PRODUCT MONOGRAPH

[Pr]phl-LEVETIRACETAM

(Levetiracetam Tablets)

250 mg, 500 mg and 750 mg

Antiepileptic

Pharmel Inc.
6111 Royalmount Ave., Suite 100
Montreal, Quebec
H4P 2T4

Date of Preparation: July 13, 2007

Control No. *115350*

Table of Contents

[Pr]phl-LEVETIRACETAM

(Levetiracetam Tablets)

250 mg, 500 mg and 750 mg

Antiepileptic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 250 mg, 500 mg, 750 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

phl-LEVETIRACETAM (levetiracetam) is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

Geriatrics (> 65 years of age): see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**.

Pediatrics (<18 years of age): see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**.

CONTRAINDICATIONS

- Patients who are hypersensitive to levetiracetam or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Withdrawal of Anti-Epileptic Drugs
As with all antiepileptic drugs, levetiracetam should be withdrawn gradually to minimize the potential of increased seizure frequency.

Hematologic

Hematological Abnormalities
Minor but statistically significant decreases compared to placebo were seen in total mean RBC count, mean hemoglobin, and mean hematocrit in levetiracetam-treated patients in controlled trials. For hemoglobin values, the percentage of levetiracetam or placebo treated patients with possibly clinically significant abnormalities were less than 0.5% each. For hematocrit values, a total of 5.1% of levetiracetam-treated versus 3.2% of placebo patients had at least one possibly significant decrease in hematocrit ($\leq$ 37% in males and 32% in females).

For white blood cells (WBC), 2.9% of treated versus 2.3% of placebo patients had at least one possibly clinically significant decrease in WBC count ($\leq 2.8 \times 10^9$/L), while 2.6% of treated vs. 1.7% of placebo patients had at least one possibly significant decrease in neutrophil count ($\leq 1.0 \times 10^9$/L). Of the levetiracetam treated patients with a low neutrophil count, all but one rose towards or reached baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Neurologic
Levetiracetam use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioral/psychiatric symptoms and 3) coordination difficulties.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. Somnolence/asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment and usually resolved while patients remained on treatment. In the case of behavioral/psychiatric symptoms (including such adverse events as aggression, agitation, anger, anxiety, emotional lability, hostility, irritability), approximately half of the patients reported these events within the first four weeks, with the remaining events occurring throughout the duration of the trials.

The following CNS adverse events were observed in controlled clinical trials (see Table 1).

Table 1: Total Combined Incidence Rate for Each of the Three Categories of CNS Adverse Events in Placebo-Controlled Add-On Clinical Trials

Category of CNS Adverse Event	Levetiracetam*+ AED therapy (N=672)	Placebo + AED therapy (N=351)
Somnolence and Fatigue Somnolence Asthenia	 15% 14%	 10% 10%
Behavioral/ Psychiatric Symptoms		
Nonpsychotic[1]	14%	6%
Psychotic[2]	1%	0%
Coordination Difficulties[3]	3%	2%

*Reflects levetiracetam doses of 1000 mg, 2000 mg, 3000 mg, and 4000 mg per day.

[1] "Non-psychotic behavioral/psychiatric symptoms" encompasses the following terms: agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, emotional lability, euphoria, hostility, nervousness, neurosis, personality disorder and suicide attempt.

[2] "Psychotic behavioral/psychiatric symptoms" encompasses the following terms: hallucinations, paranoid reaction, psychosis and psychotic depression.

[3] "Coordination difficulties" encompasses the following terms: ataxia, abnormal gait, uncoordination.

See Adverse Effects, Table 2 for incidence rate of individual AEs contained within the categories.

Behavioral/psychiatric symptoms (including agitation, emotional lability, hostility, anxiety etc.) have been reported approximately equally in patients with and without a psychiatric history.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. In a controlled study including a dose of 4000 mg, administered without titration, the incidence rate of somnolence during the first four weeks of treatment for patients receiving the high dose was 42%, compared to 21% for patients receiving 2000 mg/day.

Renal

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, pharmacokinetic studies in renally-impaired patients indicate that apparent clearance is significantly reduced in subjects with renal impairment (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations).

In patients with renal impairment levetiracetam dosage should be appropriately reduced. Patients with end stage renal disease, i.e. those undergoing dialysis should be given supplemental doses after dialysis (See DOSAGE AND ADMINISTRATION).

Special Population

Pregnant Women:

There are no adequate and well-controlled studies on the use of levetiracetam in pregnant women. Levetiracetam and/or its metabolites cross the placental barrier in animal species. In reproductive

toxicity studies in rats and rabbits, levetiracetam induced developmental toxicity at exposure levels similar to or greater than the human exposure. There was evidence of increased skeletal variations/minor anomalies, retarded growth, embryonic death, and increased pup mortality. In the rat, fetal abnormalities occurred in the absence of overt maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure. The potential risk for humans is unknown. Levetiracetam should not be used during pregnancy unless potential benefits to mother and fetus are considered to outweigh potential risks to both. Discontinuation of antiepileptic treatments may result in disease worsening, which can be harmful to the mother and the fetus.

Pregnancy Exposure Registry
To facilitate monitoring of fetal outcomes of pregnant women exposed to levetiracetam, physicians should encourage patients to register, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Nursing Women:
Levetiracetam is excreted in breast milk. Therefore, there is a potential for serious adverse reactions from levetiracetam in nursing infants. Recommendations regarding nursing and epilepsy medication should take into account the importance of the drug to the mother, and the as yet uncharacterized risks to the infant. Typically, recommendations are made in the context of the necessary prior risk-benefit judgement, regarding pregnancy and epilepsy medication

Pediatrics (<18 years of age):
Safety and efficacy in patients below the age of 18 have not been established.

