

Material Code:	N/A	ECL Common Text#:	TBD	Description:	ECL USA LEVETIRACETAM XR 1000MG USA
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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 (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

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

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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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treatment dose was reduced in 0.8% of adult patients treated with immediate release levetiracetam tablets, compared to 0.6% 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 psychotic 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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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 1. Dosing Adjustment Regimen for Adult Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min/1.73m ²)	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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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, hyperkinesia, 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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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 0.45%, 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.

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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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INSIDE PAGES 3.5625" / 90.488 mm 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 he is treating. 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. 17	INSIDE PAGES 3.5625" / 90.488 mm 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 levetiracetam extended release tablets. 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. 18
INSIDE PAGES 3.5625" / 90.488 mm 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 3000 mg/day. In a study in which there was no titration, about 45% of patients receiving 4000 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 0.6% 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. 19	INSIDE PAGES 3.5625" / 90.488 mm 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. 20
INSIDE PAGES 3.5625" / 90.488 mm 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 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 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 levetiracetam extended release tablets. 21	INSIDE PAGES 3.5625" / 90.488 mm 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 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 levetiracetam extended release tablets. In controlled trials, a minor but statistically significant decrease (compared to placebo) in total mean RBC count ($0.03 \times 10^6/\text{mm}^3$), mean hemoglobin ($0.09 \text{ g/dL}$), and mean hematocrit ($0.35\%$), 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. 22
INSIDE PAGES 3.5625" / 90.488 mm had at least one possibly significant ($\leq 2 \times 10^9/\text{L}$) 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 ($\leq 1.0 \times 10^9/\text{L}$) 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 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 pre-existing ataxia. These events occurred most frequently within the first 4 weeks of treatment. 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. 23	INSIDE PAGES 3.5625" / 90.488 mm In the controlled pediatric cognitive and neuropsychological safety study, two subjects (8.1%) in the placebo group and 5 subjects (6.6%) in the immediate release levetiracetam tablets treated group had high eosinophil count values that were possibly clinically significant ($\geq 10\%$ or $\geq 0.7 \times 10^9/\text{L}$). 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 adverse reactions are discussed in more detail in other sections of 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)) 24

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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 investigator's. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative

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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 Inflammations		
Influenza	6	4
Nasopharyngitis	7	5
Nervous System Disorders		
Somnolence	8	3
Dizziness	5	3
Psychiatric Disorders		
Irritability	7	0

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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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Body System / Adverse Reaction	Immediate Release Levetiracetam Tablets (N=769) %	Placebo (N=430) %
Dizziness	4	1
Depression	4	2
Nervousness	4	2
Algia	3	1
Vergo	2	1
Amnesia	2	1
Anxiety	2	1
Hallucinations	2	1
Parosmia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3

