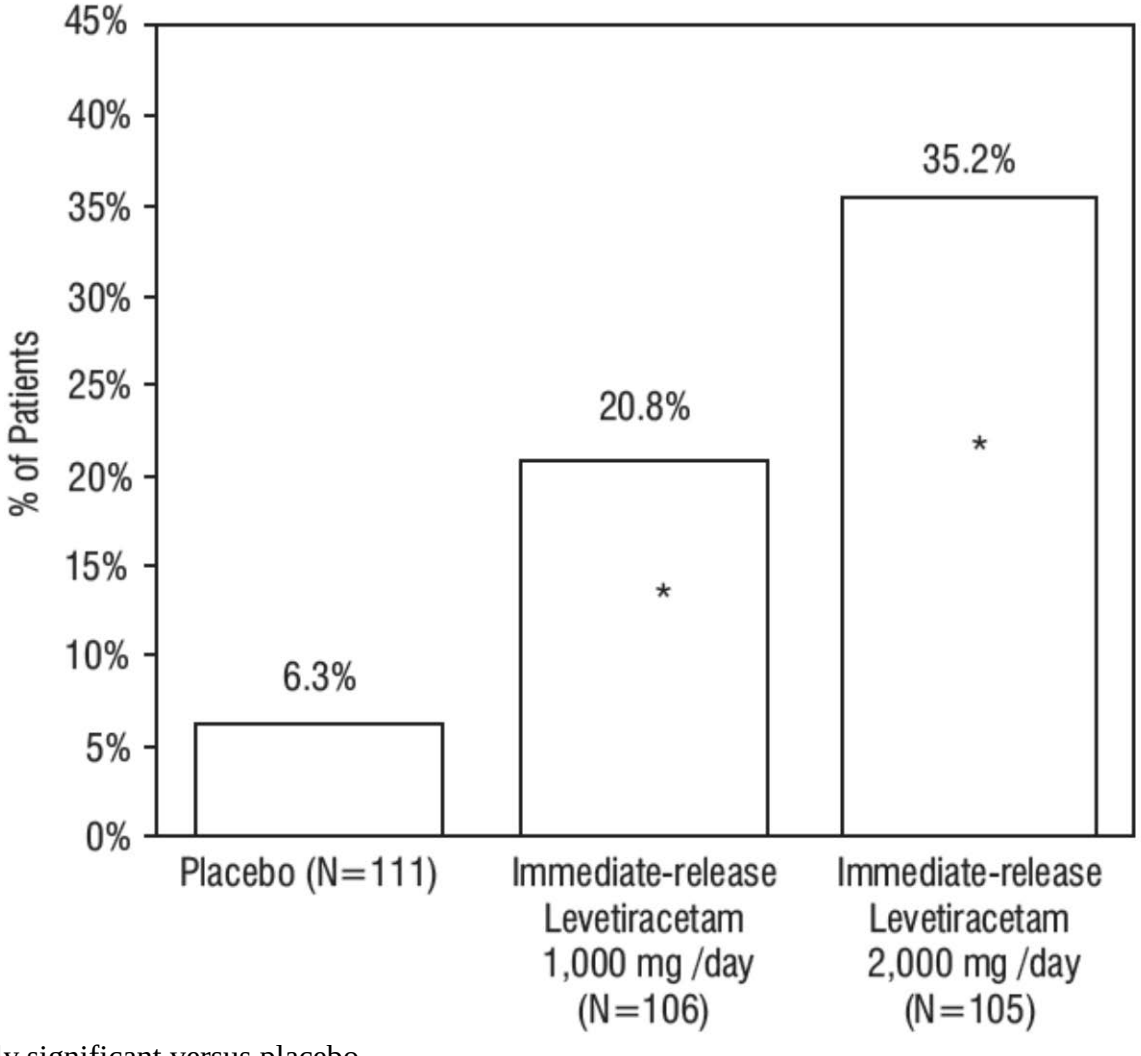
Table 7: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures In Study 3: Period A

	Placebo (N=111)	Immediate-release Levetiracetam 1,000 mg/day (N=106)	Immediate-release Levetiracetam 2,000 mg/day (N=105)
Percent reduction in partial seizure frequency over placebo	–	17.1%*	21.4%*

* statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction from baseline in weekly partial onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the three treatment groups (x-axis) in Study 3 is presented in Figure 2.