Geriatrics (>65 years of age):
Renal function can be decreased in the elderly and levetiracetam is known to be substantially excreted by the kidney, the risk of adverse reactions to the drug may be greater in patients with impaired renal function. A pharmacokinetic study in 16 elderly subjects (age 61-88 years) showed a decrease in clearance by about 40% with oral administration of both single dose and 10 days of multiple twice-daily dosing. This decrease is most likely due to the expected decrease in renal function in these elderly subjects. Care should therefore be taken in dose selection for elderly patients, and it may be useful to monitor renal function.

There were insufficient numbers of elderly patients in controlled trials of epilepsy to adequately assess the efficacy or safety of levetiracetam in these patients. Nine of 672 patients treated with levetiracetam were 65 or over.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction

information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Commonly Observed

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, dizziness and infection. Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first four weeks of treatment with levetiracetam.

Incidence of AEs in Controlled Clinical Trials

Table 2: Incidence (%) of Treatment-Emergent Adverse Events In Placebo-Controlled, Add-on Studies By Body System. (Adverse Events Occurred in at Least 1% of levetiracetam-treated Patients and Occurred More Frequently than Placebo-treated Patients) (Studies N051, N052, N132 and N138)

Body System/ Adverse Event	**Levetiracetam + AED therapy (N=672)**	**Placebo + AED therapy (N=351)**
Body as a Whole		
Asthenia	14%	10%
Infection[a]	13%	7%
Digestive System		
Tooth Disorders	2%	1%
Hemic and Lymphatic System		
Ecchymosis	2%	1%
Nervous System		
Amnesia	2%	0%
Anxiety	2%	1%
Ataxia	3%	1%
Depression	4%	2%
Dizziness	9%	4%
Emotional Lability	2%	0%
Hostility	2%	1%
Nervousness	4%	2%
Personality Disorders	1%	0%
Somnolence	15%	10%
Thinking Abnormal	2%	1%
Vertigo	3%	1%
Respiratory System		
Pharyngitis	6%	4%
Rhinitis	4%	3%
Sinusitis	2%	1%

***** In levetiracetam-treated patients, the majority of "Infection" events (93%) were coded to reported terms of "common cold" or "infection upper respiratory".

Additional Events Observed in Placebo Controlled Trials

Lack of Dose-Related Incidence of Adverse Events within Therapeutic Range

Based on the data from the controlled clinical trials, there was no evidence of dose relationship within the recommended dose range of 1000 to 3000 mg/day.

Discontinuation or Dose Reduction in Well-Controlled Clinical Studies
In well-controlled clinical studies, 14.3% of patients receiving levetiracetam and 11.7% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in Table 3.

Table 3: Adverse Events Most Commonly Associated With Discontinuation or Dose Reduction in Placebo-Controlled Studies in Patients with Epilepsy

	Levetiracetam (N = 672)	**Placebo (N = 351)**
Asthenia	9 (1.3%)	3 (0.9%)
Headache	8 (1.2%)	2 (0.6%)
Convulsion	16 (2.4%)	10 (2.8%)
Dizziness	11 (1.6%)	0
Somnolence	31 (4.6%)	6 (1.7%)
Rash	0	5 (1.4%)

The overall adverse experience profile of levetiracetam was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

Post-market Adverse Drug Reactions

In post-marketing experience, nervous system and psychiatric disorders have most frequently been reported. In addition to adverse reactions during clinical studies, and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic disorders: leukopenia, neutropenia, pancytopenia, thrombocytopenia.

DRUG INTERACTIONS

Overview

In Vitro Studies on Metabolic Interaction Potential
In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (paracetamol UGT i.e. UGT1A6, ethinyl estradiol UGT i.e. UGT1A1 and p-nitrophenol UGT i.e. UGT [pI6.2]) and epoxide hydrolase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid. In human hepatocytes in culture, levetiracetam did not cause enzyme induction.

Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; therefore clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Thus in vitro data, in combination with the pharmacokinetic characteristics of the drug, indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions.

Clinical Pharmacokinetic Data
Other Antiepileptic Drugs (AEDs)
Potential drug interactions between levetiracetam and other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data suggest that 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.

For two of these AEDs (phenytoin and valproate) formal pharmacokinetic interaction studies with levetiracetam were performed. Levetiracetam was co-administered with either phenytoin or valproate at doses of 3000 mg/day and 1000 mg/day respectively. No clinically significant interactions were observed.

Drug-Drug Interactions

Oral Contraceptives
A pharmacokinetic clinical interaction study has been performed in healthy subjects between the oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgesterol, and the lowest therapeutic dose of levetiracetam (500 mg bid). 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.

Digoxin
Levetiracetam (1000 mg bid) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin
Levetiracetam (1000 mg bid) did not influence the pharmacokinetics of R and S warfarin (2.5 mg, 5 mg, or 7.5 mg daily). 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 bid). C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid and the renal clearance of the metabolite ucb L057 was decreased by 60%; this alteration is likely related to competitive inhibition of tubular secretion of ucb L057. The effect of levetiracetam on probenecid was not studied.