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

In the controlled clinical study using levetiracetam extended release tablets, 52% of patients receiving levetiracetam extended release tablets and 25% 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 ulcers, 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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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=430) %
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=430) %
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Optic Atrophy	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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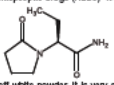
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Table 5: Incidence (%) of Adverse Reactions in Pooled Placebo-Controlled Add-On Studies in Pediatric Patients Ages 4 to 16 Years Experiencing Partial Onset Seizures by Body System. Adverse Reactions Occurred in At Least 2% of Patients Treated With Immediate Release Levetiracetam Tablets And Occurred More Frequently Than Patients on Placebo <table border="1"> <thead> <tr> <th>Body System/ Adverse Reaction</th> <th>Immediate Release Levetiracetam Tablets (N=165) %</th> <th>Placebo (N=131) %</th> </tr> </thead> <tbody> <tr> <td>Ear and Labyrinth Disorders</td> <td></td> <td></td> </tr> <tr> <td>Ear Pain</td> <td>2</td> <td>1</td> </tr> <tr> <td>Eye Disorders</td> <td></td> <td></td> </tr> <tr> <td>Conjunctivitis</td> <td>2</td> <td>0</td> </tr> <tr> <td>Gastrointestinal Disorders</td> <td></td> <td></td> </tr> <tr> <td>Vomiting</td> <td>15</td> <td>12</td> </tr> <tr> <td>Abdominal Pain Upper</td> <td>9</td> <td>6</td> </tr> <tr> <td>Dyschezia</td> <td>6</td> <td>5</td> </tr> <tr> <td>Constipation</td> <td>5</td> <td>1</td> </tr> </tbody> </table> 33	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	Dyschezia	6	5	Constipation	5	1	Table 6: 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 <table border="1"> <thead> <tr> <th>Body System/ Adverse Reaction</th> <th>Immediate Release Levetiracetam Tablets (N=165) %</th> <th>Placebo (N=131) %</th> </tr> </thead> <tbody> <tr> <td>General Disorders and Administration Site Conditions</td> <td></td> <td></td> </tr> <tr> <td>Fatigue</td> <td>11</td> <td>5</td> </tr> <tr> <td>Infections and Infestations</td> <td></td> <td></td> </tr> <tr> <td>Respiratory Infection</td> <td>15</td> <td>12</td> </tr> <tr> <td>Influenza</td> <td>3</td> <td>1</td> </tr> <tr> <td>Gastroenteritis</td> <td>2</td> <td>0</td> </tr> <tr> <td>Pharyngitis</td> <td>2</td> <td>0</td> </tr> <tr> <td>Injury, Poisoning and Procedural Complications</td> <td></td> <td></td> </tr> <tr> <td>Head Injury</td> <td>4</td> <td>0</td> </tr> <tr> <td>Contusion</td> <td>3</td> <td>1</td> </tr> <tr> <td>Fall</td> <td>3</td> <td>2</td> </tr> <tr> <td>Joint Sprain</td> <td>2</td> <td>1</td> </tr> </tbody> </table> 34	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			Respiratory Infection	15	12	Influenza	3	1	Gastroenteritis	2	0	Pharyngitis	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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Eye Disorders																																																																															
Conjunctivitis	2	0																																																																													
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Vomiting	15	12																																																																													
Abdominal Pain Upper	9	6																																																																													
Dyschezia	6	5																																																																													
Constipation	5	1																																																																													
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Fatigue	11	5																																																																													
Infections and Infestations																																																																															
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Pharyngitis	2	0																																																																													
Injury, Poisoning and Procedural Complications																																																																															
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Fall	3	2																																																																													
Joint Sprain	2	1																																																																													
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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 isozymes, 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. 39	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/m² 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/m² basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m² 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 ≥500 mg/kg/day (4 times the MRHD on a mg/m² basis) and increased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m² basis). The developmental no effect dose was 200 mg/kg/day (equivalent to the MRHD on a mg/m² basis). Maternal toxicity was also observed at 1500 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. 40																																																																														

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INSIDE PAGES 3.5625" / 90.488 mm 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 MHD on a mg/m² 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. 41	INSIDE PAGES 3.5625" / 90.488 mm 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 42
INSIDE PAGES 3.5625" / 90.488 mm 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 Letter 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 standard validated tool used to assess a child's competencies and behavior/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 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m² basis) did not indicate a potential for age specific toxicity. 43	INSIDE PAGES 3.5625" / 90.488 mm 8.5 Geriatric Use There were sufficient 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 sufficient 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)]. 44
INSIDE PAGES 3.5625" / 90.488 mm 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 Overdose 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 45	INSIDE PAGES 3.5625" / 90.488 mm 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, stimulation 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. 46
INSIDE PAGES 3.5625" / 90.488 mm 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 C₁₀H₁₅N₂O₂ 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 g/100 mL). It is freely soluble in chloroform (5.5 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.) 47	INSIDE PAGES 3.5625" / 90.488 mm Levetiracetam extended release tablets, USP contain the labeled amount of levetiracetam. Inactive ingredients: hypromellose, colloidal silicon dioxide, hydroxypropylcellulose, 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 picrotoxin 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 48

