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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TORLEVA

(Levetiracetam Tablets 250 mg / 500 mg / 750 mg & 1000 mg)

DESCRIPTION

Levetiracetam is a white to off-white powder with a faint odour and a bitter taste. It is very soluble in water (104g/100mL). It is freely soluble in chloroform (65.3mg/100mL) and in methanol (53.6g/100mL), soluble in ethanol (16.5g/100mL), sparingly soluble in acetonitrile (5.7g/100mL) and practically insoluble in n-hexane.

CLINICAL PHARMACOLOGY

Mechanism of action

The precise mechanism of action by which levetiracetam induces seizure protection is unknown, but appears unrelated to the mechanisms of current anti-epileptic drugs. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. No interaction with traditional drug targets involved in inhibitory and excitatory neurotransmission have been observed. 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.

Pharmacodynamics

In animals

Levetiracetam is not active in the classical screening models for anticonvulsants however induces potent protection in a broad range of animal models of partial and primary generalised seizures, with an unusually high safety margin between therapeutic doses and doses inducing adverse effects. Levetiracetam also displays potential antiepileptogenic properties by dose-dependently inhibiting the development of kindling, even after discontinuation of the active substance. Withdrawal from chronic treatment did not decrease the seizure threshold. Anxiolytic action and an absence of undesirable effects on cognitive function have also been observed. The major metabolite, ucb L057, is inactive in seizure models.

In man

Both partial and generalised epilepsy models (epileptiform discharge/photoparoxysmal response) confirmed the broad spectrum preclinical pharmacological profile.

Pharmacokinetics

The pharmacokinetic profile is 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 adult healthy volunteers and adult patients with epilepsy.

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%. Peak plasma concentrations (C_{max}) are achieved at 1.3 hours after dosing. Steady state is achieved after two days of a twice daily administration schedule. Peak concentrations (C_{max}) are typically 31 μg/mL and 43 μg/mL following a single 1,000mg dose and repeated 1,000mg b.i.d. 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 major metabolite (ucb L057) 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.

Metabolism

The major metabolic pathway (24% of the dose) is an enzymatic hydrolysis of the acetamide group. Production of this metabolite, ucb L057, is not supported by 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 for only 0.6% of the dose. No enantiomeric interconversion was evidenced in vivo for either levetiracetam or its major metabolite ucb L057.

Elimination

The plasma half-life in adults was 7.2 ± 1.1 hours and did not vary either with dose, route of administration or repeated administration. The total body clearance was a mean of 0.96 ± 0.14 mL/min/kg.

The major route of excretion was via urine, accounting for a mean 95% of the dose, with approximately 93% of the dose 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 (ucb L057) accounted for 66% and 24% of the dose respectively during the first 48 hours.

The renal clearance of levetiracetam is 0.6 mL/min/kg, indicating that it is excreted by glomerular filtration with subsequent tubular reabsorption. The renal clearance of the major metabolite, ucb L057, is 4.2 mL/min/kg indicating active tubular secretion in addition to glomerular filtration.

Elderly

In elderly patients, the half-life is increased by about 40% (10 to 11 hours) and is attributed to the decrease in renal function in this population (refer DOSAGE AND ADMINISTRATION).

Children (6 to 12 years)

Following single dose administration (20mg/kg) to epileptic children, the half-life of levetiracetam was 6.0 ± 1.1 hours. The apparent body clearance was approximately 30% higher than in epileptic adults.

Renal impairment

The apparent body clearance of both levetiracetam and its major metabolite (ucb L057) 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 (refer DOSAGE AND ADMINISTRATION).

In anuric end-stage renal disease subjects the half-life was approximately 25 and 3.1 hours during inter- and intra-dialytic 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 concomitant renal impairment (refer DOSAGE AND ADMINISTRATION).

INDICATIONS

TORLEVA is indicated in epileptic patients aged 16 years and older, as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation.

CONTRAINDICATIONS

Hypersensitivity to any component of this product (refer to PRESENTATION). Breast feeding. (refer to USE IN LACTATION).

PRECAUTIONS

In accordance with current clinical practice, if TORLEVA has to be discontinued it is recommended to withdraw it gradually.

The administration of TORLEVA to patients with renal impairment may require dose adaptation. Monitoring of renal function in severely hepatically impaired patients is recommended before dose selection (refer to DOSAGE AND ADMINISTRATION).

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

To date, there are no data to support the use of levetiracetam in patients less than 16 years of age. No data on the interaction of levetiracetam with alcohol are available.

Impaired renal function

The administration of TORLEVA to patients with renal impairment may require dose adaptation. Monitoring of renal function in severe hepatic impaired patients is recommended before dose selection (refer DOSAGE AND ADMINISTRATION).

