LUMARK XR
(Levetiracetam)

500 mg

Extended-Release Tablet

COMPOSITION

Lumark-500 mg Tablet
Each film coated extended released tablet contains:
Levetiracetam…….....500mg (Searle's Spec)

Therapeutic Indications

Lumark XR 500 mg tablets are indicated as an adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy.

Dosage and Administration

For adults and adolescent patients, the recommended dosing for monotherapy and adjunctive therapy is the same; as outlined below.

Adults and Adolescents 12 Years of Age and Older Weighing 50 kg or More

Initiate treatment with a dose of 1000 mg once daily. The once daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg/day once daily.

Lumark XR is administered once daily. Lumark XR tablets should be swallowed whole. The tablets should not be chewed, broken, or crushed.

Dosage Adjustments in Adult Patients with Renal Impairment

Lumark XR dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults are shown in Table 1. In order to calculate the dose recommended for patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated.

Table 1 : Dosage Adjustment in Adult Patients with Renal Impairment

Group	Creatinine Clearance (mL/min/1.73m^2)	Dosage (mg)	Frequency
Normal	> 80	1000 to 3000	Every 24 hours
Mild	50-80	1000 to 2000	Every 24 hours
Moderate	30-50	500 to 1500	Every 24 hours
Severe	<30	500 to 1500	Every 24 hours

Contraindications

Lumark XR is contraindicated in patients with a hypersensitivity to Levetiracetam. Reactions have included anaphylaxis and angioedema.

Warnings and precautions

Behavioural Abnormalities and Psychotic Symptoms

Lumark XR may cause behavioural abnormalities and psychotic symptoms. Patients treated with Lumark XR should be monitored for psychiatric signs and symptoms.

Behavioural abnormalities

A total of 7% of Lumark XR-treated patients experienced non-psychotic behavioural disorders (reported as irritability and aggression) compared to 0% of placebo-treated patients. Irritability was reported in 7% of Lumark XR-treated patients. Aggression was reported in 1% of Lumark XR-treated patients. No patient discontinued treatment or had a dose reduction as a result of these adverse reactions.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs) including Lumark XR, increase the risk of suicidal thoughts or behaviour 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 behaviour, and/or any unusual changes in mood or behaviour.

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 of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour 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 behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour 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 behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour 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 below shows absolute and relative risk by indication for all evaluated AEDs.

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

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

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour 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 behaviour , or the emergence of suicidal thoughts, behaviour , or thoughts about self-harm. Behaviours of concern should be reported immediately to healthcare providers.

Somnolence and Fatigue

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

Somnolence

In the Levetiracetam XR double-blind, controlled trial in patients experiencing partial onset seizures, 8% of Lumark XR-treated patients experienced somnolence compared to 3% of placebo-treated patients.

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

Anaphylaxis and Angioedema

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

Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with Levetiracetam. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with Levetiracetam has also been reported. Lumark XR should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Coordination Difficulties

Coordination difficulties were not observed in the Levetiracetam XR controlled trial.

Withdrawal Seizures

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

Hematologic Abnormalities

Lumark XR can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in red blood cell (RBC) counts, haemoglobin, and hematocrit, and increases in eosinophils counts. Decreased white blood cell (WBC) and neutrophil counts also occurred in clinical trials. Cases of agranulocytosis have been reported in the post marketing setting.

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.

Adverse Drug Reactions

- Behavioural abnormalities and Psychotic Symptoms
- Suicidal Behavior and Ideation
- Somnolence and Fatigue
- Anaphylaxis and Angioedema
- Serious Dermatological Reactions
- Coordination Difficulties
- Hematologic Abnormalities

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. Levetiracetam XR tablets In the controlled clinical study in patients with partial onset seizures, the most common adverse reactions in patients receiving Lumark XR 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 receiving Lumark XR in the placebo-controlled study and were numerically more common than in patients treated with placebo. In this study, either Lumark XR or placebo was added to concurrent AED therapy.

Table 3 : Adverse Reactions in the Placebo-Controlled, Add-On Study in Patients Experiencing Partial Onset Seizures

ADRs	LUMARK XR (N=77) %	Placebo (N=79) %
Influenza	8	4
Somnolence	8	3
Irritability	7	0
Nasopharyngitis	7	5
Dizziness	5	3
Nausea	5	3

Discontinuation or Dose Reduction in the Levetiracetam XR Controlled Clinical Study

In the controlled clinical study, 5% of patients receiving Levetiracetam XR and 3% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions that resulted in discontinuation and that occurred more frequently in Levetiracetam XR-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 XR-treated patient and no placebo-treated patients.