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INSIDE PAGES 3.5625" / 90.488 mm 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. <i>In vitro</i> and <i>in vivo</i> 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 hypersynchronous or 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), reuptake sites, and second messenger systems. Furthermore, <i>in vitro</i> 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, <i>in vitro</i> 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. 49	INSIDE PAGES 3.5625" / 90.488 mm 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 (1000 mg or 500 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTC was below 50 milliseconds. Therefore, there was no evidence of significant QTC prolongation in this study. 50
INSIDE PAGES 3.5625" / 90.488 mm 12.3 Pharmacokinetics Overview Oral bioavailability of levetiracetam extended release tablets is similar to that of the immediate release levetiracetam tablets. The pharmacokinetic (AUC and C_{max}) were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg extended release levetiracetam tablets. Plasma half-life of extended release levetiracetam is approximately 7 hours. 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 hours. The half-life is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment. 51	INSIDE PAGES 3.5625" / 90.488 mm 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. Single administration of two 500 mg extended release levetiracetam tablets once daily produced comparable maximal plasma concentrations and area under the plasma concentration versus time as did the administration of one 500 mg immediate release tablet twice daily in fasted 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_{24h} were lower by 17% and 26% after multiple dose extended release levetiracetam tablets intake in comparison to multiple dose immediate release tablets intake. Intake of a high fat, high-calorie breakfast before the administration of extended release levetiracetam tablets resulted in a higher peak concentration and longer median time to peak. The median time to peak (T_{max}) was 2 hours longer in the fed state. Two 750 mg extended release levetiracetam tablets were bioequivalent to a single administration of 52 three 500 mg extended release levetiracetam tablets. 52
INSIDE PAGES 3.5625" / 90.488 mm 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, 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 0.86 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 <i>Use in Specific Populations (6.6) and Dosage and Administration (2.1)</i>). 53	INSIDE PAGES 3.5625" / 90.488 mm Special Populations Elderly There are sufficient 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 65 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 levetiracetam extended release tablets in pediatric patients (13 to 16 years old) and in adults (18 to 55 years old) with epilepsy. Levetiracetam extended release oral tablets (54 (1000 mg to 3000 mg) were administered once daily with a minimum of 4 days and a maximum 54
INSIDE PAGES 3.5625" / 90.488 mm 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 levels may decrease during pregnancy. Gender Extended release levetiracetam C_{max} was 21.30% higher and AUC was 8.16% higher 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 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. 55	INSIDE PAGES 3.5625" / 90.488 mm 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 of levetiracetam extended release tablets on renal function would be similar to that seen in controlled studies of immediate release levetiracetam tablets. In patients with end-stage renal disease on dialysis, it is recommended that immediate release levetiracetam be used instead of levetiracetam extended release 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 50 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. 56

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INSIDE PAGES 3.5625" / 90.488 mm 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 <i>In vitro</i> 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_{50} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isozymes, epoxide hydrolase or UDP glucuronidation enzymes. In addition, levetiracetam does not affect the <i>in vitro</i> glucuronidation of valproic acid. 57	INSIDE PAGES 3.5625" / 90.488 mm 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. 58
INSIDE PAGES 3.5625" / 90.488 mm 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 0.02 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the levonorgestrel 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. 59	INSIDE PAGES 3.5625" / 90.488 mm 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_{max} of the metabolite ucb L057 was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to complete inhibition of tubular secretion of ucb L057. The effect of 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 600 mg/kg/day. The highest dose is 6 times the maximum recommended daily human dose. 60
INSIDE PAGES 3.5625" / 90.488 mm (MRHD) of 3000 mg on a mg/m² basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans (see table 1). There was no evidence of carcinogenicity in mice, oral administration of levetiracetam for 90 weeks (dose up to 900 mg/kg/day) or 2 years (dose up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerance) 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/m² basis. Mutagenesis Levetiracetam was not mutagenic in the Ames test or in mammalian cells <i>in vitro</i> in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an <i>in vitro</i> analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an <i>in vivo</i> mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or in the <i>in vivo</i> 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/m² or systemic exposure (AUC) basis). 61	INSIDE PAGES 3.5625" / 90.488 mm 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 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. 62
INSIDE PAGES 3.5625" / 90.488 mm 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 5 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). 63	INSIDE PAGES 3.5625" / 90.488 mm 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. 64

