APOTEX ADVANCING GENERICS

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

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

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

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

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

Group	Creatinine Clearance (mL/min/1.73m²)	Dosage (mg)	Frequency
Normal	> 80	1000 to 3000	Every 24 hours
Mild	50 to 80	1000 to 2000	Every 24 hours
Moderate	30 to 50	500 to 1500	Every 24 hours
Severe	< 30	500 to 1000	Every 24 hours

3 DOSAGE FORMS AND STRENGTHS

Levetiracetam extended release 1000 mg tablets, USP are white, oval, biconvex film coated tablets, engraved with "APO" on one side, "LXR 1000" on the other side

4 CONTRAINDICATIONS

None

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5 WARNINGS AND PRECAUTIONS

5.1 Psychiatric Reactions

Patients on levetiracetam extended release tablets 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 patients 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

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observed with immediate release levetiracetam 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 levetiracetam extended release tablets

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

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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

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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 levetiracetam extended release tablets, 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

14 number is too small to allow any conclusion about drug effect on suicide

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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 (5 100 years) in the clinical trials analyzed Table 2 shows absolute and relative risk by indication for all evaluated AEDs

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

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 with Events per 1000 Patients
Epilepsy	1 0	3 4	3 5	2 4
Psychiatric	5 7	8 5	1 5	2 9
Other	1 0	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 levetiracetam extended release tablets 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

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and mortality and an increased r sk of suic dal thoughts and behavior Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to cons der whether the emergence of these symptoms n any given patient may be related to the ilness be ng treated

Patients, their caregivers, and fam lies 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 suic dal thoughts, behavior, or thoughts about se f harm Behaviors of concern should be reported immediately to healthcare prov ders

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 exper ence on levetiracetam extended release tablets to gauge whether it adversely affects their ability to dr ve or operate machinery In cl nical trials of immediate release levetiracetam tablets, somnolence and asthenia occurred most frequently within the first 4 weeks of treatment

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Levetiracetam Extended Release Tablets

In the levetiracetam extended release tablets double blind, controlled trial in patients exper encing 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 s 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 pat ents receiving levetiracetam extended release tablets

Immediate Release Levetiracetam Tablets

In general, the inc dences of somnolence and fat gue in the pediatric partial onset seizure studies were comparable to those of the adult partial onset seizure studies

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In controlled tr als 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 3000 mg/day In a study in which there was no titration, about 45% of patients rece ving 4000 mg/day reported somnolence The somnolence was considered serious in 0 3% of patients treated with immediate release levet racetam 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 levet racetam tablets were hospitalized due to somnolence

In controlled tr als of adult patients with epilepsy experiencing partial onset seizures, 14 7% of patients treated with mmediate release levetiracetam tablets reported asthen a, compared to 9 1% of patients on placebo Treatment was discont nued 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 asthen a in 0 5% of patients treated w th mmediate release levetiracetam tablets and in 0 2% of patients on placebo

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5.4 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens Johnson syndrome (SJS) and tox c epidermal necrolysis (TEN), have been reported in both ch ldren 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 discont nued 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 d fficulties and advised not to drive or operate machinery unt l they have gained sufficient experience on level racetam extended release tablets to gauge whether it could adversely affect their ability to drive or operate machinery

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A total of 3 4% of adult pat ents treated with immediate release levetiracetam tablets experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordinat on), compared to 1 6% of patients on placebo A total of 0 4% of patients in contro led trials discontinued immediate release levetiracetam tablets treatment due to ataxia, compared to no pat ents 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 pre existing 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 tr al experience with levetiracetam extended release tablets than with immed ate release levetiracetam tablets, and some adverse reactions observed with immed ate release levetiracetam tablets may not have been detected in levetiracetam extended release tablets clin cal tr als because of limited number of patients These adverse reactions may however occur in patients rece ving levetiracetam extended release tablets

