SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

LEVIGRESS 500 (Levetiracetam Tablets USP 500 mg)

Strength : 500 mg

Pharmaceutical form: Oral dosage form in the form of tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION :

Each film coated tables contains :
Levetiracetam..... 500mg
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM:

Oral dosage form in the form of tablets
Yellow, oval shaped, biconvex, film coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications:

Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures in patient's ≥ 16 years of age with epilepsy.

4.2 Posology and method of administration:

Treatment should be started with 250 mg initially and gradually titrated to higher doses orally. Treatment should be initiated with a dose of 1000 mg once daily for extended release formulation. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg.

4.3 Contraindications:

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in tablets or oral solution.

4.4 Special warnings and precautions for use:

WARNING & PRECAUTION:
Suicidal Behavior and Ideation:

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

Withdrawal Seizures

Antiepileptic drugs, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Precautions:

Renal and hepatic impairment; pregnancy, lactation; patients undergoing haemodialysis. If psychotic symptoms (e.g. hallucination) and behavioural symptoms (e.g. agitation, anxiety) occur, reduce dosage. Abrupt withdrawal may result in increased seizure frequency. May impair ability to drive or operate machinery during initial therapy.

Paediatric Use

Safety and effectiveness in patients below 4 years of age have not been established.

Geriatric Use

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.

4.5 Interaction with other medicinal products and other forms of interaction:

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions.

Drug-Drug interaction:

Phenytoin:

Levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate:

Levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or

extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite.
Potential drug interactions between Levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Effect of AEDs in Pediatric Patients

There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

Other Drug Interactions Oral Contraceptives

Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin

Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin

Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

4.6 Fertility, pregnancy, and lactation:

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

4.7 Effects on ability to drive and use machines:

Levetiracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving 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.

4.8 Undesirable effects:

Body as a whole: Asthenia, Headache,
infection, pain Digestive system: Anorexia
Nervous system: somnolence, dizziness, depression,
nervousness, ataxia, vertigo, amnesia, anxiety,
hostility, emotional lability
Respiratory system: Pharyngitis, Rhinitis, Cough increased, sinusitis
Special sense: Diplopia.

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 via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'.

4.9 Overdose:

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest known dose of levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events 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 levetiracetam overdoses in post marketing use.

Treatment or Management of Overdose

There is no specific antidote for overdose with levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage;

usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with levetiracetam.

Hemodialysis

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

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.

5.2 Pharmacokinetic properties:

Levetiracetam is rapidly and almost completely absorbed after oral administration. The extent of bioavailability of levetiracetam is not affected by food. 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. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

5.3 Preclinical Safety Data

Attached after SmPC

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Sr. No.	Name of Excipients
1.	Microcrystalline Cellulose Plain
2.	Croscarmellose Sodium
3.	Povidone (Povidone K30)
4.	Purified Water
5.	Hypromellose- 6cps
6.	Polacrilin Potassium
7.	Sodium Lauryl Sulphate
8.	Magnesium Stearate
9.	Purified Talc
10.	Polyethylene glycol-6000
11.	Titanium dioxide
12.	Quinoline Yellow
13.	Isopropyl Alcohol
14.	Dichloromethane

6.2 Incompatibilities:

Not applicable

6.3 Shelf life: 24 months

6.4 Special precautions for storage:

Store at a temperature not exceeding 30°C. Protect from light and moisture.

6.5 Nature and contents of the container:

10 tablets in a blister, 3 such blisters are packed in a primary carton along with the package insert.

6.6 Special precautions for disposal <and other handling>:

Not applicable

7 MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

La Renon Healthcare Pvt. Ltd.
207-208, ISCON Elegance, Circle-P, Prahlad Nagar Cross Roads, S.G. Highway, Ahmedabad-380015, Gujarat, India.

8 MARKETING AUTHORIZATION NUMBER:

H2019/CTD6181/920ER

9 DATE OF FIRST <REGISTRATION> / RENEWAL OF THE DATE OF FIRST <REGISTRATION> : 15- 08-2018

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