Figure 2: Responder Rate (≥50% Reduction From Baseline) In Study 3: Period A



* statistically significant versus placebo

The comparison of immediate-release levetiracetam 2,000 mg/day to immediate-release levetiracetam 1,000 mg/day for responder rate in Study 3 was statistically significant (P=0.02). Analysis of the trial as a cross-over study yielded similar results.

Study 4

Study 4 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing immediate-release levetiracetam 3,000 mg/day (N=180) and placebo (N=104) in patients with refractory partial onset seizures, with or without secondary generalization, receiving only one concomitant AED. Study drug was given in two divided doses. After a prospective baseline period of 12 weeks, patients in Study 4 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 in Study 4 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 8 displays the results of Study 4.

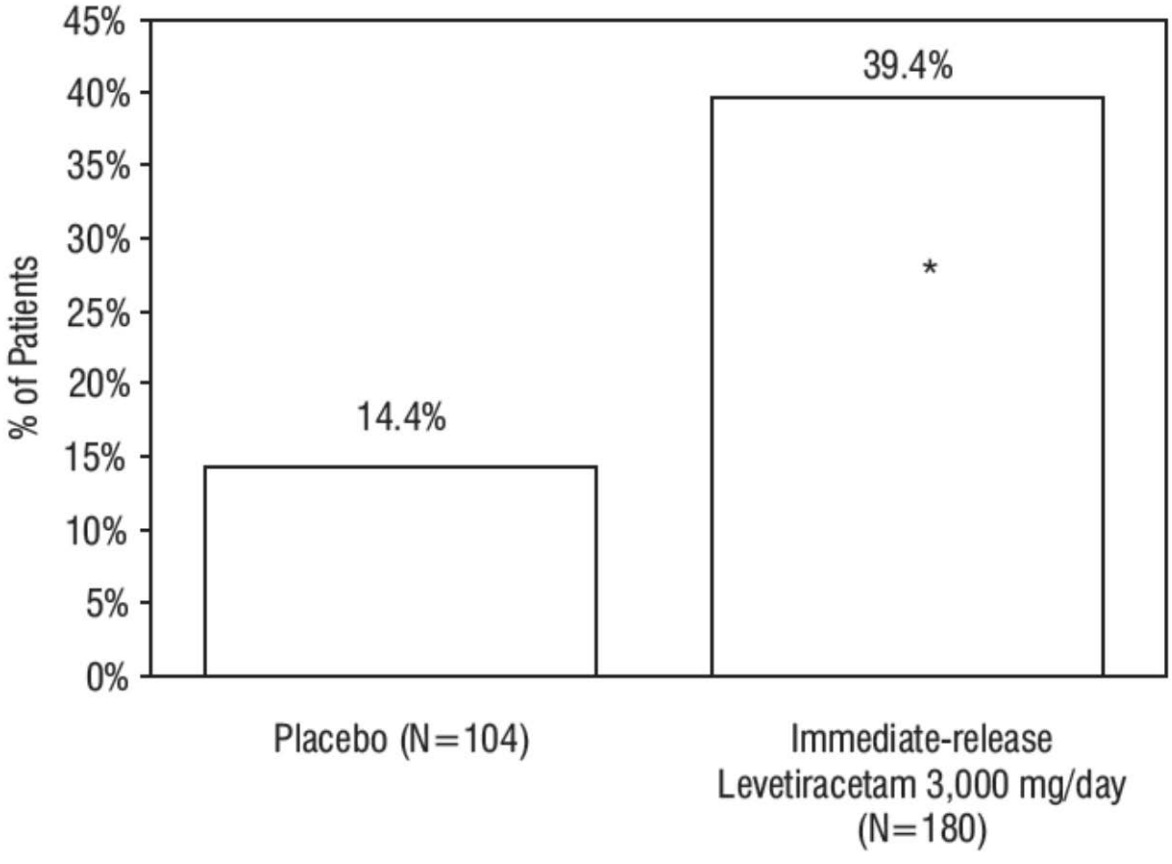
Table 8: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures In Study 4

	Placebo (N=104)	Immediate-release Levetiracetam 3,000 mg/day (N=180)
Percent reduction in partial seizure frequency over placebo	–	23%*

* statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥50% reduction from baseline in weekly partial onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) in Study 4 is presented in Figure 3.