Drug-Food Interactions
Food does not affect the extent of absorption of levetiracetam, although the rate is decreased.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

General
Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, reduced doses are recommended for patients with renal impairment.

Adults
Treatment should be initiated at a dose of 1000 mg/day, given as twice daily dosing (500 mg bid). Depending on clinical response and tolerability, the daily dose may be increased every two weeks by increments of 1000 mg, to a maximum recommended daily dose of 3000 mg.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice a day dosing, were shown to be effective. Although there was a tendency toward greater response rate with higher dose, a consistent statistically significant increase in response with increased dose has not been shown. There are limited safety data from controlled clinical trials at doses higher than 3000 mg/day (approximately 40 patients); therefore these doses are not recommended.

Patients with Impaired Renal Function
Levetiracetam dosage should be reduced in patients with impaired renal function (see Table 4 below). Patients with end stage renal disease should receive supplemental doses following dialysis. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

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

Table 4: Dosing Adjustment for Patients with Impaired Renal Function

Group	**Creatinine Clearance (mL/min)**	**Dosage and Frequency**
Normal	≥ 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe*	<30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis[(1)]	-	500 to 1000 mg once daily

* Or according to best clinical judgement

(1) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

Patients with Impaired Hepatic Function

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <70 mL/min.

Geriatrics

Dose selection and titration should proceed cautiously in elderly patients, as renal function decreases with age.

Administration

Levetiracetam is given orally with or without food.

OVERDOSAGE

Symptoms

The highest reported levetiracetam overdose is approximately 10 times the therapeutic dose. In the majority of overdose cases, multiple drugs were involved. Somnolence, agitation, aggression,

depressed level of consciousness, respiratory depression, and coma were observed with levetiracetam overdoses. The minimal lethal oral dose in rodents is at least 233 times the maximum clinically studied dose.

Treatment
There is no antidote for overdose with levetiracetam; treatment is symptomatic and may include hemodialysis. 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 clinical status of the patient.

Standard hemodialysis procedures result in significant removal 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Levetiracetam is a drug of the pyrrolidine class chemically unrelated to existing antiepileptic drugs (AEDs). Levetiracetam exhibits antiseizure and antiepileptogenic activity in several models of chronic epilepsy in both mice and rats, while being devoid of anticonvulsant activity in the classical screening models of acute seizures.

The mechanism of action of levetiracetam has not yet been fully established, however, it appears to be unlike that of the commonly used AEDs. In vitro studies show that levetiracetam, at concentrations of up to 10 μM did not result in significant ligand displacement at known receptor sites such as benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate) re-uptake sites or second messenger systems. Furthermore, levetiracetam does not modulate neuronal voltage-gated sodium and T-type calcium currents and does not induce conventional facilitation of the GABAergic system.

Pharmacokinetics
Summary:
Single- and multiple-dose pharmacokinetics of levetiracetam have included healthy volunteers, adult and pediatric patients with epilepsy, elderly subjects, and subjects with renal and hepatic impairment. Results of these studies indicate that levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. Food does not affect the extent of absorption of levetiracetam, although the rate is decreased. Levetiracetam is not 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 the dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The

metabolites have no known pharmacodynamic activity and are renally excreted. Plasma half-life of levetiracetam across studies is 6-8 hours. Plasma half life is increased in subjects with renal impairment, and in the elderly primarily due to impaired renal clearance.

Based on its pharmacokinetic characteristics, levetiracetam is unlikely to produce or to be subject to metabolic interactions.

The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg body weight. Therefore, there is no need for plasma level monitoring of levetiracetam.

Human Pharmacology

Pharmacokinetics
The pharmacokinetics of levetiracetam have been characterized in single-and multiple-dose PK studies, with doses up to 5000 mg; these studies included healthy volunteers (N=98), patients with epilepsy (N=58 adult patients and N=24 pediatric patients), elderly subjects (N=16) and subjects with renal and hepatic impairment (N=36 and 16, respectively).

Absorption and Distribution
Levetiracetam is rapidly and almost completely absorbed after oral administration. The oral bioavailability of levetiracetam tablets is 100%. Plasma peak concentrations (C_{max}) are achieved at 1.3 hours after dosing. The extent of absorption is independent of both dose and the presence of food, but the latter delays T_{max} by 1.5 hours and decreases C_{max} by 20%. The pharmacokinetics of levetiracetam are linear over the dose range of 500–5000 mg. Steady-state is achieved after two days of a twice daily administration schedule. Mean peak concentrations (C_{max}) are 31 and 43 μg/mL, respectively, following a single 1000 mg dose, and a repeated 1000 mg twice daily dose.

Neither levetiracetam nor its primary metabolite is significantly bound to plasma proteins (<10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg, a value that is close to the total body water volume. No tissue distribution data for humans are available.

Metabolism
Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the pharmacologically inactive carboxylic acid metabolite, ucb L057 (24% of dose). The production of this metabolite is not dependent on any liver cytochrome P450 isoenzymes and is mediated by serine esterase(s) in various tissues, including blood cells. 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 evidence for enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7±1 hours and was unaffected by dose, route of administration or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug, which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. Approximately 93% of the dose was excreted within 48 hours. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The primary 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 and clearance is thus reduced in patients with impaired renal function (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Special Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly patients, ranging in age from 61-88 years, with 11 of the 16 patients aged 75 years of age or over with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of 500 mg bid for 10 days, total body clearance decreased by 38% and the half-life was increased about 40% (10 to 11 hours) when compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pediatrics (6 to 12 years)

Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after a single dose. The apparent clearance of levetiracetam adjusted to body weight was approximately 40% higher than in epileptic adults.

