LEVETIRACETAM
FOCALE®
250 mg, 500 mg and 1 g FILM-COATED TABLET
ANTIEPILEPTICS

FORMULATION

Each film-coated tablet contains:
Levetiracetam………………………………. 250 mg, 500 mg or 1 g

PRODUCT DESCRIPTIONS

Levetiracetam (Focale®) 250 mg is a blue, oblong, film-coated tablet.
Levetiracetam (Focale®) 500 mg is a yellow, oblong, film-coated tablet.
Levetiracetam (Focale®) 1 g is a white, oblong, film-coated tablet.

PHARMACODYNAMICS

Levetiracetam, a pyrrolidine derivative, is an anticonvulsant agent that is structurally unrelated to other available anticonvulsants. The mechanism of anticonvulsant action of levetiracetam is unknown.

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

At concentrations of up to 10μM, levetiracetam did not exhibit binding affinity for benzodiazepines, γ-aminobutyric acid (GABA), glycine or N-methyl-D-aspartate (NMDA) receptors, reuptake sites, or second messenger systems. *In vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents; levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, *in vitro* studies have shown that the drug opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cell culture.

Levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue, the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam's affinity for binding to the synaptic vesicle protein 2A correlates to the potency of its anti-seizure protection in the mouse audiogenic model of epilepsy and suggests that such interaction contributes to the drug's antiepileptic mechanism of action.

PHARMACOKINETICS

Levetiracetam is rapidly and close to 100% absorbed after oral administration. The pharmacokinetics are linear (over the dose range of 500 to 5,000 mg) and time invariant with low intra- and inter-subject variability. Peak plasma concentrations (C_{max}) are achieved in about an hour after oral dose in fasted subjects. Steady state is achieved after two days of a multiple twice-daily dosing. Peak concentrations are typically 31 g/mL and 43 μg/mL after a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively. The extent of absorption is dose-independent. Coadministration with food does not affect the bioavailability but reduces the C_{max} by 20% and delays it by 1.5 hours.

Neither levetiracetam nor its metabolite (ucbL057) are significantly protein-bound (<10%); clinically significant interaction with other drugs through competition for protein binding sites are therefore unlikely. Levetiracetam's volume of distribution is 0.5 to 0.7 L/kg, a value close to the volume of intracellular and extracellular water.

Levetiracetam is only partially metabolized and the major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucbL057 (24% of the dose) and is not dependent on any liver cytochrome P450 isoenzymes. Two minor metabolites were identified.

One was obtained as the product of hydroxylation of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). In healthy volunteers, the time of maximum serum concentration (t_{max}) of the drug is approximately one hour, and the half-life ($t_{1/2}$) is 7 to 8 hours which is unaffected by either dose, route of administration or repeated administration. The $t_{1/2}$ is 2.5 hours longer in the elderly.

Levetiracetam's mean total body clearance is 0.96 mL/min/kg. The major route of excretion is via urine, accounting for a mean 95% of the dose, with approximately 93% of the dose excreted within 48 hours. Excretion via feces accounted for only 0.3% of the dose. The cumulative urinary excretion of levetiracetam and its major metabolite (ucb L057) accounted for 66% and 24% of the dose, respectively, during the first 48 hours. Levetiracetam's renal clearance is 0.6 mL/min/kg, indicating that it is excreted by glomerular filtration with subsequent tubular reabsorption. The renal clearance of the major metabolite, ucb L057, is 4.2 mL/min/kg indicating active tubular secretion in addition to glomerular filtration.

INDICATIONS

Partial onset seizures

- As monotherapy in the treatment of partial onset seizures, with or without secondary generalization, in adults (16 years and older).
- As adjunctive therapy in the treatment of partial onset seizures, with or without secondary generalization, in adults, adolescents and children one month of age and older with epilepsy.

Myoclonic seizures in patients with juvenile myoclonic epilepsy

- As adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years and older with juvenile myoclonic epilepsy.

Primary generalized tonic-clonic seizures

- As adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years and older with idiopathic generalized epilepsy.

DOSAGE AND ADMINISTRATION

<table>
<tr><th colspan="2">USUAL RECOMMENDED ORAL LEVETIRACETAM DOSE</th></tr>
<tr><td colspan="2"><i>To be administered orally, with or without food.</i></td></tr>
<tr><th colspan="2">Partial Onset Seizures</th></tr>
<tr><th>Adults
(16 years and older)</th><th>Children and Adolescents
(4 to <16 years old)</th></tr>
<tr><td>The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1,500 mg twice daily.</td><td>Initial Dose: 20 mg/kg body weight/day in two divided doses (10 mg/kg BID);
The daily dose should be increased every two weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg BID).
If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced.
<i>Note: See table below on the guideline for tablet dosing based on weight during titration to 60 mg/kg/day.</i></td></tr>
</table>