Figure 3: Responder Rate (≥50% Reduction From Baseline) In Study 4



* statistically significant versus placebo

14.3 Immediate-release Levetiracetam in Pediatric Patients 4 Years to 16 Years

The use of levetiracetam extended-release tablets in pediatric patients 12 years of age and older is supported by Study 5, which was conducted using immediate-release levetiracetam. Levetiracetam extended-release tablets are not indicated in children below 12 years of age.

Study 5

The effectiveness of immediate-release levetiracetam as adjunctive therapy in pediatric patients was established in a multicenter, randomized double-blind, placebo-controlled study, conducted at 60 sites in North America, in children 4 to 16 years of age with partial seizures uncontrolled by standard antiepileptic drugs (Study 5). 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 immediate-release levetiracetam or placebo. The enrolled population included 198 patients (levetiracetam N=101; placebo N=97) with refractory partial onset seizures, with or without secondarily generalization. Study 5 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, the immediate-release 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 in Study 5 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 9 displays the results of this study.

Table 9: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures in Study 5

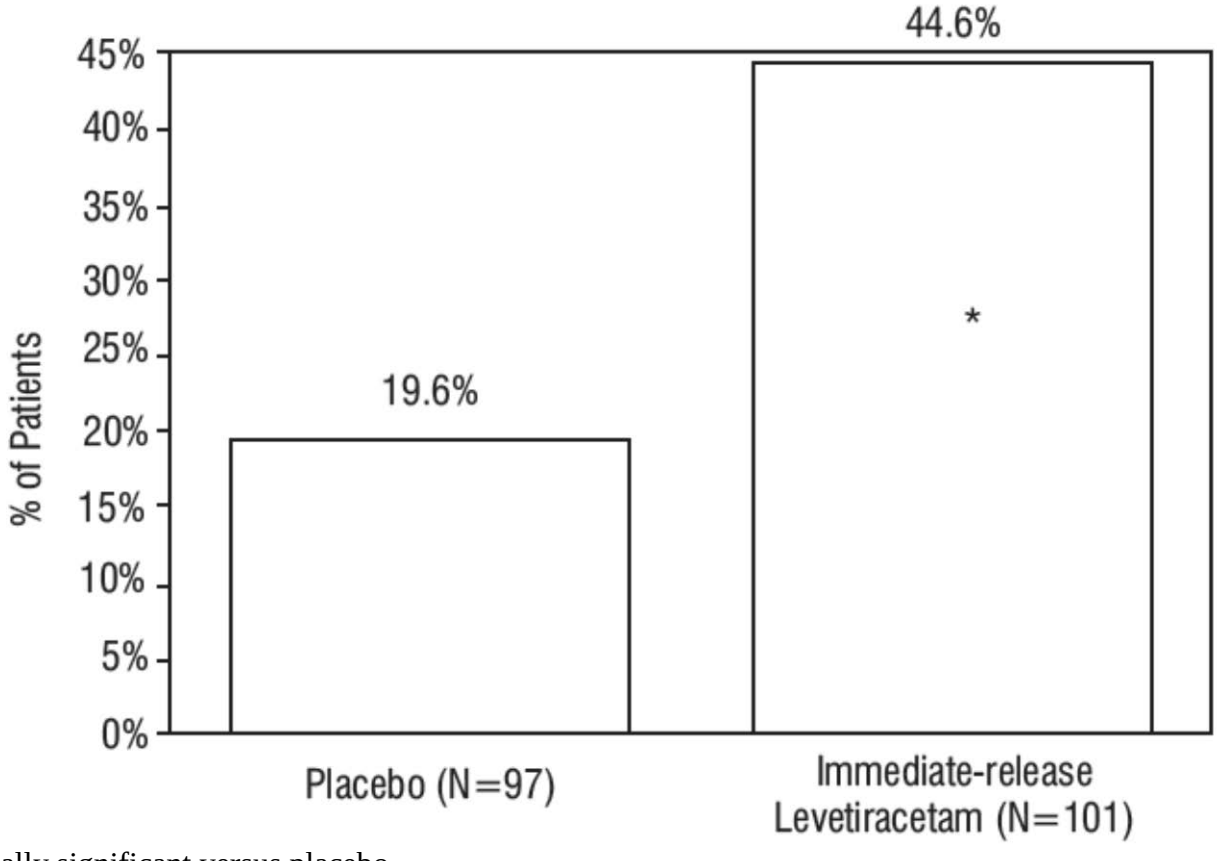
	Placebo (N=97)	Immediate-release Levetiracetam