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5.6 Withdrawal Seizures

Antiepileptic drugs, including levetiracetam extended release tablets, 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 exper ence with levetiracetam extended release tablets than with immediate release levet racetam tablets, and some adverse reactions observed with mmediate release levetiracetam tablets may not have been detected in levetiracetam extended release tablets clin cal trials because of limited number of patients These adverse reactions may however occur n patients receiv ng levet racetam extended release tablets

In controlled trials, a minor but statistically significant decrease (compared to placebo) n total mean RBC count (0 03 x 10^6/mm^3), mean hemoglobin (0 09 g/dL), and mean hematocrit (0 38%), was seen in adult patients treated with mmediate release levetiracetam tablets A total of 3 2% of adult patients treated with immediate release levetiracetam tablets, and 1 8% of patients on placebo

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had at least one possibly significant (≤2 8 x 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 (≤1 0 x 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 n WBC and neutrophil counts were seen in pat ents treated w th immediate release levetiracetam tablets, as compared to placebo The mean decreases from baseline in the immediate release levet racetam tablets group were 0 4 x 10^9/L and 0 3 x 10^9/L, respectively, whereas there were small increases in the placebo group A significant increase in mean relative lymphocyte counts was observed in 1 7% of patients treated w th 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

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In the controlled pediatr c cognit ve 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 sign ficant (≥10% or ≥0 7X10^9/L)

5.8 Seizure Control During Pregnancy

Physiological changes may gradually decrease plasma levels of levet racetam throughout pregnancy This decrease is more pronounced during the third trimester If s 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 react ons are discussed in more deta ls in other sections of labeling

- Psychiatric Reactions [*see Warnings and Precautions (5 1)*]
- Suicidal Behavior And Ideation [*see Warn ngs and Precautions (5 2)*]
- Somnolence And Fatigue [*see Warnings and Precaut ons (5 3)*]

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- 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

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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 Adverse reactions were usually mild to moderate in intensity

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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 Tablet 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

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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 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 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

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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 Adverse reactions were usually mild to moderate in intensity

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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 Tablet 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

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Body System/ Adverse Reaction	Immediate Release Levetiracetam Tablets (N=769) %	Placebo (N=439) %
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

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Body System/ Adverse Reaction	Immediate Release Levetiracetam Tablets (N=769) %	Placebo (N=439) %
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 Adverse reactions were usually mild to moderate in intensity

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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
Abdominal Pain Upper	9	6
Diarrhea	6	5
Constipation	3	1

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Body System/ Adverse Reaction	Immediate Release Levetiracetam Tablets (N=165) %	Placebo (N=131) %
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

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Body System/ Adverse Reaction	Immediate Release Levetiracetam Tablets (N=165) %	Placebo (N=131) %
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

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Body System/ Adverse Reaction	Immediate Release Levetiracetam Tablets (N=165) %	Placebo (N=131) %
Psychiatric Disorders		
Aggression	10	5
Abnormal Behavior	7	4
Irritability	7	1
Insomnia	5	3
Agitation	4	1
Depression	3	1
Mood Altered	3	1
Affect Lability	2	1
Anxiety	2	1
Confusional State	2	0
Mood Swings	2	1

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Body System/ Adverse Reaction	Immediate Release Levetiracetam Tablets (N=165) %	Placebo (N=131) %
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.

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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 use; recovery was observed in majority of cases where immediate release levetiracetam tablets were discontinued.

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7 DRUG INTERACTIONS

No significant pharmacokinetic interactions were observed between levetiracetam or its major metabolite and concomitant medications via human liver cytochrome P450 isoforms, epoxide hydrolase, UDP glucuronidation enzymes, P glycoprotein, or renal tubular secretion *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Levetiracetam 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. Levetiracetam extended release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

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

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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 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis)

Pregnancy Registry

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

8.2 Labor and Delivery

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

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8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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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 1800 mg/kg/day (approximately 2 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.

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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 tablets 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 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)]*.

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8.6 Use in Patients with Impaired Renal Function

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 levetiracetam extended release tablet 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)]*. Dose adjustment is recommended for patients with impaired renal function *[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 received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few

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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 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.