Gender

Levetiracetam C_{max} and AUC were 20% higher in women (N=11) 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. Because levetiracetam is primarily renally excreted and there are no known important racial differences in creatinine clearance, significant pharmacokinetic differences due to race are not expected.

Renal Impairment

Single dose pharmacokinetics were performed in 20 subjects with renal impairment (N=7 mild/CLcr of 50-79 mL/min; N=8 moderate/CLcr of 30-49 mL/min; N=5 severe/CLcr <30 mL/min), and N=11 matching healthy volunteers. Clearance of levetiracetam is correlated with creatinine clearance and levetiracetam pharmacokinetics following repeat administration were well predicted from single dose data. The apparent body clearance of the parent drug levetiracetam is reduced in patients with impaired renal function by approximately 40% in the mild group, 50% in the moderate group, and 60% in the severe renal impairment group. For the primary metabolite ucb L057, the decrease in clearance values from baseline was greater than that seen for the parent drug in all subject groups.

In anuric (end stage renal disease) patients, the apparent body clearance was approximately 30% compared to that of normal subjects. Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

A single-dose pharmacokinetic study was performed in 16 subjects with hepatic impairment (N=5 mild/Child-Pugh Grade A; N=6 moderate/Grade B; N=5 severe/Grade C vs. 5 healthy controls). For the mild and moderate subgroups neither mean nor individual pharmacokinetic values were clinically different from those of controls. In patients with severe hepatic impairment, mean apparent body clearance was 50% that of normal subjects, with decreased renal clearance accounting for most of the decrease. Patients with severe hepatic impairment thus require a reduced dosage of levetiracetam (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

phl-LEVETIRACETAM Tablets should be stored between 15º C and 30º C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

phl-LEVETIRACETAM 250 mg Tablets are supplied as blue modified capsule-shaped, unscored coated tablets, debossed with "LV250" on one side and plain on the other side.

phl-LEVETIRACETAM 500 mg Tablets are supplied as yellow modified capsule-shaped, coated tablets debossed with "LV500" on one side and unscored on the other side.

phl-LEVETIRACETAM 750 mg Tablets are supplied as peach modified capsule-shaped, coated tablets debossed with "LV750" on one side and unscored on the other side.

phl-LEVETIRACETAM Tablets are packaged in bottles in the following configurations:

250 mg Tablets:
HDPE bottle 60 cc of 100 tablets

500 mg Tablets:
HDPE bottle 150 cc of 100 tablets
HDPE bottle 625 cc of 500 tablets

750 mg Tablets
HDPE bottle 200 cc of 100 tablets

Composition

phl-LEVETIRACETAM (levetiracetam) Tablets contain 250 mg, 500 or 750 mg levetiracetam. phl-LEVETIRACETAM Tablets also contain the following inactive ingredients (alphabetically): Colloidal Silicon Dioxide, Corn Starch, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Purified Water, Sodium Starch and Talc.

phl-LEVETIRACETAM 250 mg tablets contain also the following excipients:
FD&C Blue # 2, Hydroxypropyl Methylcellulose, Polyethylene Glycol, Polysorbate and Titanium Dioxide.

phl-LEVETIRACETAM 500 mg tablets contain also the following excipients:
Hydroxypropyl Methylcellulose, Iron Oxide Black, Iron Oxide Yellow, Polyethylene Glycol and Titanium Dioxide.

phl-LEVETIRACETAM 750 mg tablets contain also the following excipients:
Hydroxypropyl Methylcellulose, Iron Oxide Red, Polyethylene Glycol and Titanium Dioxide.

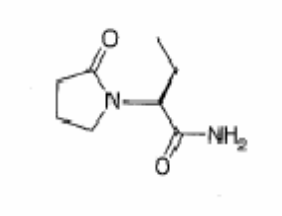
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	levetiracetam
Chemical Name:	(-)-(S)-a-ethyl-2-oxo-1-pyrrolidine acetamide
Molecular formula and molecular mass:	$C_8H_{14}N_2O_2$ 170.21 g/mol

Structural formula:



Physicochemical properties:	Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste.
Solubility:	it is very soluble in water (y104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.
pKa and pH values:	The pKa of levetiracetam is <-2 and cannot be determined with accuracy due to the chemical instability of the protonated form. The protonation of levetiracetam starts at H_0 values between -1 and -2.
Partition co-efficient:	Δ log P (log $P_{octanol}$ -log $P_{cyclohexane}$) was calculated at pH 7.4 using phosphate buffered saline and at pH 1.0 using KCl/HCl. The Δ log P at pH 7.4 is 3.65 and at pH 1.0 is 3.10.
Melting Range:	115-119˚C

CLINICAL TRIALS

Clinical Efficacy

The efficacy of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in a total of 904 adult patients who had a history of partial onset seizures with or without secondary generalization.

General Methodology

Patient Population
Patients in these three studies had refractory partial onset seizures for a minimum of 1 (or 2) year(s) prior to enrolment. They had previously taken a minimum number of classical AEDs (either one or two), and at the time of the study were taking a stable dose regimen of at least one AED. During the baseline period, it was required that patients experienced a minimum of 12 partial onset seizures over 12 weeks (Study N132) or 4 partial onset seizures during each 4-week period (Study N051) or 2 partial onset seizures per 4-week period (Study N138).