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

*statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥ 50% reduction in weekly partial onset seizure frequency over the entire randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) in Study 5 is presented in Figure 4.

Figure 4: Responder Rate (≥ 50% Reduction From Baseline) in Study 5



*statistically significant versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Levetiracetam extended-release tablets, 1,000 mg are oval biconvex, coated, blue and white to off-white, bilayer tablet with drilled portal on the blue layer; imprinted with "574" with black ink on one side and plain on the other side. They are supplied as follows:

Bottles of 30with child resistant cap…..... NDC 47133-574-83
Bottles of 100 with child resistant cap…..... NDC 47133-574-88
Bottles of 500 with non-child resistant cap……. NDC 47133-574-13

Levetiracetam extended-release tablets, 1,500 mg are oval biconvex, coated, blue and white to off-white, bilayer tablet with drilled portal on the blue layer; imprinted with "575" with black ink on one side and plain on the other side. They are supplied as follows:

Bottles of 30 with child resistant cap…..... NDC 47133-575-83
Bottles of 100 with child resistant cap…..... NDC 47133-575-88
Bottles of 500 with non-child resistant cap……. NDC 47133-575-13

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Dispense in tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved Patient Labeling (Medication Guide).

Suicidal Behavior and Ideation
Counsel patients, their caregivers, and/or families that antiepileptic drugs (AEDs), including ELEPSIA XR, may increase the risk of suicidal thoughts and behavior and advise patients to be alert for the emergence or worsening of symptoms of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their caregivers, and/or families to immediately report behaviors of concern to a healthcare provider *[see Warnings and Precautions (5.2)]*.

Psychiatric Reactions and Changes in Behavior
Advise patients that ELEPSIA XR may cause changes in behavior (e.g. irritability and aggression). In addition, patients should be advised that they may experience changes in behavior that have been seen with other formulations of levetiracetam, which include agitation, anger, anxiety, apathy, depression, hostility, and, in rare cases, psychotic symptoms *[see Warnings and Precautions (5.1)]*.

Effects on Driving or Operating Machinery
Inform patients that ELEPSIA XR may cause dizziness and somnolence. Inform patients not to drive or operate machinery until they have gained sufficient experience on levetiracetam extended-release tablets to gauge whether it adversely affects their ability to drive or operate machinery *[see Warnings and Precautions (5.3)]*.

Dermatological Adverse Reactions
Advise patients that serious dermatological adverse reactions have occurred in patients treated with levetiracetam and instruct them to call their physician immediately if a rash develops *[see Warnings and Precautions (5.4)]*.

Dosage and Administration
Instruct patients to only take ELEPSIA XR once daily and to swallow the tablets whole. The tablet should not be chewed, broken, split, or crushed *[see Dosage and Administration (2.1)]*.

Each coated bilayer tablet consists of a distinctly visible blue layer and a white to off white layer. Do not consume the tablet if one layer is absent and report this to your pharmacist *[see Dosage Forms and Strengths (3)]*.

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

MEDICATION GUIDE
ELEPSIA™ XR (e lep' see a ex are)
(levetiracetam)
extended-release tablets

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

What is the most important information I should know about ELEPSIA XR?

