SCHEDULING STATUS S3

PROPRIETARY NAME (AND DOSAGE FORM)

REDILEV 250 (film-coated tablet)

REDILEV 500 (film-coated tablet)

REDILEV 750 (film-coated tablet)

COMPOSITION

REDILEV 250: Each film-coated tablet contains levetiracetam 250 mg.

Sugar free.

REDILEV 500: Each film-coated tablet contains levetiracetam 500 mg.

Sugar free.

REDILEV 750: Each film-coated tablet contains levetiracetam 750 mg.

Sugar free.

REDILEV 250, 500 and **750** film-coated tablets contain the following inactive ingredients:

Colloidal silicon dioxide, corn starch, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, povidone, purified talc, sodium starch glycolate and titanium dioxide.

In addition:

REDILEV 250 contains FD&C Blue #2/Indigo carmine aluminium lake and polysorbate 80.

REDILEV 500 contains iron oxide black and iron oxide yellow.

REDILEV 750 contains iron oxide red.

PHARMACOLOGICAL CLASSIFICATION

A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Levetiracetam has anti-seizure properties. Levetiracetam is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing anti-epileptic active substances.

The precise mechanism of action by which levetiracetam induces seizure protection is unknown. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. The mechanism of action may relate to an interaction with a specific and stereoselective binding site that is only found within the central nervous system.

Pharmacokinetic properties

The pharmacokinetic profile is dose linear with low intra- and inter-subject variability. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Absorption

Levetiracetam is rapidly and almost completely absorbed after oral administration. Peak plasma concentrations (Cmax) are achieved at 1,3 hours after dosing. The extent of absorption is dose-independent and is not altered by food. Steady-state is achieved after two days on a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 and 43 µg/ml, following a single 1 000 mg dose and repeated 1 000 mg twice-daily dose, respectively.

Distribution

No tissue distribution data are available in humans. Neither levetiracetam nor its major metabolite are significantly bound to plasma proteins (< 10 %). The volume of distribution of levetiracetam is approximately 0,5 to 0,7 litres/kg, a value close to the volume of distribution of intracellular and extracellular water.

Metabolism

The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of this metabolite does not involve the liver cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including whole blood but not plasma. Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1,6 % of the dose) and the other one by opening of the pyrrolidone ring (0,9 % of the dose). Other unidentified components accounted only for 0,6 % of the dose. No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its major metabolite.

Elimination

The plasma half-life in adults was 7 hours ± 1 hour and did not vary with dose, route of administration or repeated administration. The total body clearance was a mean of 0,96 ml/min/kg. The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0,3 % of the dose. The cumulative urinary excretion of levetiracetam and its major metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours. The renal clearance of levetiracetam and its metabolite is 0,6 and 4,2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the major metabolite is also excreted by active tubular secretion in addition to glomerular filtration. In the elderly the half-life is increased by about 40 % [10 to 11 hours]. This is

related to the decrease in renal function in this population. Following single dose administration (20 mg/kg) to epileptic children 6 to12 years, the half-life of levetiracetam was 6,0 hours.

The apparent clearance was approximately 30 % higher than in epileptic adults. The apparent body clearance of both levetiracetam and of its metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end-stage renal disease subjects, the half-life was approximately 25 and 3,1 hours during interdialytic and intradialytic periods respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session. In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50 % due to a concomitant renal impairment.

INDICATIONS

REDILEV is indicated in adults and adolescents (from 16 years of age)

- as monotherapy, for the treatment of newly diagnosed partial onset seizures with or without secondary generalisation
- as adjunctive therapy to treat partial onset seizures, with or without secondary generalisation.

REDILEV is also indicated as adjunctive therapy in the treatment of

- myoclonic seizures in adults, and juvenile myoclonic epilepsy in adolescents (from 12 years of age)
- primary generalised tonic-clonic seizures in adults, and idiopathic generalised epilepsy in adolescents (from 16 years of age).

CONTRAINDICATIONS

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients of **REDILEV**.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

If **REDILEV** has to be discontinued, it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg:
500 mg twice daily decrements every two to four weeks; in adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks).

There is only limited data for the use in elderly patients (65 years and older).

The administration of **REDILEV** to patients with renal impairment may require dose adaptation. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection. (see **DOSAGE AND DIRECTIONS FOR USE**).

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of **REDILEV** expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of **REDILEV**, except in renal and hepatic insufficiency.

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in

patients treated with anti-epileptic medicines including **REDILEV**. Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Effects on ability to drive and use machines

Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment with **REDILEV** or following a dosage increase, somnolence or other CNS related symptoms. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery.

INTERACTIONS

Data indicate that levetiracetam did not influence the serum concentrations of existing antiepileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbitone, lamotrigine, gabapentin and primidone) and that these antiepileptic medicines did not influence the pharmacokinetics of levetiracetam.

It is expected that other medicines excreted by active tubular secretion could reduce the renal clearance of the metabolite.

The effect of levetiracetam on other actively secreted medicines, e.g. NSAIDs, sulphonamides and methotrexate is unknown.

Co-administration of **REDILEV** with topiramate, increases the risk of anorexia.

Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl oestradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified.

Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified.

Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

No data on the influence of antacids on the absorption of **REDILEV** are available.

The extent of absorption of **REDILEV** was not altered by food but the rate of absorption was slightly reduced. No data on the interaction of **REDILEV** with alcohol are available.

PREGNANCY AND LACTATION

There is no information on the use of levetiracetam during pregnancy.

Animal studies have shown reproductive toxicity.

Therefore, **REDILEV** is contraindicated in pregnancy and lactation (see **CONTRAINDICATIONS**).