Carcinogenicity/Mutagenicity

There was no evidence of carcinogenicity following dietary administration of levetiracetam to rats at doses up to 1800mg/kg/day for 104 weeks and to mice at doses up to 960mg/kg/day for 80 weeks. In rats, the highest dose achieved systemic exposure (plasma AUC) approximately 6 times that in humans at the maximal recommended clinical dose of 3000mg/day. In mice, the highest dose achieved systemic exposure (plasma AUC) approximately twice that in humans at the maximal recommended clinical dose. Because adequate doses have not been studied in mice, the carcinogenic potential in this species has not been fully evaluated

Assays for gene mutations (reverse mutation in bacteria, Chinese hamster ovary/HGPRT locus assay) and chromosomal damage (Chinese hamster ovary cells in vitro, mouse micronucleus test) did not provide evidence of genotoxic potential of levetiracetam. The hydrolysis product and major human metabolite (ucb L057) was not mutagenic in bacterial reverse mutation assays or the in vitro mouse lymphoma assay.

Impairment of Fertility

There are no human data on the effects of LEVETIRACETAM on male or female fertility. No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses of levetiracetam up to 1800mg/kg/day (corresponding to approximately 6 times the maximal recommended clinical dose on a mg/m^2 basis) administered for at least two weeks prior to, and throughout, mating.

Use in Pregnancy (Category B3)

In rats and rabbits, levetiracetam and/or its metabolites cross the placenta and the fetal levels approximate maternal plasma levels. In these species, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

Oral administration to female rats from two weeks prior to mating and throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses (350mg/kg/day (approximately equivalent to the maximal recommended clinical dose of 3000mg/day on a mg/m^2 basis) and with increased pup mortality and offspring behavioural alterations at a dose of 1800mg/kg/day (6 times the maximal human dose on a mg/m^2 basis). The developmental no-effect dose was 70mg/kg/day (equivalent to 0.2 times the maximal human dose on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Oral administration to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses (600mg/kg/day (about 3 times the maximal human dose on a mg/m^2 basis) and in decreased fetal weights and increased incidences of minor fetal skeletal anomalies at a dose of 1800kg/mg/day (10 times the maximal human dose on a mg/m^2 basis). The developmental no-effect dose was 200mg/kg/day (approximately the maximal human dose on a mg/m^2 basis). Maternal toxicity was also observed at 1800mg/kg/day.

Oral administration to pregnant rats during the period of organogenesis resulted in reduced fetal weight and increased incidence of embryofetal mortality and increased incidence of fetal skeletal variations at a dose of 3600mg/kg/day (11 times the maximal human dose on a mg/m^2 basis). The developmental no-effect dose was 1200mg/kg/day (4 times the maximal human dose on a mg/m^2 basis). There was no overt maternal toxicity.

Oral administration to pregnant mice during the period of organogenesis did not produce teratogenic or embryotoxic effects at doses up to 3000mg/kg/day. This dose corresponds to approximately 5 times the maximal human dose on a mg/m^2 basis.

Oral administration to rats during the late gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800mg/kg/day (6 times the maximal human dose on a mg/m^2 basis).

To date, no clinical data on exposed pregnancies are available. TORLEVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

Levetiracetam and/or its metabolites are excreted in milk in lactating rats; peak milk concentrations occurred 3 hours after oral administration (milk:plasma ratio 0.9). Levetiracetam is excreted in breast milk. Because of the potential for serious adverse reactions in breastfeeding infants from TORLEVA, a decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Interactions with other drugs

In vitro, levetiracetam and its major metabolite (ucb L057) have been shown not to inhibit the major human liver cytochrome P450 isoforms, glucuronyl transferase, (valproic acid) and epoxide hydroxylase activities. In human hepatocytes in culture, levetiracetam did not cause enzyme induction. The interaction of TORLEVA with other drugs, or vice versa, is considered unlikely.

Probenecid has been shown to inhibit the renal clearance of the major metabolite (ucb L057) but not levetiracetam. Nevertheless, the concentration of ucb L057 remains low. It is expected that other drugs excreted by active tubular secretion could also reduce the renal clearance of the metabolite.

With other antiepileptic drugs

The pharmacokinetics of levetiracetam was not modified when coadministered with other antiepileptic drugs, including carbamazepine, phenytoin, valproate, lamotrigine, phenobarbital, primidone and gabapentin.

Pharmacokinetic studies demonstrated a lack of interaction with digoxin, oral contraceptives (ethinyl-estradiol and levonorgestrel) and warfarin. Endocrine parameters (LH and progesterone) and prothrombin times were not modified. The extent of absorption of levetiracetam was not altered by food or reduced in subjects receiving antacids.

Effect on ability to drive or operate machinery

No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience, at the beginning of treatment 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.

ADVERSE REACTIONS

The following adverse events were reported in published clinical trails :

The very common (>10%) adverse events reported were mention in the table-1 and Common adverse events (> 1%, < 10%) were reported in table-2.