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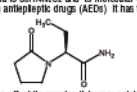
11 DESCRIPTION

Levetiracetam extended release tablets, USP are an antiepileptic drug available as 1000 mg (white) 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 powder. It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent.)

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Levetiracetam extended release tablets, USP contain the labeled amount of levetiracetam. Inactive ingredients: hypromellose, colloidal silicon dioxide, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

USP Dissolution Test Pending

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

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of human complex partial seizures, both during kindling development and in the fully kindled state The predict ve value of these animal models for specific types of human ep lepsy is uncerta n

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

Levet racetam at concentrat ons of up to 10 µM d d not demonstrate blind ng affinity for a variety of known receptors, such as those associated with benzodiazep nes, GABA (gamma aminobutyric acid), glycine, NMDA (N methyl D aspartate), re uptake sites, and second messenger systems Furthermore, *in vitro* studies have failed to f nd 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 descr bed for levetiracetam Experimental data indicate that this binding s te is the synaptic vesicle 49

protein SV2A, thought to be involved n 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 activ ty in aud ogenic seizure prone mice These find ngs suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechan sm 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 (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 ev dence of significant QTc prolongation in this study 50

12.3 Pharmacokinetics

Overview

B oava lability of levetiracetam extended release tablets is similar to that of the immediate release levetiracetam tablets The pharmacokinet cs (AUC and C_{max}) were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg extended release levet racetam Plasma half life of extended release levetiracetam is approximately 7 hours

Levet racetam s almost completely absorbed after oral administration The pharmacokinet cs of levetiracetam are linear and time invariant, with low intra and inter subject var ability Levet racetam is not significantly protein bound (<10% bound) and its volume of distribution is close to the volume of ntracellular 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 renal y excreted Plasma half life of levetiracetam across studies is approximately 6 8 hours The half life is increased in the elderly (primarily due to mpaired renal clearance) and in subjects with renal impairment 51

Absorption and Distribution

Extended release levetiracetam peak plasma concentrat ons occur in about 4 hours The time to peak plasma concentrations is about 3 hours longer with extended release levet racetam than with immediate release tablets

Single administration of two 500 mg extended release levetiracetam tablets once daily produced comparable maximal plasma concentrations and area under the plasma concentrat on versus t me as did the adm nistration of one 500 mg immediate release tablet tw ce da ly in fast ng conditions After multiple dose extended release levetiracetam tablets intake, extent of exposure (AUC_{0-24}) was similar to extent of exposure after multiple dose immediate release tablets intake C_{max} and $C_{m n}$ were lower by 17% and 26% after multiple dose extended release levet racetam tablets intake in comparison to multiple dose immediate release tablets ntake Intake of a high fat, high calorie breakfast before the administrat on of extended release levet racetam tablets resulted in a higher peak concentration, and longer median time to peak The median time to peak (T_{max}) was 2 hours longer n the fed state

Two 750 mg extended release levetiracetam tablets were bioequivalent to a single administrat on of three 500 mg extended release levetiracetam tablets 52

Metabolism

Levetiracetam is not extensively metabolized in humans The major metabolic pathway s 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 soenzymes The major metabolite is inactive in animal seizure models Two minor metabolites were identified as the product of hydroxylation of the 2 oxo pyrrolidine r ng (2% of dose) and opening of the 2 oxo pyrrolidine ring n position 5 (1% of dose) There s no enantiomeric interconversion of levetiracetam or ts major metabolite

Elimination

Levetiracetam plasma ha f life n adults is 7 ± 1 hour and is unaffected by either dose or repeated administration Levetiracetam s eliminated from the system c 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 metabol te ucb L057 s excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg Levetiracetam elim nation 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)*] 53

Special Populations

Elderly

There are nsufficient pharmacokinetic data to specifically address the use of extended release levetiracetam n the elderly population

Pharmacok netics of immed ate 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 Th s is most l kely 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 levetiracetam extended release tablets in pediatric patients (13 to 16 years old) and in adults (18 to 55 years old) with epilepsy Levet racetam extended release oral tablets (1000 mg to 3000 mg) were administered once daily with a minimum of 4 days and a maximum 54

