PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DYNA LEVETIRACETAM 250 mg film coated tablets

DYNA LEVETIRACETAM 500 mg film coated tablets

DYNA LEVETIRACETAM 750 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DYNA LEVETIRACETAM 250 mg tablet contains 250 mg levetiracetam.

Each DYNA LEVETIRACETAM 500 mg tablet contains 500 mg levetiracetam.

Each DYNA LEVETIRACETAM 750 mg tablet contains 750 mg levetiracetam.

DYNA LEVETIRACETAM tablets are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

DYNA LEVETIRACETAM 250 mg:

Blue, oblong-shaped, biconvex film coated tablets debossed with '250'

on one side and a score line on the other side.

DYNA LEVETIRACETAM 500 mg:

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Yellow, oblong-shaped, biconvex film coated tablets debossed with

'500' on one side and a score line on the other side.

DYNA LEVETIRACETAM 750 mg:

Peach coloured, oblong-shaped, biconvex film coated tablets debossed with '750' on one side and a score line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DYNA LEVETIRACETAM is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

DYNA LEVETIRACETAM is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults and children over 16 years of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and children from 16 years of age with idiopathic generalised epilepsy.

4.2 Posology and method of administration

Monotherapy:

Adults and adolescents from 16 years of age:

The 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 on the clinical response. The maximum daily dose is 1 500 mg twice daily.

Add-on therapy:

Adults and adolescents older than 12 years (weighing 50 kg or more when indicated (see section 4.1)**):**

As adjunctive therapy, the therapeutic dose is 500 mg twice daily. The dose can be started on the first day of treatment. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1 500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. The maximum daily dose is 3 000 mg.

Special populations

Elderly:

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

Patients with renal impairment:

The DYNA LEVETIRACETAM dose should be individualised

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according to renal function. Refer to the table below and adjust the dose as indicated.

Dosing adjustment for adult patients with impaired renal function:

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 DYNA LEVETIRACETAM.

[2] 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 (eCL_{cr}) in mL/min is needed.

The CL_{cr} can be estimated from the serum creatinine (S_{cr}) concentration using the modified formula of Cockfort and Gault (for use in adults):

$$eCL_{cr}\ (mL/min) = [140 - age] \times Wt\ (kg) \times constant^*$$

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S_{cr} (μmol/L)

*Constant = 1,23 for males and 1,04 for females (0,85 x 1,23 = 1,04)

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 renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 mL/min.

Paediatric population

Infants and children under the age of 12 years:

Monotherapy

The safety and efficacy of DYNA LEVETIRACETAM in children and adolescents below 16 years as monotherapy treatment have not been established. No data are available.

Add-on therapy

Infants and children under the age of 12 years:

There are insufficient data available for the use of DYNA LEVETIRACETAM in children under the age of 12 years.

Adolescents (12 to 17 years) weighing less than 50 kg, when indicated (see section 4.1):

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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 doctor should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Recommended dosage for children and adolescents with normal renal function:

Weight	Starting dose (10 mg/kg twice daily)	Maximum dose (30 mg/kg twice daily)
15 kg*	150 mg twice daily	450 mg twice daily
20 kg*	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg**	500 mg twice daily	1 500 mg twice daily

* Another formulation of levetiracetam should be used.

** Dosage in children and adolescents 50 kg or more is the same as in adults.

Method of administration

The film coated tablets should be taken orally, swallowed with liquid, and may be taken with or without food. The daily dose is administered in two equally divided doses.

Missed dose:

If a dose is missed, the tablet should be taken as soon as the missed dose is remembered. Two tablets should not be taken to make up for the missed dose.

4.3 Contraindications

- Hypersensitivity to levetiracetam or other pyrrolidine derivatives, or to any of the ingredients of DYNA LEVETIRACETAM
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines (including levetiracetam as in DYNA LEVETIRACETAM). Analysis of randomized placebo-controlled trials of anti-epileptic medicines has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known. 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 (see section 4.8).

Reduced doses of DYNA LEVETIRACETAM are recommended for patients with renal impairment (see section 4.2). Patients receiving dialysis may be given a loading dose of 750 mg when starting DYNA LEVETIRACETAM followed by doses of

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500 to 1 000 mg once daily, a supplemental dose of 250 to 500 mg is recommended after dialysis. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section 4.2).

The use of DYNA LEVETIRACETAM has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months.

DYNA LEVETIRACETAM should be used with caution in patients with severe hepatic impairment. No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, see section 4.2.

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leukopenia, thrombocytopenia, and pancytopenia) have been described in association with DYNA LEVETIRACETAM administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections, or coagulation disorders (see section 4.8).