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

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

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

Do not stop ELEPSIA XR without first talking to a healthcare provider.

- Stopping ELEPSIA XR suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus).

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

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

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.

- Keep all follow-up visits with your healthcare provider as scheduled.

- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

What is ELEPSIA XR?

ELEPSIA XR is a prescription medicine taken by mouth that is used with other medicines to treat partial onset seizures in people 12 years of age and older with epilepsy.

It is not known if ELEPSIA XR is safe or effective in people under 12 years of age.

What should I tell my healthcare provider before starting ELEPSIA XR?

Before taking ELEPSIA XR, 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 ELEPSIA XR will harm your unborn baby. You and your healthcare provider will have to decide if you should take ELEPSIA XR while you are pregnant. If you become pregnant while taking ELEPSIA XR, 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. The purpose of this registry is to collect information about the safety of ELEPSIA XR and other antiepileptic medicine during pregnancy.
- are breast feeding. ELEPSIA XR can pass into your milk and may harm your baby. You and your healthcare provider should discuss whether you should take ELEPSIA XR or breast-feed; you should not do both.

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

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

How should I take ELEPSIA XR?

Take ELEPSIA XR exactly as your healthcare provider tells you to take it.

- Your healthcare provider will tell you how much ELEPSIA XR to take and when to take it. ELEPSIA XR is taken 1 time a day.
- Your healthcare provider may change your dose. **Do not** change your dose without talking to your healthcare provider.
- Take ELEPSIA XR with or without food.
- Swallow the tablets whole. **Do not** chew, break, split or crush tablets.
- Each coated tablet has 2 layers, a blue layer and a white to off-white layer. If you **do not** see the blue or white to off-white layer, **do not** take the tablet and talk to your pharmacist.

- If you take too much ELEPSIA XR, call your local Poison Control Center or go to the nearest emergency room right away.

What should I avoid while taking ELEPSIA XR?

Do not drive, operate machinery or do other dangerous activities until you know how ELEPSIA XR affects you. ELEPSIA XR may make you dizzy or sleepy.

What are the possible side effects of ELEPSIA XR?

ELEPSIA XR may cause serious side effects, including:

- See "What is the most important information I should know about ELEPSIA XR?"

ELEPSIA XR can cause serious side effects.

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
- problems with muscle coordination (problems walking and moving)
- a skin rash. Serious skin rashes can happen after you start taking ELEPSIA XR. There is no way to tell if a mild rash will become a serious reaction.

Common side effects seen in people who take ELEPSIA XR and other formulations of levetiracetam include:

- sleepiness
- weakness
- infection
- dizziness

These side effects can happen at any time but happen more often within the first 4 weeks of treatment except for infection.

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 ELEPSIA XR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may also report side effects to FDA at 1-800-FDA-1088.

How should I store ELEPSIA XR?

- Store ELEPSIA XR at room temperature, between 68°F to 77°F (20°C to 25°C) away from light.

Keep ELEPSIA XR and all medicines out of the reach of children.

General information about the safe and effective use of ELEPSIA XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELEPSIA XR for a condition for which it was not prescribed. Do not give ELEPSIA XR to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ELEPSIA XR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ELEPSIA XR that is written for health professionals. You can also call Sun Pharmaceutical Industries, Inc. at 1-800-818-4555.

What are the ingredients of ELEPSIA XR?

Active ingredient: levetiracetam
Inactive ingredients: povidone, hypromellose, amino methacrylate copolymer, colloidal silicon dioxide, magnesium stearate, talc, silicified microcrystalline cellulose, crospovidone, sodium lauryl sulfate, FD&C Blue #1 aluminum lake, ethylcellulose, dibutyl sebacate, triethyl citrate, polysorbate 20, polyvinyl alcohol, polyethylene glycol, and polysorbate 80. The imprinting ink contains shellac glaze, iron oxide black, N-butyl alcohol, propylene glycol, and ammonium hydroxide.

ELEPSIA XR does not contain lactose or gluten.

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

*Keppra XR is the registered trademark of its respective owner.

Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

Manufactured by:
Sun Pharmaceutical Ind. Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

PJPI0393
Issued 03/2015