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

Levet racetam levels may decrease during pregnancy

Gender

Extended release levetiracetam C_{max} was 21 30% h gher and AUC was 8 18% h gher in women (N=12) 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 with extended release or immediate release levet racetam Cross study compar sons 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 55

Renal Impairment

The effect of levet racetam extended release tablets on renally impaired patients was not assessed in the controlled study However, it is expected that the effect on levetiracetam extended release treated pat ents would be similar to that seen n controlled studies of immediate release levetiracetam tablets In patients with end stage renal disease on dialysis, it s recommended that immediate release levetiracetam be used instead of levetiracetam extended release tablets

The disposition of immediate release levetiracetam was studied n 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 m ld group (CLcr = 50 to 80 mL/min), 50% in the moderate group (CLcr = 30 to 50 mL/min) and 60% in the severe renal impairment group (CLcr <30 mL/m n) Clearance of levetiracetam is correlated with creatin ne clearance

In anur c (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr >80mL/min) Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialys s procedure 56

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Dosage should be reduced in patients with impaired renal function receiving levetiracetam; immediate release levetiracetam should be given to patients on dialysis [*see Dosage and Administration (2.1)*]

Hepatic Impairment

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

Drug Interactions

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

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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 (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

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

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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 (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.

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Warfarin

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

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of 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 1800 mg/kg/day. The highest dose is 6 times the maximum recommended daily human dose

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(MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity in mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a mg/m^2 basis.

Mutagenesis

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

Impairment of Fertility

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

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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

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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 1000 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 46.1% in the levetiracetam extended release tablets 1000 mg treatment group (N=74) and 33.4% in the placebo group (N=78). The estimated percent reduction over placebo in weekly partial onset seizure frequency over the treatment period was 14.4% (statistically significant).

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

14.2 Immediate Release Levetiracetam Tablets in Adults

The effectiveness of immediate release levetiracetam tablets 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 1000 mg, levetiracetam 2000 mg, or levetiracetam 3000 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.

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Study 2

Study 2 was a double blind, placebo contro led, parallel group study conducted at 41 sites in the United States, comparing Immediate release levetiracetam tablets 1000 mg/day (N=97), Immediate release levetiracetam tablets 3000 mg/day (N=101), and placebo (N=95), given in equally divided doses twice daily After a prospective baseline per od 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 per od, fo lowed by a 12 week fixed dose evalua on period, during which concomitant AED regimens were held constant The pr mary measure of effectiveness in Study 2 was a between group comparison of the percent reduction n weekly partial seizure frequency relative to placebo over the entire randomized treatment per od (t itration + evaluation period) Secondary outcome var ables included the responder rate (incidence of pat ents with ≥50% reduction from baseline in partial onset seizure frequency) The results of Study 2 are displayed in Table 6

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

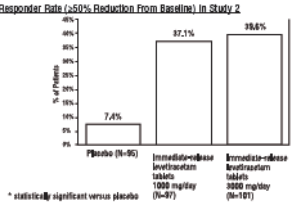
	Placebo (N=95)	Immediate release levetiracetam tablets 1000 mg/day (N=97)	Immediate release levetiracetam tablets 3000 mg/day (N=101)
Percent reduct on in partial seizure frequency over placebo		26 1%*	30 1%*

*statist cally 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 + evalua on per od) within the three treatment groups (x ax s) n Study 2 is presented in Figure 1

66

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



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Study 3

Study 3 was a double blind, placebo contro led, crossover study conducted at 62 centers in Europe, comparing Immediate release levetiracetam tablets 1000 mg/day (N=106), Immediate release levetiracetam tablets 2000 mg/day (N=105), and placebo (N=111), given in equally div ded doses twice daily

The first period of the study (Period A) was designed to be analyzed as a parallel group study After a prospect ve 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 cons sted of the 4 week titration period followed by a 12 week fixed dose evalua on period, dur ng 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 part al seizure frequency relative to placebo over the entire randomized treatment period (t itration + evaluation period) Secondary outcome variables included the responder rate (ncidence of patients with ≥50% reduction from baseline in partial onset seizure frequency) The results of the analysis of Period A are displayed n Table 7