<table>
<tr><th colspan="2">Myoclonic Seizures in Patients 12 years and older with Juvenile Myoclonic Epilepsy</th></tr>
<tr><td colspan="2">Initial Dose: 1,000 mg/day, given as twice-daily dosing (500 mg BID);
Dosage should be increased by 1,000 mg/day every two weeks to the recommended daily dose of 3,000 mg.
The effectiveness of doses lower than 3,000 mg/day has not been established.</td></tr>
<tr><td colspan="2">Or, as prescribed by a physician.</td></tr>
<tr><th colspan="2">Primary Generalized Tonic-Clonic Seizures</th></tr>
<tr><th>Adults (16 years and older)</th><th>Children and Adolescents (6 to <16 years old)</th></tr>
<tr><td>Initial Dose: 1,000 mg/day, given as twice-daily dosing (500 mg BID);
Dosage should be increased by 1,000 mg/day every two weeks to the recommended daily dose of 3,000 mg.
The effectiveness of doses lower than 3,000 mg/day has not been established.</td><td>Initial Dose: 20 mg/kg body weight/day in two divided doses (10 mg/kg BID);
The daily dose should be increased every two weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg BID).
<i>Note: See table below for tablet dosing based on weight during titration to 60 mg/kg/day.</i></td></tr>
</table>

Levetiracetam Tablet Weight-Based Dosing Guide for Children

Patient Weight	Daily Levetiracetam Oral Dose		
	20 mg/kg/day	**40 mg/kg/day**	**60 mg/kg/day**
20.1 to 40 kg	500 mg/kg/day (250 mg BID)	1,000 mg/kg/day (500 mg BID)	1,500 mg/kg/day (750 mg BID)
>40 kg	1,000 mg/kg/day (500 mg BID)	2,000 mg/kg/day (2 x 500 mg BID)	3,000 mg/kg/day (2 x 750 mg BID)

SPECIAL POPULATION:

Patients with Renal Impairment: The daily dose of levetiracetam must be individualized according to patient's renal function.

Recommended Adult Levetiracetam Oral Dose in Adult and Adolescents (weighing more than 50 kg with impaired renal function)

Group	Creatinine Clearance (mL/min.1.73m^2)	Oral Levetiracetam Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 hours
Mild	50 to 79	500 to 1,000	Every 12 hours
Moderate	30 to 49	250 to 750	Every 12 hours
Severe	< 30	250 to 500	Every 12 hours
*End-stage renal disease patients undergoing dialysis	-	500 to 1,000	

* A 750 mg loading dose is recommended on the first day of treatment with levetiracetam

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

To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is needed. The CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

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

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

Children with Renal Impairment: The daily dose of levetiracetam must be individualized according to renal function. This recommendation is based on a study in adult renally impaired patients.

The CL_{Cr} in mL/min/1.73 m^2 may be estimated from serum creatinine (mg/dL) determination, for young adolescents and children using the following formula (Schwartz formula):

$$CL_{cr} \text{ (mL/min/1.73 } m^2) = \frac{\text{Height (cm) x ks}}{\text{Serum Creatinine (mg/dL)}}$$

ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for children and adolescents patients weighing less than 50 kg with impaired renal function:

Recommended Levetiracetam Oral Dose for Children and Adolescents (weighing less than 50 kg with impaired renal function)

Group	Creatinine Clearance (mL/min.1.73m^2)	Dose and frequency
		Children from 4 years and adolescents weighing less than 50 kg
Normal	> 80	10 to 30 mg/kg (0.10 to 0.30 mL/kg) twice daily
Mild	50 to 79	10 to 20 mg/kg (0.10 to 0.20 mL/kg) twice daily
Moderate	30 to 49	5 to 15 mg/kg (0.05 to 0.15 mL/kg) twice daily
Severe	< 30	5 to 10 mg/kg (0.05 to 0.10 mL/kg) twice daily
*End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0.10 to 0.20 mL/kg) once daily(1) (2)

(1) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

(2) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 mL/kg) supplemental dose is recommended.

Patients with Hepatic Impairment:

Severe Hepatic Impairment: A 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <70 mL/min. No dose adjustment is needed for patients with mild to moderate hepatic impairment.

CONTRAINDICATION

Known hypersensitivity to levetiracetam or to any ingredient in the formulation

WARNINGS AND PRECAUTIONS

Psychiatric Reactions / Behavioral Abnormalities and Psychotic Symptoms

In some patients, levetiracetam causes behavioral abnormalities. The incidences of behavioral abnormalities in the myoclonic and primary generalized tonic-clonic seizure studies were comparable to those of the adult and pediatric partial onset seizure studies.

Suicidal behavior and ideation

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

The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed.

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

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.