Dosing Schedules
After a prospective baseline period of approximately 12 weeks, patients were randomized to placebo, or levetiracetam at 1000 mg, 2000 mg or 3000 mg/day (depending on the study), given as twice daily doses. In all trials, there was a 2 or 4 week titration period, followed by a 12-14 week maintenance period.

Measures of Efficacy
The primary measure of efficacy was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire randomized treatment period (titration + maintenance). Secondary efficacy parameters include the 50% and 100% responder rate in partial onset seizure frequency over the entire randomized treatment period. Efficacy results are based on the ITT population with the exception of a few patients lacking evaluable seizure frequency data.

The above trial description applies to all three studies below. Thus for each trial, only primary distinguishing information is stated below.

Study N132

Study N132 was a parallel-group study conducted in the United States comparing placebo, levetiracetam 1000 mg/day, and levetiracetam 3000 mg/day in 95, 98, and 101 randomized patients, respectively. The efficacy for Study N132 is displayed in Table 5.

Table 5: Median Percent Reduction from Baseline in Weekly Frequency of Partial Onset Seizures in Study N132

	AEDs + Placebo	AEDs + Levetiracetam 1000 mg/day	AEDs + Levetiracetam 3000 mg/day
N	95	97	101
Median Baseline Seizure Frequency	1.77	2.53	2.08
Percent Reduction in Partial Seizure Frequency from Baseline	6.9%	36.9%*	38.1%*

* $P<0.001$ versus placebo.

Study N051

Study N051 was a crossover study conducted in Europe comparing placebo, levetiracetam 1000 mg/day, and levetiracetam 2000 mg/day in 112, 106, and 106 randomized patients, respectively.

The first period of the study (Period A) was designed to be analyzed as a parallel-group study. The efficacy results for Period A are displayed in Table 6.

Table 6: Median Percent Reduction from Baseline in Weekly Frequency of Partial Onset Seizures in Study N051

Period A

	AEDs + Placebo	AEDs + Levetiracetam 1000 mg/day	AEDs + Levetiracetam 2000 mg/day
N	111	106	105
Median Baseline Seizure Frequency	2.46	2.82	2.59
Percent Reduction in Partial Seizure Frequency from Baseline	1.1%	20.7%*	24.4%*

* $P<0.001$ versus placebo.

Study N138

Study N138 was a parallel-group study conducted in Europe comparing placebo and levetiracetam 3000 mg/day in 105 and 181 randomized patients, respectively. Table 7 displays the efficacy results for Study N138.

Table 7: Median Percent Reduction from Baseline in Weekly Frequency of Partial Onset Seizures in Study N138

	AEDs + Placebo	AEDs + Levetiracetam 3000 mg/day
N	104	180
Median Baseline Seizure Frequency	1.78	1.67
Percent Reduction in Partial Seizure Frequency from Baseline	7.3%*	36.8%*

* $P<0.001$ versus placebo.

Responder Rates

Each patient is categorized according to their efficacy data: percent reduction from baseline in weekly frequency of partial onset seizures, calculated over the entire randomized treatment period. The percentage of patients who remained on levetiracetam for at least 21 days and achieved ≥50% reduction, or a 100% reduction (seizure free) within each of the three pivotal studies is presented in Table 8.

Table 8: Partial Onset Responder Rate over the Entire Treatment Period by Randomized Dose

Percent Reduction	AEDs + Placebo	AEDs + Levetiracetam 1000 mg/day	AEDs + Levetiracetam 2000 mg/day	AEDs + Levetiracetam 3000 mg/day
Study N132				
N	95	97	—	101
≥ 50%	7%	36%		40%
Seizure free (100%)	0%	3%	—	6%
Study N051				
N	111	106	105	—
≥ 50%	6%	21%	34%	
Seizure free (100%)	1%	2%	3%	—
Study N138				
N	104	—	—	180
≥ 50%	14%		—	39%
Seizure free (100%)	0%	—	—	7%

Comparative Bioavailability Studies

A single-dose, crossover, comparative bioavailability study of phl-LEVETIRACETAM 750 mg Tablets, Lot # EC5016, manufactured by Dr. Reddy's Laboratories Limited on March 2005 was

performed versus PrKEPPRA®, Lot # 04C26G, manufactured by UCB S.A. Belgium and administered as 1 x 750 mg Tablet in healthy male volunteers in the Fasting State. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Levetiracetam (1 x 750 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_{0-t} (µg·h/mL)	183.519 185.115 (12.5)	180.028 181.428 (12.3)	101.94	100.35-103.55
AUC_I (µg·h/mL)	192.031 193.839 (13.1)	188.176 189.819 (13.1)	102.05	100.29-103.84
C_{max} (µg/mL)	22.530 23.135 (21.3)	23.109 23.615 (22.4)	97.49	90.08-105.52
T_{max}§ (h)	0.50 (0.33-4)	0.50 (0.33-1.25)		
$T_{½}$€ (h)	8.10 (10.0)	8.05 (11.6)		

* phl-LEVETIRACETAM
† Keppra® was manufactured by, UCB S.A., Belgium, distributed by Lundbeck, Canada, and were purchased in Canada
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV%)

DETAILED PHARMACOLOGY

Animal Pharmacology

The pharmacological activity of levetiracetam has been assessed in a variety of animal models of acute seizures and chronic epilepsy. Many studies included standard antiepileptic drugs (AEDs) as comparative agents.