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

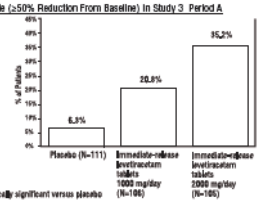
	Placebo (N=111)	Immediate release levetiracetam tablets 1000 mg/day (N=106)	Immediate release levetiracetam tablets 2000 mg/day (N=105)
Percent reduction in partial seizure frequency over placebo		17 1%*	21 4%*

*statist cally significant versus placebo

The percentage of patients (y ax s) who achieved ≥50% reduction from baseline in weekly partial onset seizure frequency over the ent re randomized treatment period (titration + evaluat on period) within the three treatment groups (x axis) In Study 3 is presented in Figure 2

69

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



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The comparison of Immediate release levetiracetam tablets 2000 mg/day to Immediate release levetiracetam tablets 1000 mg/day for responder rate in Study 3 was statistically significant (*P*=0 02) Analys s of the trial as a cross over study yielded sim lar results

Study 4

Study 4 was a double blind, placebo controlled, parallel group study conducted at 47 centers in Europe comparing Immediate release levetiracetam tablets 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 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 pr mary measure of effectiveness in Study 4 was a between group comparison of the percent reduction in weekly seizure frequency relative to placebo over the ent re randomized treatment period (titration + evaluation period) Secondary outcome variables included the responder rate (incidence of patients with ≥50% reduction from basel ne in part al onset seizure frequency) Table 8 displays the results of Study 4

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

	Placebo (N=104)	Immediate release levetiracetam tablets 3000 mg/day (N=180)
Percent reduct on in partial seizure frequency over placebo		23 0%*

*statist cally 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 + evaluat on per od) within the two treatment groups (x axis) in Study 4 is presented in F gure 3

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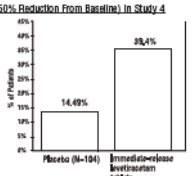
Figure 3 Responder Rate (≥50% Reduction From Baseline) in Study 4



* statistically significant versus placebo

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14.3 Immediate Release Levetiracetam Tablets 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 tablets. Levetiracetam extended release tablets are not indicated in children below 12 years of age.

Study 5

The effectiveness of immediate release levetiracetam tablets 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 2 AEDs, who still experienced at least 4 partial onset seizures during the 4 weeks prior to screening, as well as at least 4 part al onset seizures in each of the two 4 week baseline periods, were randomized to receive either immediate release levetiracetam tablets 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

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20 mg/kg/day in two divided doses. During the treatment period, the immediate release levetiracetam tablets 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 tablets (N=101)
Percent reduction in partial seizure frequency over placebo		26.6%*

*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.

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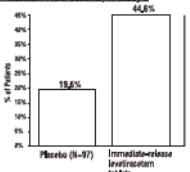
Figure 4 Responder Rate (≥ 50% Reduction From Baseline) in Study 5



* statistically significant versus placebo

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Levetiracetam Extended Release 1000 mg Tablets, USP are white, oval, biconvex film coated tablets, engraved with "APO" on one side, "LXR 1000" on the other side. They are supplied as follows:

Bottles of 60s (NDC 60505 3518 6)

16.2 Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

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

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Counsel patients on the benefits and risks of receiving levetiracetam extended release tablets. Provide the Medication Guide to patients and/or caregivers, and instruct them to read the Medication Guide prior to taking levetiracetam extended release tablets. Instruct patients to take levetiracetam extended release tablets only as prescribed.

Suicidal Behavior and Ideation

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

Psychiatric Reactions and Changes in Behavior

Advise patients that levetiracetam extended release tablets 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.

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Effects on Driving or Operating Machinery

Inform patients that levetiracetam extended release tablets 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.

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.

