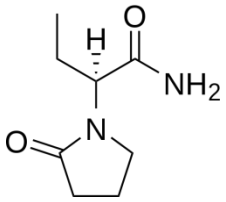
Levetiracetam-AFT

Oral Solution
Concentrate Solution for Infusion

NAME OF THE MEDICINE

Non-proprietary name: levetiracetam
Chemical name: (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide
Chemical structure:



Molecular formula: C8H14N2O2
CAS number: 102767-28-2

DESCRIPTION

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

PHARMACOLOGY

Mechanism of action

The precise mechanism of action by which levetiracetam induces seizure protection still remains to be fully elucidated, but appears to be 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.

In vitro studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in in vitro studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. levetiracetam and related analogues show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that

the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the drug.

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

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear and time-independent 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).

A single dose of 1500 mg levetiracetam diluted in 100 mL of a compatible diluent and infused intravenously over 15 minutes is bioequivalent to 1500 mg levetiracetam oral intake, given as three 500 mg tablets.

The intravenous administration of doses up to 4000 mg diluted in 100 mL of 0.9 % sodium chloride infused over 15 minutes and doses up to 2500 mg diluted in 100 mL of 0.9 % sodium chloride infused over 5 minutes was evaluated. The pharmacokinetic and safety profiles did not identify any safety concerns.

Adults and Adolescents

Absorption

Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100 %. Peak plasma concentrations (Cmax) are achieved at 1.3 hours after dosing. Steady state is achieved after two days of a twice daily administration schedule. Peak concentrations (Cmax) are typically 31 µg/mL and 43 µg/mL following a single 1000 mg dose and repeated 1000 mg b.i.d. dose respectively. The extent of absorption is dose-independent and is not altered by food, but the rate of absorption is slightly reduced.

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. 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 for only 0.6 % of the dose.

No enantiomeric interconversion was evidenced in vivo for either levetiracetam or its major metabolite ucb L057.

In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 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 vitro, levetiracetam had no effect on CYP1A1/2 or UGT isoform activities (including ethinylestradiol conjugation). Levetiracetam caused mild induction of CYP2B6 and CYP3A4, but only at high concentrations not considered to be clinically relevant. Therefore the interaction of levetiracetam with other substances, or vice versa, is unlikely.

Excretion

The plasma half-life in adults was 7 ± 1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 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 (4 to 12 years of age)

Following single dose administration (20 mg/kg) to epileptic children (6 to 12 years of age), the halflife of levetiracetam was 6.0 ± 1.1 hours. The apparent body clearance was approximately 30 % higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years of age), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 mL/min/kg.

Infants and children (1 month to 4 years of age)

Following single dose administration (20 mg/kg) of a 10 % oral solution to epileptic children (1 month to 4 years of age), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that halflife was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 mL/min/kg) than for adults (0.96 mL/min/kg).

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-AFT, based on creatinine clearance in patients with moderate and severe renal impairment (refer DOSAGE AND ADMINISTRATION).

In anuric end-stage renal disease adult 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

Levetiracetam-AFT is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam-AFT is indicated as adjunctive therapy in the treatment of:

- partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.
- myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

Levetiracetam-AFT concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

CONTRAINDICATIONS

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients (refer to DESCRIPTION).

WARNINGS AND PRECAUTIONS

Discontinuation

If Levetiracetam-AFT has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing 50 kg or more: reduce dose by 500 mg twice daily every two to four weeks; children and adolescents weighing less than 50 kg: dose reductions should not exceed 10 mg/kg twice daily every two weeks).

An increase in seizure frequency of more than 25% has been reported in 14% of levetiracetam treated adult and paediatric patients with partial onset seizures, whereas it was reported in 26% and 21% of placebo treated adult and paediatric patients, respectively.

When levetiracetam was used to treat primary tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences.

Renal or hepatic impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see section Dosage and Administration).

Acute Kidney Injury

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

Blood cell counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with 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 Adverse Reactions).

Psychiatric Reactions

Behavioural abnormalities including psychotic symptoms, suicidal ideation, irritability and aggressive behaviour have been observed. Monitor patients for psychiatric signs and symptoms. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered.

A total of 13.3% of adult levetiracetam -treated patients and 37.6% of paediatric levetiracetam -treated patients (4 to 16 years of age) compared to 6.2% and 18.6% of adult and paediatric placebo patients respectively, experienced non-psychotic behavioural symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder).

A total of 1.7% of adult levetiracetam -treated patients discontinued treatment due to behavioural adverse events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of adult levetiracetam -treated patients and in 0.5% of placebo patients. Overall, 10.9% of levetiracetam -treated pediatric patients experiences behavioural symptoms associated with discontinuation or dose reduction, compared to 6.2% of placebo patients.

One percent of adult levetiracetam -treated patients experienced psychotic symptoms compared to 0.2% in the placebo patients.

Two (0.3%) adult levetiracetam -treated patients were hospitalized and their treatment was discontinued due to psychosis. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. There was no difference between drug and placebo-treated patients in the incidence of the paediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

Depression and/or suicidal ideation

Suicide, suicide attempt and suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known. 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.