Levetiracetam displayed protection against seizures in animal models of chronic epilepsy involving genetic and kindled animals with spontaneous, recurrent seizures. This contrasts to a lack of anticonvulsant activity in two primary screening tests for AEDs, the maximal electroshock (MES) test and the maximal pentylenetetrazol (PTZ) test. In general, levetiracetam is devoid of any activity against single seizures induced by maximal stimulation and in threshold

tests. An exception is the antiseizure protection observed against secondarily generalized activity from focal seizures induced by the chemoconvulsants pilocarpine and kainic acid. Overall, this profile of activity across the different types of animal models distinguishes levetiracetam from established AEDs that are typically active both in models of acute seizures and models of chronic epilepsy.

The precise mechanisms by which levetiracetam exerts its antiepileptic effect is unknown and does not appear to derive from any interaction with classical mechanisms involved in inhibitory or excitatory neurotransmission, including ion channel proteins, glutamate receptor-mediated neurotransmission, benzodiazepine, GABA (gamma-aminobutyric acid), glycine, and NMDA (N-methyl-D-aspartate) receptors as well as re-uptake sites or second messenger systems. In vitro studies have demonstrated a saturable and stereoselective neuronal binding site in rat brain tissue; however, the identification and function of this binding site is currently unknown.

TOXICOLOGY

General Toxicity

The general toxicity of levetiracetam was evaluated after oral administration in acute (mouse, rat, dog and monkey), subacute and chronic (two to 52 weeks or longer in the mouse, rat and dog) studies. Acute (mouse, rat and dog) and two-week (rat and dog) toxicity studies were also conducted using iv administration.

The single-dose studies in mice, rats and dogs indicate a low acute toxicity potential. Lethality was only reached after iv dosing in these studies; although in a subsequent study in mice (micronucleus test), lethality was reached at 10000 mg/kg orally. Oral administration is associated with only transient clinical signs (emesis, salivation, tremors, decreased motor activity, ataxia, tachypnea and side lying). In dogs, emesis is a dose-limiting effect. Repeat administration of levetiracetam is well tolerated. Mortality is observed only following iv administration of 900 mg/kg in rats. In general, clinical signs are minimal across studies and species with the most consistent observations being neuromuscular effects, salivation, and emesis in dogs. In the rodent only, treatment-related changes in the liver and kidney were reported. In the liver, a reversible increase in liver weight and hypertrophy of centrilobular hepatocytes was observed in both sexes in rats and mice. Centrilobular vacuolation associated with lipid deposition occurred in male rats and in mice. Kidney pathology consisting of hyaline droplet nephropathy, exacerbation of chronic progressive nephropathy and associated changes was observed in male rats.

These changes are considered to be a male rat-specific pathology associated with $\alpha 2$-microglobulin accumulation in the proximal tubules that is not toxicologically relevant to man. There was no target organ identified in the dog. No lethality, organ failure or other irreversible toxicity was observed after long-term oral treatment up to 1800 mg/kg/day in the rat, 960 mg/kg/day in the mouse and 1200 mg/kg/day in the dog.

Studies in neonatal or juvenile animals do not indicate any greater potential for toxicity compared to adult animals. Investigations involving oral administration of for up to 2 weeks of ucb L057, the major human metabolite, indicate a low potential for toxicity in rats and dogs.

Reproductive Toxicology
No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day.

Administration to rats before mating and throughout pregnancy and lactation was associated with slightly retarded fetal growth and skeletal ossification in utero and slight increase in pup mortality between birth and day 8 postpartum at 1800 mg/kg/day and slightly retarded skeletal ossification at 350 mg/kg/day.

When female rats were administered levetiracetam orally up to 1800 mg/kg/day from day 15 of pregnancy to weaning (day 21 postpartum), no effects were observed on litter parameters, pup survival and development. The dose of 1800 mg/kg/day corresponds to 30-fold the upper recommended daily dose in man on a mg/kg/day basis or 6-fold when calculated on a mg/m^2 body surface area basis.

In pregnant rats treated at 400, 1200 and 3600 mg/kg/day from day 6 to 15 of pregnancy, the no adverse effect level for embryo-fetal survival, growth and development is 1200 mg/kg/day. There was a slight increase in the proportion of fetuses with supernumerary ribs (thoracolumbar border) and a marginal reduction in skeletal ossification at 3600 mg/kg/day. This dose was toxic for the mothers. This dose represents 60-fold the upper recommended dose in man on a mg/kg/day basis, or 12-fold on a mg/m^2 basis.

In pregnant rabbits, the no-adverse effect level for embryo-fetal survival, growth and development was 200 mg/kg/day, a dose producing adverse effects in the mothers. At the highest dose of 1800 mg/kg/day, a 2.5-fold increase in fetal abnormalities was observed together with marked maternal toxicity. This was not seen in two other studies. The dose of 1800 mg/kg/day corresponds to 30-fold the upper recommended dose in man on a mg/kg/day basis or 11-fold when calculated on a mg/m^2 basis.

In a study in pregnant mice, levetiracetam administered at 3000 mg/kg/day from day 6 to 15 of pregnancy produced a slight retardation of growth and skeletal ossification and no effect on survival and morphological development. Plasma levetiracetam concentrations at approximate peak time were 20-fold higher than peak concentrations measured in man after 3000 mg/day.

Carcinogenesis and Mutagenesis

Carcinogenesis
Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. There was no evidence of carcinogenicity. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day. Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

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.