Dosing and Administration

Patients should be instructed to only take levetiracetam extended release tablets once daily and to swallow the tablets whole. They should not be chewed, broken, or crushed.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during levetiracetam extended release tablets therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry if they become pregnant. This

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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.

APOTEX INC.
LEVETIRACETAM EXTENDED RELEASE TABLETS, USP
1000 mg

Manufactured by
Apotex Inc
Toronto, Ontario
Canada M9L 1T9

Manufactured for
Apotex Corp
Weston, Florida
33326

Revision 3
Revised August 2014

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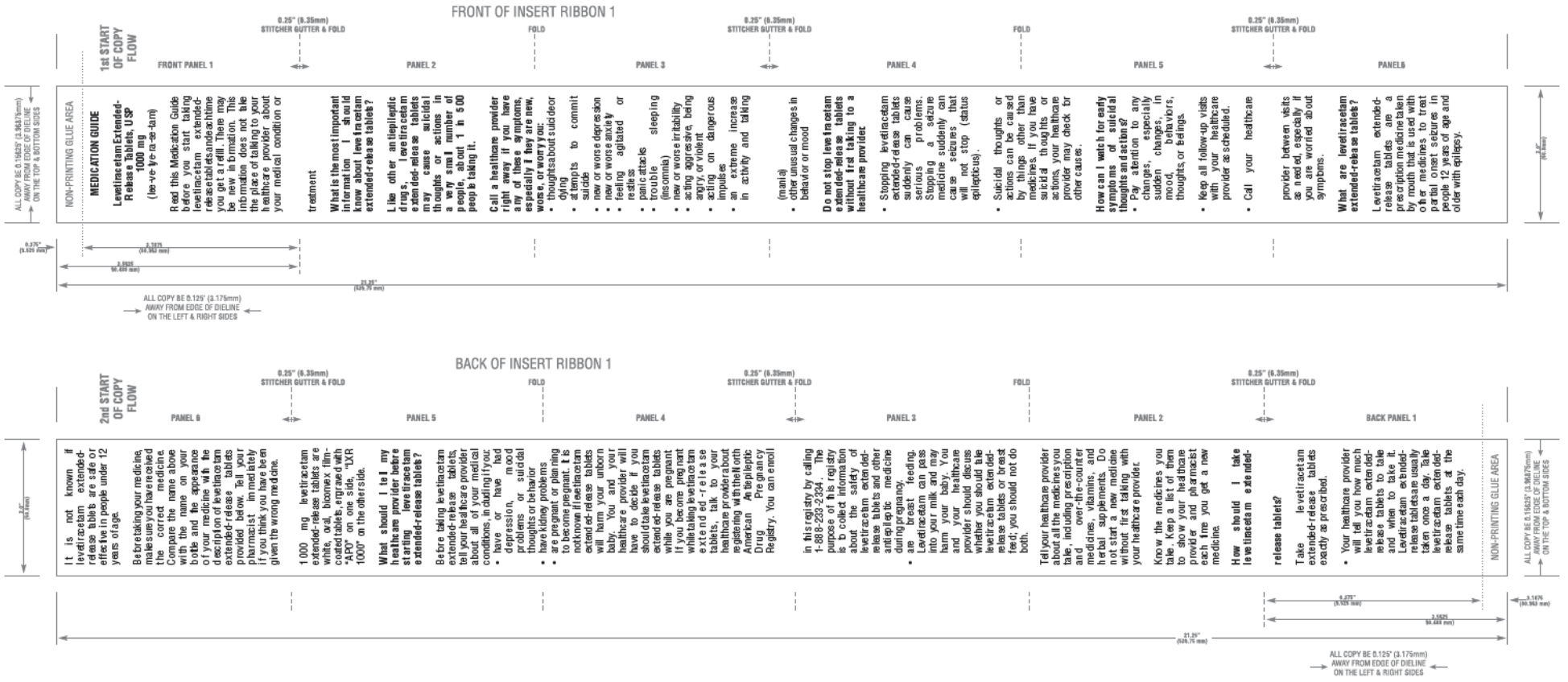

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