DYNA LEVETIRACETAM may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness. Patients treated with DYNA LEVETIRACETAM should be monitored for developing psychiatric signs suggesting important mood and/or personality changes. If such behaviours are noticed, treatment adaptation or gradual

discontinuation should be considered. If discontinuation is considered, please refer to section 4.2.

Withdrawal of DYNA LEVETIRACETAM or transition to or from another type of anti-epileptic therapy should be made gradually (e.g., 500 mg twice daily decrements every two to four weeks in adults; 10 mg/kg twice daily decrements every two weeks in children) to avoid precipitating an increase in the frequency of seizures.

Paediatric population

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty, and childbearing potential in children remain unknown.

4.5 Interaction with other medicines and other forms of interaction

- Potential interactions with existing anti-epileptic medicines (such as phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, and primidone) have not been demonstrated.
- Probenecid (500 mg daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other medicines excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on

probenecid was not studied. The effect of levetiracetam on other actively secreted medicines e.g., NSAIDs and sulphonamides is unknown.

- 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 medicines.
- DYNA LEVETIRACETAM did not influence the pharmacokinetics of oral contraceptives (ethinyl oestradiol and levonorgestrel), endocrine parameters (luteinising hormone (LH) and progesterone) were not modified. DYNA LEVETIRACETAM 2 000 mg daily did not influence the pharmacokinetics of digoxin and warfarin, prothrombin times were not modified. Co-administration with digoxin, oral contraceptives or warfarin had no influence on the pharmacokinetics of levetiracetam.
- No information on the influence of antacids on the absorption of levetiracetam is available.
- There have been isolated reports of decreased levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking levetiracetam.
- The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.
- No information on the interaction of levetiracetam with alcohol is available.

4.6 Fertility, pregnancy, and lactation

Pregnancy

DYNA LEVETIRACETAM is contraindicated in pregnancy and lactation (see section 4.3).

Breastfeeding

Levetiracetam is excreted in human breast milk. Patients using DYNA LEVETIRACETAM must not breastfeed.

4.7 Effects on ability to drive and use machines

Caution is recommended in patients performing skilled tasks, e.g. driving vehicles or operating machinery. At the beginning of treatment or after a dosage increase, some patients may experience somnolence or other CNS related symptoms.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue, and dizziness. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

b. Tabulated list of adverse effects

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent Less frequent	Nasopharyngitis Infection
Blood and lymphatic system disorders	Less frequent	Leukopenia*, neutropenia*, pancytopenia*, thrombocytopenia*, agranulocytosis
Immune system disorders	Less frequent	Drug reaction with eosinophilia and systemic symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis).
Metabolism and nutrition disorders	Frequent Less frequent	Anorexia Decreased weight*, increased weight, hyponatraemia
Psychiatric disorders	Frequent Less frequent	Anxiety, depression, hostility, aggression, insomnia, nervousness, irritability Psychotic disorders*, mood swings*, agitation, personality disorder, emotional lability, suicide attempt*, suicidal ideation*, completed suicide*, abnormal behaviour*, hallucination*, anger*, confusional state*, panic attack affect, mood swings, thinking abnormal*

Nervous system disorders	Frequent Less frequent	Dizziness, headache, somnolence, convulsion, balance disorder, lethargy, tremor Paraesthesia*, amnesia, memory impairment, abnormal coordination, ataxia, disturbance in attention, choreoathetosis, dyskinesia, hyperkinesia
Eye disorders	Frequent	Diplopia, blurred vision
Ear and labyrinth disorders	Frequent	Vertigo
Respiratory, thoracic, and mediastinal disorders	Frequent Less frequent	Pharyngitis, rhinitis, cough Sinusitis
Gastrointestinal disorders	Frequent Less frequent	Diarrhoea, dyspepsia, nausea, vomiting, abdominal pain Pancreatitis.
Hepato-biliary disorders	Less frequent	Abnormal liver function tests*, hepatic failure*, hepatitis*
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash Alopecia, eczema*, pruritus*, toxic epidermal necrolysis*, Stevens-Johnson syndrome*, erythema multiforme*
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Ataxia, muscular weakness, myalgia Rhabdomyolysis and blood creatine phosphokinase increased**
Renal and urinary disorders	Less frequent	Acute kidney injury

General disorders and administrative site conditions	Frequent	Asthenia, fatigue
Injury and poisoning	Less frequent	Injury

*Post marketing side effects

** Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients

c. Description of selected adverse reactions

The risk of anorexia is higher when levetiracetam is co-administered with topiramate.