Table 1: Incidence (%) of very common treatment-emergent adverse events in placebo-controlled studies, by body system:

Body System / Adverse Event	Levetiracetam group (N = 672) %	Placebo group (N=351) %
Body as a Whole		
Accidental Injury	10.3	16.5
Asthenia	14.1	9.7
Headache	13.1	13.7
Infection	13.2	7.4
Nervous System		
Somnolence	14.9	9.7

The incidence and severity of the CNS related adverse events decrease over time and appear to be dose related. More than 93% of events categorised under the term "Infection" are symptoms of community acquired infections (common cold and upper respiratory tract infections). There was no increase in incidence of other infections (lower respiratory tract infections, urinary tract infections, etc.).

Common adverse events (> 1%, < 10%):

Table 2: Incidence (%) of common treatment-emergent adverse events in placebo-controlled studies, by body system:

Body System / Adverse Event	Levetiracetam group (N = 672) %	Placebo group (N=351) %
Body as a Whole		
Abdominal Pain	3.7	5.2
Back Pain	4.0	4.6
Chest Pain	1.3	1.1
Drug Level Increased	1.3	0.9
Fever	1.3	1.7
Flu Syndrome	4.2	6.0
Hostility	2.1	0.6
Pain	6.5	6.6
Digestive System		
Anorexia	2.4	2.0
Diarrhoea	4.2	5.1
Dyspepsia	2.8	3.4
Gastroenteritis	1.2	0.9
Gingivitis	1.2	0.6
Nausea	4.2	4.6
Tooth Disorder	1.5	0.6
Vomiting	2.2	2.0
Haemic and Lymph System		
Ecchymosis	1.5	1.1
Metabolic / Nutr Dis		
Weight gain	1.2	1.1
Nervous system		
Amnesia	1.6	0.3
Anxiety	1.6	1.1
Ataxia	2.5	1.4
Convulsion	6.0	6.8
Depression	4.0	2.3
Dizziness	9.2	4.3
Emotional Lability	1.6	0.3
Insomnia	3.0	2.8
Nervousness	3.9	1.7
Paraesthesia	1.9	1.7
Thinking abnormal	1.5	1.4
Tremor	1.5	1.7
Vertigo	2.5	1.4
Respiratory System		
Bronchitis	1.3	1.4
Cough Increased	2.1	1.7
Pharyngitis	5.7	3.7
Rhinitis	4.3	2.6
Sinusitis	2.1	0.9
Skin and Appendages		
Rash	2.8	4.0
Special Senses		
Amblyopia	1.2	1.4
Diplopia	2.4	1.7
Otitis media	1.2	0.9
Urogenital System		
Urinary Tract Infection	1.9	3.4

DOSAGE AND ADMINISTRATION

The film-coated tablets 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.

Adults and adolescents older than 16 years

As adjunctive therapy, the therapeutic dose is 500mg twice daily. This 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 1500mg twice daily. Dose changes can be made in 500mg twice daily increments or decrements. The maximum recommended daily dose is 3000mg.

Elderly

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

Children (under 16 years of age) To date, there are no data to support the use of levetiracetam in patients less than 16 years of age.

Patients with renal impairment The TORLEVA daily dose must be individualised according to renal function. Refer to the following table and adjust the dose as indicated.

Table 3:Dosage schedule based on renal function.

Group	Creatinine clearance (mL/min)	Dosage (mg)	Frequency (daily)
Normal	> 80	500 to 1,500	Twice
Mild	50-79	500 to 1,500	Twice
Moderate	30-49	250 to 750	Twice
Severe	< 30	250 to 500	Twice
End-stage renal disease patients undergoing dialysis (1)	-	500 to 1,000	Once (2)

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

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

Patients with hepatic impairment No dose adjustment is needed in patients with mild and 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.

OVERDOSAGE

Cases of somnolence, agitation and aggression were observed with TORLEVA overdoses. There is no specific antidote for levetiracetam. Treatment for an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the major metabolite (ucb L057).

STORAGE

STORE BELOW 30^{o}C

PRESENTATION

TORLEVA film-coated tablets are blister packed and available in strengths of 250mg, 500mg, 750mg and 1000mg levetiracetam.

250 mg Blue colored, oval shaped, film coated tablets debossed with breakline separating '250'and 'MG' on one side and '1014' on other side. Available in a blister pack containing 60 tablets.

500 mg Yellow colored, oval shaped, film coated tablets debossed with breakline separating '500' and 'MG' on one side and '1015' on other side. Available in a blister packs containing 10, 60 and 100 tablets.

750 mg Orange colored, oval shaped, tablets debossed with breakline separating '750' and 'MG' on one side and '1016' on other side. Available in a blister pack containing 60 tablets.

1000 mg White to off white, oval shaped, film coated tablets debossed with breakline separating '1000' and 'MG' on one side and '1017' on other side. Available in a blister packs containing 10, 60 and 100 tablets.

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