DYNA LEVETIRACETAM 250 mg
DYNA LEVETIRACETAM 500 mg
DYNA LEVETIRACETAM 750 mg
DYNA LEVETIRACETAM 1000 mg

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:
DYNA LEVETIRACETAM 250 mg film coated tablets
DYNA LEVETIRACETAM 500 mg film coated tablets
DYNA LEVETIRACETAM 750 mg film coated tablets
DYNA LEVETIRACETAM 1000 mg film coated tablets

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.
Each **DYNA LEVETIRACETAM 1000 mg** tablet contains 1000 mg levetiracetam.

Inactive ingredients: Croscarmellose sodium, magnesium, stearate, maize starch, microcrystalline cellulose, povidone, purified talc, purified water, silica colloidal.

Additional inactive ingredients:
DYNA LEVETIRACETAM 250 mg – contains Opadry blue
DYNA LEVETIRACETAM 500 mg – contains Opadry yellow
DYNA LEVETIRACETAM 750 mg – contains Opadry pink
DYNA LEVETIRACETAM 1000 mg – contains Opadry white

PHARMACOLOGICAL CLASSIFICATION:
A.2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
Levetiracetam is an anti-epileptic medicine. It is a pyrrolidone 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 exert 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.

Pharmacokinetics:

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. Peak concentrations (C_{max}) are typically 31 and 43 µg/ml following a single 1000 mg dose and repeated 1000 mg dose respectively. The extent of absorption is dose-independent and is not altered by food.
Distribution:
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.
Elimination:
The plasma half-life in adults has been reported as 7 ± 1 hour. The total body clearance is a mean of 0,96 ml/min/kg. Approximately 95 % are excreted in the urine, 65 % of which is unchanged and 24 % is metabolised by hydrolysis of the acetamide group. Levetiracetam neither induces nor is a high-affinity substrate for cytochrome P450 isoforms of glucoronidation enzymes and thus is devoid of known interactions with other antiseizure medicines, oral contraceptives or anticoagulants.

INDICATIONS:
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.

CONTRA – INDICATIONS:
Hypersensitivity to levetiracetam or other pyrrolidone derivatives, or to any of the ingredients of **DYNA LEVETIRACETAM**.
Pregnancy and lactation. (see "**PREGANACY AND LACTATION**").

WARNINGS:
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), see "**Special Precautions**".

INTERACTIONS:
Potential interactions with existing anti-epileptic agents (such as phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) have not been demonstrated.

No interaction between probenecid and levetiracetam was observed, however probenecid decreased the renal clearance of the inactive metabolite of levetiracetam by 60 %.

Co-administration of levetiracetam with digoxin, oral contraceptives or warfarin had no influence on the pharmacokinetics of levetiracetam.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. It is not known if levetiracetam is distributed into breast milk.

DOSAGE AND DIRECTIONS FOR USE:

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.

Adults and children older than 16 years:

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 1500 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 3000 mg.

Elderly:

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

Children under the age of 16 years:

There are insufficient data available for the use of **DYNA LEVETIRACETAM** in children under the age of 16 years.

Patients with renal impairment:

The **DYNA LEVETIRACETAM** dose should be individualised according to renal function. Refer to the table below and adjust the dose as indicated. 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):

$$eCL_{cr}\ (ml/min) = \frac{[140 - age] \times Wt\ (kg) \times constant^*}{S_{cr}\ (\mu mol/l)}$$

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

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[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.

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 < 50ml/min.

SIDE–EFFECTS AND SPECIAL PRECAUTIONS:
Side-effects:
Infections and infestations:
Less frequent: Infection.
Blood and lymphatic system disorders:
The following has been reported but frequency is unknown: Leukopenia, neutropenia, pancytopenia, thrombocytopenia.
Endocrine disorders:
The following has been reported but frequency is unknown: Pancreatitis.
Metabolism and nutrition disorders:
Less frequent: Anorexia.
Psychiatric disorders:
Frequent: Mood or mental changes, agitation, amnesia, anxiety, apathy, depersonalisation, depression, emotional lability, hostility, convulsions.
Less frequent: Aggression, confusion, hallucinations, psychotic disorders.
Nervous system disorders:
Frequent: Dizziness, headache, somnolence.
Less frequent: Paraesthesia, nervousness, tremor.
Eye disorders:
Frequent: Diplopia.
Ear and labyrinth disorders:
Frequent: Vertigo.
Gastrointestinal disorders:
Frequent: Diarrhoea, dyspepsia, nausea.
Respiratory, thoracic and mediastinal disorders:
Frequent: Pharyngitis, rhinitis.
Less frequent: Sinusitis, coughing.
Skin and subcutaneous tissue disorders:
Frequent: Rash.
The following has been reported but frequency is unknown: Alopecia.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Ataxia.
General disorders and administrative site conditions:
Frequent: Asthenia, fatigue.
Injury and poisoning:
Frequent: Accidental injury.

Special precautions:
Withdrawal of DYNA LEVETIRACETAM therapy:
Withdrawal of **DYNA LEVETIRACETAM** or transition to or from another type of antiepileptic therapy should be made gradually (e.g. 500 mg twice daily decrements every two to four weeks). See "**WARNINGS**".
Patients with renal impairment:
Reduced doses of **DYNA LEVETIRACETAM** are recommended for patients with renal impairment (see "**DOSAGE AND DIRECTIONS FOR USE**"). Patients receiving dialysis may be given a loading dose of 750 mg when starting **DYNA LEVETIRACETAM** followed by doses of 500 to 1000 mg once daily, a supplemental dose of 250 to 500 mg is recommended after dialysis.
Patients with hepatic impairment:
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 "**DOSAGE AND DIRECTIONS FOR USE**"**).**
***Effects on the ability to drive vehicles or operate machinery*:**
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.

KNOWN SYPMTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Symptoms:
Experience with levetiracetam overdose is very limited. Symptoms that may occur with **DYNA LEVETIRACETAM** overdose include: drowsiness, aggression, agitation, coma, depressed level of consciousness, respiratory depression and somnolence.
Treatment:
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. Approximately 50 % is removed in 4 hours.

IDENTIFICATION:
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:

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.

DYNA LEVETIRACETAM 1000 mg:

White to off white, oblong-shaped, biconvex film coated tablets debossed with “1000” on one side and a score line on the other side.

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

Store at or below 30°C.

KEEP OUT OF REACH OF CHILDREN