Comparison of Gender, Age and Race

There are insufficient data for Levetiracetam XR to support a statement regarding the distribution of adverse reactions by gender, age, and race.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com.

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 Cmax levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP glucuronidation enzymes. In addition, Levetiracetam does not affect the in vitro glucuronidation of valproic acid. Potential pharmacokinetic

interactions of or with Levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, Probenecid). The potential for drug interactions for Lumark XR is expected to be essentially the same as that with immediate-release Lumark tablets.

Use in specific populations

Pregnancy

Lumark XR levels may decrease during pregnancy.

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. Lumark XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of Levetiracetam to female rats throughout pregnancy and lactation led to increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m2 basis) and with increased pup mortality and offspring behavioural 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 ≥600 mg/kg/day (4 times MRHD on a mg/m2 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/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 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.

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/m2 basis).

Labour and Delivery

The effect of Lumark XR on labour and delivery in humans is unknown.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in paediatric patients 12 years of age and older has been established based on pharmacokinetic data in adults and adolescents using Lumark XR.

Geriatric Use

There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Levetiracetam XR 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.

Renal Impairment

The effect of levetiracetam XR on renally impaired patients was not assessed in the controlled study.

Overdose

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The signs and symptoms for Lumark XR overdose are expected to be similar to those seen with immediate-release Lumark 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 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 Lumark overdoses in post marketing use.

Management of Overdose

There is no specific antidote for overdose with Levetiracetam XR. 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.

Haemodialysis

Standard haemodialysis procedures result in significant clearance of Levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although haemodialysis 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.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

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

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

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

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

Pharmacodynamic properties

Effects on QTc Interval

The effects of Lumark XR on QTc prolongation is expected to be the same as that of immediate-release Lumark. The effect of immediate-release Levetiracetam on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of Levetiracetam (1000 mg or 5000 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of significant QTc prolongation in this study.

Pharmacokinetic properties

Overview

Bioavailability of Lumark XR tablets is similar to that of the immediate-release Lumark tablets. The pharmacokinetics (AUC and Cmax) were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg extended-release Levetiracetam. Plasma half-life of extended-release Levetiracetam is approximately 7 hours.

Levetiracetam is almost completely absorbed after oral administration. The pharmacokinetics of Levetiracetam is 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 6-8 hours. The half-life is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Absorption and Distribution

Extended-release Levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release Levetiracetam.

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 fasting conditions. After multiple dose extended release Levetiracetam tablets intake, extent of exposure (AUC0-24) was similar to extent of exposure after multiple dose immediate-release tablets intake. Cmax and Cmin 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 (Tmax) was 2 hours longer in the fed state.

Metabolism

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

Elimination

Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function.

Specific Populations

Elderly:

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

Pharmacokinetics of immediate-release Levetiracetam were evaluated in 16 elderly subjects (age 61-88 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 XR in paediatric patients (13 to 16 years old) and in adults (18 to 55 years old) with epilepsy. Levetiracetam XR oral tablets (1000 mg to 3000 mg) were administered once daily with a minimum of 4 days and a maximum of 7 days of treatment to 12 pediatric patients and 13 adults in the study. Dose-normalized steady-state exposure parameters, Cmax and AUC, were comparable between pediatric and adult patients.

Pregnancy:

Levetiracetam XR levels may decrease during pregnancy.

Gender:

Extended-release Levetiracetam Cmax was 21-30% higher and AUC was 8-18% 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.

Renal Impairment:

The effect of Levetiracetam XR on renally impaired patients was not assessed in the controlled study. However, it is expected that the effect on Lumark XR-treated patients would be similar to that seen in controlled studies of immediate-release Lumark 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 (CLcr = 50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min) and 60% in the severe renal impairment group (CLcr <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 (CLcr >80mL/min). Approximately 50% of the pool of Levetiracetam in the body is removed during a standard 4- hour haemodialysis.

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.

Summary of Clinical studies

The effectiveness of Levetiracetam XR 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 Lumark immediate-release tablets 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 Lumark XR and immediate-release formulations in adults. The effectiveness for Levetiracetam 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 XR in adults and adolescents.

Levetiracetam XR in Adults

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

Study

Patients enrolled in the study 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 XR (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 XR 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). The relationship between the effectiveness of the same daily dose of Levetiracetam XR and immediate-release Lumark has not been studied and is unknown.

PRECLINICAL STUDIES

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 (MRHD) of 3000 mg on a mg/m2 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/m2 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/m2 or systemic exposure [AUC] basis).

PRESENTATION

Lumark XR-500 tablets are available in alu alu blister pack of 10's.

STORAGE INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

LUMARK XR-500 TABLET: 085930

MANUFACTURING LICENCE NO.: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Mfg. U.S.P. Specs.

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