REFERENCES

Mechanism of Action

1. Birnstiel, S., Wülfert, E., Beck, S.G. Levetiracetam (L059) affects *in vitro* models of epilepsy in CA3 pyramidal neurons without altering normal synaptic transmission. Naunyn-Schmiedeberg's Arch. Pharmacol. 1997 356, 611-618.

2. Klitgaard H. Levetiracetam: the preclinical profile of a new class of antiepileptic drugs? Epilepsia. 2001; 42 Suppl 4:13-8. Review.

3. Lukyanetz EA, Shkryl VM, Kostyuk PG. Selective blockade of N-type calcium channels by levetiracetam. Epilepsia. 2002 Jan;43(1):9-18.

4. Margineanu, D.G., Wülfert, E. ucb L059, a novel anticonvulsant, reduces bicuculline-induced hyperexcitability in rat hippocampal CA3 *in vivo*. Eur. J. Pharmacol. (1995) 286, 321-325.

5. Margineanu, D.-G., Klitgaard, H.,. Inhibition of neuronal hypersynchrony in vitro differentiates levetiracetam from classical antiepileptic drugs. Pharmacol. Res. 2000 42 (4):281-285.

6. Rigo JM, Hans G, Nguyen L, Rocher V, Belachew S, Malgrange B, Leprince P, Moonen G, Selak I, Matagne A, Klitgaard H. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. Br J Pharmacol. 2002 Jul; 136(5):659-72.

7. Noyer, M., Gillard, M., Matagne, A., Hénichart, J.P., Wülfert, E. The novel antiepileptic drug levetiracetam (ucb L059) appears to act via a specific binding site in CNS membranes. Eur. J. Pharmacol. 1995 286:137-146.

8. Sills GJ, Leach JP, Fraser CM, Forrest G, Patsalos PN, Brodie MJ. Neurochemical studies with the novel anticonvulsant levetiracetam in mouse brain. Eur J Pharmacol. 1997 Apr 23; 325(1):35-40.

9. Tong X, Patsalos PN. A microdialysis study of the novel antiepileptic drug levetiracetam: extracelluar pharmacokinetics and effect on taurine in rat brain. Br J Pharmacol. 2001 Jul; 133(6):867-74.

10. Zona C, Niespodziany I, Marchetti C, Klitgaard H, Bernardi G, Margineanu DG. Levetiracetam does not modulate neuronal voltage-gated Na+ and T-type Ca2+ currents. Seizure. 2001 Jun; 10(4):279-86.

Pharmacology - Animal Pharmacology

11. Klitgaard, H., Matagne, A., Gobert, J., Wülfert, E. Evidence for a unique profile of levetiracetam in rodent models of seizures and epilepsy. Eur. J. Pharmacol. 1998 353:191-206.

12. Lamberty, Y., Margineanu, D.G., Klitgaard, H., 2000. Absence of Negative Impact of Levetiracetam on Cognitive Function and Memory in Normal and Amygdala-Kindled Rats. Epilepsy and Behavior.

13. Löscher, W., Hönack, D. Profile of ucb L059, a novel anticonvulsant drug, in models of partial and generalized epilepsy in mice and rats. Eur. J. Pharmacol. 1993 232:147-158.

14. Löscher, W., Hönack, D., Rundfeldt, C. Antiepileptogenic effects of the novel anticonvulsant levetiracetam (ucb L059) in the kindling model of temporal epilepsy. J. Pharmacol. Exp. Ther. 1998 284:474-479.

Clinical References

15. Ben-Menachem E.; Falter U. Efficacy and tolerability of levetiracetam 3000 mg/day in patients with refractory partial onset seizures: a multicentre, double-blind, responder-selected study evaluating monotherapy. Epilepsia in press.

16. Betts T.; Waegemans T.; Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure 2000, 9:80-87.

17. Browne T.R.; Szabo G.K.; Leppik I.E.; Josephs E.; Paz J.; Baltes E.; Jensen C.M. Absence of pharmacokinetic drug interaction of levetiracetam with Phenytoin in patients with epilepsy determined by new technique. Journal of Clinical Pharmacology, 2000 June; 40: 590-595.

18. Cereghino J.J.; Biton V.; Abou-Khalil B.; Dreifuss F.; Gauer L.J.; Leppik I. Levetiracetam for partial seizures: Results of a double-blind, randomized clinical trial. Neurology, 2000 July; 55 (2), 236-242.

19. French J.; Cereghino J.; Von Frenckell R.; Nohria V. Effectiveness of levetiracetam in reducing partial-onset seizures that are secondarily generalized (Type IC). Epilepsia, 1999 September; 40 Suppl. 2: 286-287. 23rd International Epilepsy Congress., Prague, Czech Republic 1999 September.

20. French J, Edrich P, Cramer JA. A systemic review of the safety profile of levetiracetam: a new antiepileptic drug. Epilepsy Res. 2001 Nov; 47(1-2): 77-90. Review.

21. Krakow K, Walker M, Otoul C, Sander JW. Long-term continuation of levetiracetam in patients with refractory epilepsy. Neurology. 2001 Jun 26; 56(12): 1772-4.

22. Levy RH, Ragueneau-Majlessi I, Baltes E. Repeated administration of the novel antiepileptic agent levetiracetam does not alter digoxin pharmacokinetics and pharmacodynamics in healthy volunteers. Epilepsy Res. 2001 Aug; 46(2):93-9.

23. Pellock JM, Glauser TA, Bebin EM, Fountain NB, Ritter FJ, Coupez RM, Shields WD. Pharmacokinetic study of levetiracetam in children. Epilepsia. 2001 Dec; 42(12):1574-9.

24. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. Epilepsia. 2002 Jul; 43(7); 697-702.

25. Ragueneau-Majlessi I, Levy RH, Meyerhoff C. Lack of effect of repeated administration of levetiracetam on the pharmacodynamic and pharmacokinetic profiles of warfarin. Epilepsy Res. 2001 Nov; 47(1-2):55-63.

26. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. Epilepsia. 2000 Sep; 41(9):1179-86.

27. Product Monograph - Keppra®, UCB Pharma Inc., Revision June 16, 2003.

28. Comparative Bioavailability study of phl-LEVETIRACETAM vs. Keppra®; Data on file at Pharmel Inc.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

phl-LEVETIRACETAM
levetiracetam

This leaflet is part III of a three-part "Product Monograph" published when phl-LEVETIRACETAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about phl-LEVETIRACETAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
phl-LEVETIRACETAM belongs to the family of medicines called antiepileptics for treating epilepsy. phl-LEVETIRACETAM has been prescribed for you by your doctor to reduce your number of seizures. It is taken with other seizure medications to help control seizures.

What it does:
Levetiracetam is an antiepileptic drug (AED) which is different from existing AEDs. It has antiseizure and antiepileptic activity. The exact mechanism of action is not known, but it appears to be unlike that of commonly used AEDs.

When it should not be used:
You should not use phl-LEVETIRACETAM if you are allergic to any of the ingredients in the product. See what the non-medicinal ingredients are. Contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.

What the medicinal ingredient is:
levetiracetam

What the nonmedicinal ingredients are:
phl-LEVETIRACETAM Tablets also contain the following inactive ingredients (alphabetically): Colloidal Silicon Dioxide, Corn Starch, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Purified Water, Sodium Starch and Talc.

phl-LEVETIRACETAM 250 mg tablets contain also the following excipients:
FD&C Blue # 2, Hydroxypropyl methylcellulose, Hydroxypropyl methylcellulose, Polyethylene glycol, Polysorbate and Titanium Dioxide.

phl-LEVETIRACETAM 500 mg tablets also contain the following excipients:
Hydroxypropyl methylcellulose, Iron Oxide Black, Iron Oxide Yellow, Polyethylene glycol and Titanium Dioxide.

phl-LEVETIRACETAM 750 mg tablets contain also the following excipients:
Hydroxypropyl methylcellulose, Iron Oxide Red, Polyethylene glycol and Titanium Dioxide.

What dosage forms it comes in:
Tablets: 250 mg, 500 mg and 750 mg

WARNINGS AND PRECAUTIONS

Important points you must tell your doctor before taking phl-LEVETIRACETAM:

- About all your medical conditions, especially if you have any kidney disease.
- If you are pregnant or thinking about becoming pregnant, or if you are breast-feeding.
- Any other medicines (prescription and nonprescription) you are taking.

Contract your doctor immediately if you experience any severe, unusual or allergic reactions.

- When taking phl-LEVETIRACETAM, it is very important not to perform any potentially hazardous tasks such as driving a car or operating dangerous machinery until you are sure this medication does not affect your mental alertness or physical coordination
- A very small number of people may have thoughts of suicide.
- If you are a female patient taking an oral contraceptive, watch for irregular menstruation or spotting and immediately report such occurrences to your doctor as this may be an indication that the oral contraceptive may not be working properly and you may get pregnant.

INTERACTIONS WITH THIS MEDICATION

Interactions with this medication and other drugs have not generally been observed. However, you should tell your doctor and pharmacist if you are using oral contraceptives and what prescription and non-prescription medications, vitamins, nutritional supplements and herbal products you are taking.

PROPER USE OF THIS MEDICATION

- It is very important that you take phl-LEVETIRACETAM exactly as your doctor has instructed.
- Never change the dose yourself.
- Do not stop taking it abruptly.
- phl-LEVETIRACETAM tablets are taken orally twice a day (typically morning and evening). phl-LEVETIRACETAM can be taken with or without food.
- Consult your doctor before taking any other medicines (prescription or nonprescription).

Missed dose

If you forget to take a dose, take it as soon as you remember, and then go on as usual. However, if it is almost time for your next dose, skip the dose you forgot and go on as usual.

Overdose

Contact your doctor or nearest hospital emergency department, even though you may not feel sick.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most frequently observed side effects are somnolence (sleepiness), asthenia (weakness), infection (such as common cold) and dizziness. Other side effects include: abnormal thinking, amnesia (loss of memory), anxiety, ataxia (lack of coordination), depression, ecchymosis (bruising), emotional lability (mood swings), hostility, nervousness, personality disorder, pharyngitis (sore throat), rhinitis (runny nose), sinusitis (stuffed head), tooth disorders (toothache) and vertigo (sensation of rotation).

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Extreme sleepiness or tiredness		√	
	Extreme weakness or difficulty coordinating muscles normally		√	
	Mood and behavior changes such as anxiety, irritability or anger and depression		√	

This is not a complete list of side effects. If you have any unexpected effects while taking this drug, contact your doctor or pharmacist.

HOW TO STORE IT

phl-LEVETIRACETAM Tablets should be stored between 15º C and 30º C.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Canada
Address Locator: 0701C
Ottawa, ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Pharmel Inc. at 1-888-550-6060.

This leaflet was prepared by Pharmel Inc.

Last revised: July 13, 2007.