Somnolence and fatigue

Levetiracetam may cause somnolence and fatigue. In general, the incidences of somnolence and fatigue in the pediatric partial onset seizure studies, and in pediatric and adult myoclonic and primary generalized tonic-clonic seizures studies were comparable to those of the adult partial onset seizure studies.

Somnolence and asthenia occurred most frequently within the first four weeks of treatment.

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

Serious Dermatological / Hypersensitivity Reactions

Serious dermatological / hypersensitivity reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS) have been reported in both children and adults treated with levetiracetam. Such serious skin reactions may be life-threatening, and some patients have required hospitalization with very rare reports of fatal outcome. There is no way to tell if a mild rash will become a severe skin reaction. If any of these hypersensitivity reactions are suspected, and an alternative cause cannot be established, levetiracetam should be discontinued. Recurrence of the serious skin reactions following re-challenge with levetiracetam has been reported. The median time of onset of SJS and TEN is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. The time to onset of DRESS may be longer than for SJS and TEN, e.g., Up to six weeks or more after treatment initiation. Typically, although not exclusively, DRESS initially presents with fever and rash, and then with other organ system involvement that may or may not include eosinophilia, lymphadenopathy, hepatitis, nephritis, and / or myocarditis. Since DRESS is variable in its expression, other organ system signs and symptoms not noted may also occur. Organ involvement may be more severe than skin involvement.

Coordination difficulties

Coordination difficulties were only observed in the adult partial onset seizure studies. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on levetiracetam to gauge whether it could adversely affect their ability to drive or operate machinery.

Withdrawal seizures

AEDs, including levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Hematologic Abnormalities

Hematologic abnormalities such as decrease in red blood cells (RBC) count, hemoglobin, hematocrit, and increases in eosinophil counts have occurred in clinical trials using levetiracetam. Decreased white blood cell (WBC) and neutrophil counts also occurred in clinical trials. Cases of agranulocytosis have been reported in the postmarketing setting.

Minor decreases in total mean erythrocyte count have been reported. Leukopenia, neutropenia, pancytopenia (with myelosuppression in some cases), and thrombocytopenia have also been observed, although a casual relationship to the drug has not been established.

Increase in Blood Pressure

A significantly higher risk of increased diastolic blood pressure was observed in levetiracetam-treated patients (17%) compared with placebo-controlled patients (2%). There was no overall difference in mean diastolic blood pressure between the treatment groups. This disparity was not observed in the studies of older children or in adults. It is recommended to monitor patients 1 month to <4 years of age for increases in diastolic blood pressure.

Effects on Ability to Drive and Use Machine.

No studies on the effects on the ability to drive and use machines have been performed.

Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment or following a dosage increase, somnolence or other CNS related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g., vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

Acute Kidney Injury

Levetiracetam has been very rarely associated with acute kidney injury, with a time to onset varying from a few days to several months.

INTERACTIONS WITH OTHER MEDICAMENTS

- **AEDs (e.g., phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, and primidone):** Levetiracetam may not significantly influence the plasma concentrations of these other AEDs, and that the other AEDs may not significantly influence the plasma concentrations of levetiracetam.
  Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity (e.g., nystagmus, nausea, vomiting).
- **Alcohol:** No data on the interaction of levetiracetam with alcohol is available.
- **Antacids:** No data on the influence of antacids on the absorption of levetiracetam is available.
- **Digoxin:** Concomitant use of digoxin did not influence the pharmacokinetics of levetiracetam.
- **Methotrexate:** Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.
- **Laxatives:** There have been reports on isolated cases of reduced efficacy of oral levetiracetam when it is concomitantly administered with the osmotic laxative macrogol. Thus, macrogol should not be orally administered for one hour before and for one hour after taking levetiracetam.
- **Oral Contraceptives (e.g., ethinylestradiol and levonorgestrel):** No clinically significant pharmacokinetic interactions were observed. However, pharmacokinetic interaction studies using levetiracetam as adjunctive therapy and covering the recommended dosage range have not been conducted. Therefore, physicians should advise their female patients to be alert to any irregular vaginal bleeding or spotting, and to immediately report to them any occurrences.
- **Probenecid:** Probenecid did not change the pharmacokinetics of levetiracetam when concomitantly used. The effect of levetiracetam on probenecid was not studied.
- **Warfarin:** Concomitant use of warfarin and levetiracetam did not affect the pharmacokinetics of levetiracetam. Prothrombin time was not affected by levetiracetam.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY AND LACTATION

Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although it indicates that the risk of having a child with a birth defect is greater for women on antiepileptic polytherapy, including levetiracetam as a component, than for women not treated with AEDs. Therapy with multiple AEDs is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be considered.

Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Discontinuation of antiepileptic treatments may result in disease worsening, which can be harmful to the mother and the fetus.