In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

Cases of encephalopathy generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

d. Paediatric population

The adverse reaction profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

Experience with levetiracetam overdose is limited. Symptoms that may occur with DYNA LEVETIRACETAM overdose include drowsiness, aggression, agitation, coma, depressed level of consciousness, respiratory depression, and somnolence.

Management of overdose:

There is no specific antidote for DYNA LEVETIRACETAM overdose. Treatment should be symptomatic and supportive. Emesis or gastric lavage should be attempted if indicated. Standard haemodialysis should be considered, particularly, in selected patients based on clinical state of renal impairment.

The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics.

ATC code: N03AX14

Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics.

Mechanism of action:

Levetiracetam is an anti-epileptic medicine. It is a pyrrolidine derivative, the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide, which is chemically unrelated to existing anti-epileptic active substances. Levetiracetam inhibits partial and secondarily generalised tonic-clonic seizures in the kindling model of epilepsy. It is ineffective against maximum electroshock and pentylenetetrazol induced seizures, findings consistent with effectiveness against partial and secondarily generalised tonic-clonic seizures clinically. The mechanism by which levetiracetam exerts these antiseizure effects is unknown. No evidence for an action on voltage-gated sodium Na^+ channels or either gamma-aminobutyric acid GABA- or glutamate-mediated synaptic transmission has emerged.

5.2 Pharmacokinetic properties

The pharmacokinetic profile is dose linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. 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.

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

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1,7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

Absorption:

Levetiracetam is rapidly and almost completely absorbed after oral administration, oral bioavailability is 100 %. Peak plasma concentrations (C_{max}) are achieved at 1,3 hours after dosing. Steady-state is achieved after 2 days of a twice daily administration schedule. Plasma protein binding is minimal (< 10 %). 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. The extent of absorption is dose-independent and is not altered by food.

Distribution:

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

Biotransformation:

Levetiracetam is not extensively metabolised in humans.

The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver

cytochrome P_{450} isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.

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 primary metabolite.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P_{450} isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of Keppra with other substances, or vice versa, is unlikely.

Elimination:

The plasma half-life in adults has been reported as 7 ± 1 hours 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. Approximately 95 % are excreted in the urine, (approximately 93 % of the dose was excreted within 48 hours) 66 % of which is unchanged and 24 % is metabolised by hydrolysis of the acetamide group.

Excretion via faeces accounted for only 0.3 % of the dose.

Levetiracetam neither induces nor is a high-affinity substrate for cytochrome P450 isoforms of glucuronidation enzymes and thus is devoid of known interactions with other antiseizure medicines, oral contraceptives, or anticoagulants.

Pharmacokinetics in special patient groups

Elderly:

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 (see section 4.2).

Renal impairment:

The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended that the maintenance daily dose of levetiracetam be adjusted, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2). 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.

Hepatic impairment:

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 (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, and carcinogenic potential.

Adverse effects, not observed in clinical studies but seen in the rat and to a lesser extent in the mouse, at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration, and increased liver enzymes in plasma.

No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m2 or exposure basis) in parents and F1 generation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Croscarmellose sodium

Magnesium stearate

Maize starch

Microcrystalline cellulose

Povidone

Silica colloidal

Talc

Tablet coating:

Opadry blue AMB 84F80803: (FD & C blue #2/Indigo carmine aluminium lake)

Opadry pink AMB 84F 84674: (FC & C yellow #6 Sunset yellow FCF aluminium lake, iron oxide red, iron oxide yellow)

Opadry white AMB 84F58775

Opadry yellow AMB 84F82508: (Iron oxide yellow)

Excipients common to Opadry variants:

Macrogol 3350

Macrogol 6000

Polyvinyl alcohol (part hydrolysed)

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C. Keep blisters in carton until required for use.

6.5 Nature and contents of container

Clear PVC/ Aluminium blister strips containing 10 tablets. Six (6 x 10) or three (3 x 10) blister strips are packed in an outer cardboard box.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

DYNA LEVETIRACETAM 250 mg: A44/2.5/0368

DYNA LEVETIRACETAM 500 mg: A44/2.5/0369

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DYNA LEVETIRACETAM 750 mg: A44/2.5/0370

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 01 March 2013

10. DATE OF REVISION OF THE TEXT

11 January 2023

NAMIBIA:

DYNA LEVETIRACETAM 250 mg: NAM NS2 13/2.5/0178

DYNA LEVETIRACETAM 500 mg: NAM NS2 13/2.5/0179

DYNA LEVETIRACETAM 750 mg: NAM NS2 13/2.5/0180

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