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INSIDE PAGES 3.9825" / 98.488 mm 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 tablets 1000 mg/day (N=47), immediate release levetiracetam tablets 3000 mg/day (N=101), and placebo (N=55), 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. 65	INSIDE PAGES 3.9825" / 98.488 mm Table 6. Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 2 <table border="1"> <tr> <th></th><th>Placebo (N=55)</th><th>Immediate release levetiracetam tablets 1000 mg/day (N=47)</th><th>Immediate release levetiracetam tablets 3000 mg/day (N=101)</th></tr> <tr> <td>Percent reduction in partial seizure frequency over placebo</td><td></td><td>26.1%*</td><td>30.1%*</td></tr> </table> *statist. daily 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 on period) within the three treatment groups (x axis) in Study 2 is presented in Figure 1. 66		Placebo (N=55)	Immediate release levetiracetam tablets 1000 mg/day (N=47)	Immediate release levetiracetam tablets 3000 mg/day (N=101)	Percent reduction in partial seizure frequency over placebo		26.1%*	30.1%*
	Placebo (N=55)	Immediate release levetiracetam tablets 1000 mg/day (N=47)	Immediate release levetiracetam tablets 3000 mg/day (N=101)						
Percent reduction in partial seizure frequency over placebo		26.1%*	30.1%*						
INSIDE PAGES 3.9825" / 98.488 mm Figure 1. Responder Rate (≥50% Reduction From Baseline) in Study 2 * statistically significant versus placebo 67	INSIDE PAGES 3.9825" / 98.488 mm Study 3 Study 3 was a double blind, placebo controlled, 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=106), 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. 68								
INSIDE PAGES 3.9825" / 98.488 mm Table 7. Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 3, Period A <table border="1"> <tr> <th></th><th>Placebo (N=111)</th><th>Immediate release levetiracetam tablets 1000 mg/day (N=106)</th><th>Immediate release levetiracetam tablets 2000 mg/day (N=106)</th></tr> <tr> <td>Percent reduction in partial seizure frequency over placebo</td><td></td><td>17.1%*</td><td>21.4%*</td></tr> </table> *statist. daily 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 on period) within the three treatment groups (x axis) in Study 3 is presented in Figure 2. 69		Placebo (N=111)	Immediate release levetiracetam tablets 1000 mg/day (N=106)	Immediate release levetiracetam tablets 2000 mg/day (N=106)	Percent reduction in partial seizure frequency over placebo		17.1%*	21.4%*	INSIDE PAGES 3.9825" / 98.488 mm Figure 2. Responder Rate (≥50% Reduction From Baseline) in Study 3, Period A * statistically significant versus placebo 70
	Placebo (N=111)	Immediate release levetiracetam tablets 1000 mg/day (N=106)	Immediate release levetiracetam tablets 2000 mg/day (N=106)						
Percent reduction in partial seizure frequency over placebo		17.1%*	21.4%*						
INSIDE PAGES 3.9825" / 98.488 mm 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 (A=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 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 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. 71	INSIDE PAGES 3.9825" / 98.488 mm Table 8. Reduction in Mean Over Placebo in Weekly Frequency of Partial Onset Seizures in Study 4 <table border="1"> <tr> <th></th><th>Placebo (N=104)</th><th>Immediate release levetiracetam tablets 3000 mg/day (N=180)</th></tr> <tr> <td>Percent reduction in partial seizure frequency over placebo</td><td></td><td>23.0%*</td></tr> </table> *statist. daily 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 on period) within the two treatment groups (x axis) in Study 4 is presented in Figure 3. 72		Placebo (N=104)	Immediate release levetiracetam tablets 3000 mg/day (N=180)	Percent reduction in partial seizure frequency over placebo		23.0%*		
	Placebo (N=104)	Immediate release levetiracetam tablets 3000 mg/day (N=180)							
Percent reduction in partial seizure frequency over placebo		23.0%*							

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Figure 3. Responder Rate ($\geq 50\%$ Reduction From Baseline) In Study 4

Treatment Group	Responder Rate (%)
Placebo (N=104)	14.49%
Immediate-release levetiracetam tablets 1000 mg/day (N=140)	38.4%