As with other AEDs, physiological changes during pregnancy may affect levetiracetam concentration. There have been reports of decreased levetiracetam concentrations during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). It is recommended that clinical response should be monitored carefully in women receiving levetiracetam treatment during pregnancy, and determination of changes in plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy. In the event that medication is increased during pregnancy, the dose may need to be adjusted postpartum.

The risk of having teratogenic effects as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy. It is recommended that:

- Women on AEDs receive pre-pregnancy counseling with regard to the risk of fetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for 12 weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Fertility

There are no human data on the effects of levetiracetam on male or female fertility.

Labor and Delivery

The effect of levetiracetam on labor and delivery is unknown.

Lactation

Levetiracetam is excreted in human breast milk. A decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into consideration the importance of the drug to the mother, because of the potential for serious adverse reactions in breastfeeding infants from levetiracetam.

CHILDREN

The safety and efficacy of levetiracetam in infants and children less than four years old has not been established.

ELDERLY

No overall differences in safety were observed between elderly (65 years and older) and younger subjects. 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. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection; monitoring of renal function may be useful.

RENAL IMPAIRMENT

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Dose adjustment is recommended for patients with impaired renal function and supplemental doses should be given to patients after dialysis. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

HEPATIC IMPAIRMENT

Safety and efficacy demonstrated in a limited number of epileptic patients with chronic liver disease. No dosage adjustment is necessary in patients with hepatic impairment.

UNDESIRABLE EFFECTS

Infections and Infestations: Infection, viral infection, flu syndrome, otitis media, influenza
Blood and Lymphatic System Disorders: Thrombocytopenia, leukopenia, pancytopenia, pancytopenia with bone marrow suppression, neutropenia, agranulocytosis, ecchymosis
Immune System Disorders: Hypersensitivity (including angioedema and anaphylaxis), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Metabolism and Nutrition Disorders: Anorexia, weight decreased, weight increased, hyponatremia, dehydration
Psychiatric Disorders: Depression, hostility/aggression, anxiety, insomnia, nervousness /irritability, suicide attempt, suicidal ideation, psychotic disorder, abnormal behavior, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation, completed suicide, personality disorder, thinking abnormal, hypersomnia
Nervous System Disorders: Somnolence, headache, convulsion, balance disorder, dizziness, lethargy, tremor, amnesia, memory impairment, coordination abnormal/ataxia, paresthesia, disturbance in attention, choreoathetosis, dyskinesia, hyperkinesia, ataxia, balance disorder, disturbance in attention, sedation, emotional lability, reflexes increased
Eye Disorders: Diplopia, vision blurred, amblyopia, conjunctivitis
Ear and Labyrinth Disorders: Vertigo, ear pain
Respiratory, Thoracic and Mediastinal Disorders: Cough, chest pain, bronchitis, pharyngitis, rhinitis, sinusitis, asthma, nasal congestion, pharyngolaryngeal pain, nasopharyngitis
Gastrointestinal Disorders: Abdominal pain, diarrhea, dyspepsia, vomiting, nausea, pancreatitis, gastroenteritis, gingivitis, tooth disorder, constipation
Hepatobiliary Disorders: Liver function test abnormal, hepatic failure, hepatitis
Skin and Subcutaneous Tissue Disorders: Rash, alopecia, eczema, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, skin discoloration, vesiculobullous rash
Musculoskeletal and Connective Tissue Disorders: Muscular weakness, myalgia, back pain, neck pain, arthralgia
Renal and Urinary Disorders: Urinary tract infection, albuminuria, urine abnormality,
General Disorders and Administration Site Conditions: Asthenia/fatigue, fever, pain, face edema
Investigations: Drug level increased
Injury, Poisoning and Procedural Complications: Injury, head injury, contusion, fall, joint sprain

OVERDOSE AND TREATMENT

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

There is no antidote for levetiracetam overdose; treatment is symptomatic and may include hemodialysis. After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis; 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 clinical status of the patient. The dialyzer extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite.

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in four 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.

STORAGE CONDITION

Store at temperatures not exceeding 30°C. Keep the product out of sight and reach of children.

AVAILABILITY

Levetiracetam (Focale®) 250 mg Film-coated tablet - PVC / PVdC / PE / PVC Blister Pack x 10's (Box of 30's) - DR-XY46338
Levetiracetam (Focale®) 500 mg Film-coated tablet - PVC / PVdC / PE / PVC Blister Pack x 10's (Box of 30's) - DR-XY46339
Levetiracetam (Focale®)1 g Film-coated tablet - PVC / PVdC / PE / PVC Blister Pack x 10's (Box of 30's) - DR-XY46340

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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Rua da Tapada Grande, No 2, Abrunheira, Sintra 2710-089, Portugal
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Rua da Tapada Grande, No 2, Abrunheira, Sintra 2710-089, Portugal
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No. 66 United Street, Mandaluyong City, Metro Manila, Philippines