Levetiracetam is excreted in human breast milk and therefore patients using **REDILEV** should not breastfeed.

DOSAGE AND DIRECTIONS FOR USE

REDILEV must be taken orally, swallowed with liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

- Monotherapy

Adults and adolescents from 16 years of age:

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 daily dose is 1 500 mg twice daily.

- Add-on therapy

Adults (≥ 18 years) and adolescents (12 to 17 years) weighing 50 kg or more, when indicated (see INDICATIONS):

The initial therapeutic dose is 500 mg twice daily. The dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability, the daily dose can be increased up to 1 500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Elderly (65 years and older):

Adjustment of the dose is recommended in elderly patients with compromised renal function (see **Patients with renal impairment** below).

Adolescents (12 to 17 years) weighing less than 50 kg, when indicated (see INDICATIONS):

The initial therapeutic dose is 10 mg/kg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. Dosage in children 50 kg or greater is the same as in adults.

The medical practitioner should prescribe the most appropriate formulation strength according to weight and dose.

Infants and children younger than 12 years:

REDILEV should not be used in children younger than 12 years of age.

Patients with renal impairment:

- The **REDILEV** daily dose must be individualised according to renal function.

  For adult patients refer to the following table and adjust the dose as indicated.

  To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr})

in ml/min is needed. The CL_{cr} may be estimated from serum creatinine (µmol/ℓ) determination using the following formula:

Table: Dosing adjustment for patients with impaired renal function

$$CL_{cr}\ (ml/min) = \frac{[140 - age]\ X\ Weight\ (kg)\ X\ Constant^*}{S_{cr}\ (\mu mol/\ell)}$$

Constant* = 1,23 in males and = 1,04 in females.

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	> 80	500 to 1 500 mg twice daily
Mild	50 – 79	500 to 1 000 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 1 000 mg once daily (2)

(1) A 750 mg loading dose is recommended on the first day of treatment with **REDILEV**.

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

Patients with hepatic impairment:

- 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 degree of any accompanying renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 ml/min. (see **Patients with renal impairment** and **WARNINGS AND SPECIAL PRECAUTIONS**).

SIDE-EFFECTS

The most frequently reported side-effects are somnolence, asthenia and dizziness.

Other side-effects

Infections and infestations:

Frequent: Infection, nasopharyngitis.

Blood and the lymphatic system disorders:

Less frequent: Agranulocytosis.

Frequency unknown: Leucopenia, neutropenia, pancytopenia, thrombocytopenia.

Immune system disorders:

Less frequent: Drug reaction with eosinophilia and systemic symptoms (DRESS).

Metabolism and nutrition disorders:

Frequent: Anorexia, weight gain.

Less frequent: Weight decreased, hyponatraemia.

Psychiatric disorders:

Frequent: Agitation, depression, emotional instability, lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, abnormal thinking.

Less frequent: Panic attack.

Frequency unknown: Abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, attempted suicide and suicide ideation.

Nervous system disorders:

Frequent: Somnolence, amnesia, ataxia, convulsions, dizziness, headache, tremor, balance disorder, hyperkinesia, disturbance in attention, memory impairment, lethargy.

Less frequent: Choreoathetosis, dyskinesia, paraesthesia.

Eye disorders:

Frequent: Diplopia, blurred vision.

Ear and labyrinth disorders:

Frequent: Vertigo.

Respiratory, thoracic and mediastinal disorders:

Frequent: Increased cough.

Gastro-intestinal disorders:

Frequent: Diarrhoea, abdominal pain, dyspepsia, nausea, vomiting.

Less frequent: Pancreatitis.

Hepato-biliary disorders:

Less frequent: Hepatic failure, hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: Rash, eczema, pruritus, alopecia.

Less frequent: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme.

Musculoskeletal, connective tissue disorders and bone disorders:

Frequent: Myalgia.

Less frequent: Muscular weakness.

General disorders and administration site conditions:

Frequent: Asthenia / fatigue.

Investigations:

Less frequent: Liver function test abnormal.

Injury and poisoning:

Frequent: Accidental injury.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdosage: Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma.

In acute overdosage the stomach may be emptied by induction of emesis.

There is no specific antidote for **REDILEV**. Treatment for an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the metabolite ucb L057.

IDENTIFICATION

REDILEV 250: Blue, modified capsule-shaped, film-coated tablets debossed with 'LV250' on one side and plain on other side.

REDILEV 500: Yellow, modified capsule-shaped, film-coated tablets debossed with 'LV500' on one side and plain on other side.

REDILEV 750: Peach, modified capsule-shaped, film-coated tablets debossed with 'LV750' on one side and plain on other side.

PRESENTATION

REDILEV 250, 500 and 750:

30, 120, 240 or 500 film-coated tablets in white opaque HDPE bottles with white, opaque, ribbed plastic caps with pulp liners. Packed in printed outer cardboard cartons: 20, 30 or 50 tablets as 2, 3, or 5 blister strips of 10 tablets each. The blisters are comprised of clear, transparent PVC (PVdC coated on one side) and silver coloured (paper backed) aluminium foil.

STORAGE INSTRUCTIONS

Store at or below 25 °C in a dry place.

Keep the tablets in the original bottle and keep well closed.

Keep the tablets in the blisters and the blisters in the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN

REGISTRATION NUMBERS

REDILEV 250: 41/2.5/0460

REDILEV 500: 41/2.5/0461

REDILEV 750: 41/2.5/0462

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Limited

The Place North Wing

1 Sandton Drive Sandton

2196

DATE OF PUBLICATION OF PACKAGE INSERT

25 November 2016