* statistically significant versus placebo

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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 (percentage of patients with $\geq 50\%$ 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		26.8%*

*statistically significant versus placebo

The percentage of patients (y axis) who achieved $\geq 50\%$ 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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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

Bottles of 60s (NDC 00505 3518 5)

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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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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14.2 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 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 tablets or placebo. The enrolled population included 156 patients (levetiracetam N=101; placebo N=55) with refractory partial onset seizures, with or without secondary 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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Figure 4. Responder Rate ($\geq 50\%$ Reduction From Baseline) In Study 5

Treatment Group	Responder Rate (%)
Placebo (N=97)	19.6%
Immediate-release levetiracetam tablets (N=101)	44.6%

* statistically significant versus placebo

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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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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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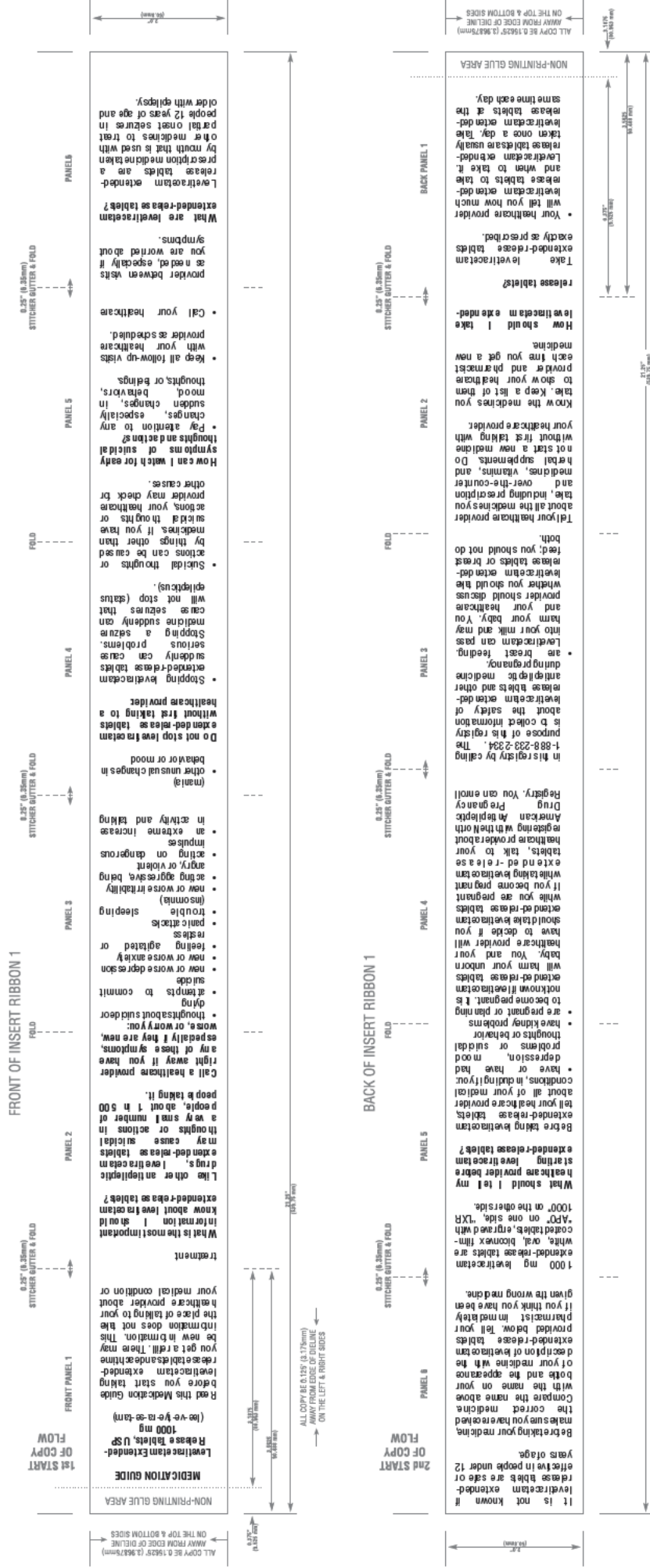
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