Paediatric population

The tablet formulation is not adapted for use in children under the age of 6 years.
Available data in children did not suggest impact on growth and puberty. However, long-term effects on learning, intelligence, growth, endocrine function, puberty and child bearing potential in children remain unknown.

Excipients

Oral Solution

Levetiracetam-AFT Oral Solution 100 mg/ml includes sodium citrate, citric acid monohydrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), ammonium glycyrrhizate, glycerine (E422), maltitol liquid (E965), acesulfame potassium (E950), grape flavour and purified water.

Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) may cause allergic reactions (possibly delayed). It also contains maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product. It contains glycerol which may cause headache, stomach upset and diarrhoea.

Solution for Infusion
This medicinal product contains sodium chloride, glacial acetic acid, sodium acetate trihydate and water for injection.

PREGNANCY AND LACTATION

Fertility
No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

Pregnancy
Levetiracetam-AFT is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity.

Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with Levetiracetam-AFT should be ensured. Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Lactation
Levetiracetam-AFT is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if Levetiracetam-AFT treatment is needed during breast-feeding, the benefit/risk of the treatment should be weighed considering the importance of breast-feeding.

ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS

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, 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.

INTERACTION WITH OTHER MEDICINES

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.

Probenecid (500 mg four times daily) 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.

Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of LEVETIRACETAM-AFT.

Consistent with formal pharmacokinetic studies in adults, there has been no clear evidence of clinically significant drug interactions in paediatric patients receiving up to 60 mg/kg/day.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine, valproate, topiramate and lamotrigine. However, data suggested that enzyme-inducing antiepileptic medicinal products increase levetiracetam clearance by 22 %. Dosage adjustment is not required.

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.

No data on the influence of antacids on the absorption of levetiracetam are available.

Laxatives

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.

Food and alcohol

The extent of absorption of Levetiracetam-AFT was not altered by food, but the rate of absorption was slightly reduced.

No data on the interaction of Levetiracetam-AFT with alcohol are available.

Methotrexate

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 drugs.

ADVERSE REACTIONS

Clinical Trial Data and Post-Marketing Data

Summary of the safety profile
The adverse event profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3,416 patients treated with levetiracetam. These data are supplemented with the use of levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. 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.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data)

Infections and infestations
Very Common: nasopharyngitis
Rare: infection

Blood and lymphatic system disorders
Uncommon: thrombocytopenia, leukopenia
Rare: pancytopenia, neutropenia, agranulocytosis

Immune system disorders
Rare: drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis)

Metabolism and nutrition disorders
Common: anorexia
Uncommon: weight decreased, weight increase
Rare: hyponatraemia

Psychiatric disorders
Common: depression, hostility/aggression, anxiety, insomnia, nervousness/irritability
Uncommon: suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation
Rare: completed suicide, personality disorder, thinking abnormal, delirium

Nervous system disorders
Very common: somnolence, headache
Common: convulsion, balance disorder, dizziness, lethargy, tremor
Uncommon: amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention
Rare: choreoathetosis, dyskinesia, hyperkinesia

Eye disorders
Uncommon: diplopia, vision blurred

Ear and labyrinth disorders
Common: vertigo

Respiratory, thoracic and mediastinal disorders
Common: cough

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, dyspepsia, vomiting, nausea
Rare: pancreatitis

Hepatobiliary disorders
Uncommon: liver function test abnormal
Rare: hepatic failure, hepatitis

Renal and urinary disorders
Rare: acute kidney injury

Skin and subcutaneous tissue disorders
Common: rash
Uncommon: alopecia, eczema, pruritus
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders
Uncommon: muscular weakness, myalgia
Rare: rhabdomyolysis and blood creatine phosphokinase increased*

General disorders and administration site conditions
Common: asthenia/fatigue

Injury, poisoning and procedural complications
Uncommon: injury

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

Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

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.

Paediatric population

In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In this paediatric age range, the data are supplemented with post-marketing experience of the use of levetiracetam.
The adverse event 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. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile.
A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that levetiracetam was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioural and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behaviour as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

DOSAGE AND ADMINISTRATION

Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

Oral solution
The oral solution may be diluted in a glass of water and may be taken with or without food. The daily dose is administered in two equally divided doses.

Concentrate for solution for infusion
Levetiracetam-AFT concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as 15-minute intravenous infusion (*see Section Incompatibilities and Use and Handling*). There is no experience with administration of intravenous Levetiracetam-AFT for longer period than 4 days.

Levetiracetam-AFT concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

For patients requiring the tablet formulation, there are other brands available.

Route of Administration

For oral use:
Levetiracetam-AFT Oral Solution 100 mg/ml

For intravenous use:

Levetiracetam-AFT Concentrate for Solution for Infusion 100 mg/ml
Please refer to Section **INCOMPATIBILITIES AND USE AND HANDLING** for recommendation on the preparation and administration of *Levetiracetam-AFT Concentrate for Solution for Infusion 100 mg/ml*.

Adults

• 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 dose is 1500 mg twice daily.

• Add-on therapy

Adults (≥18 years) and adolescents (12 to 17 years) of 50 kg or more
The initial therapeutic dose is 500 mg 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 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Children
The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose.

The tablet formulation is not adapted for use in children under the age of 6 years. Levetiracetam-AFT oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Levetiracetam-AFT oral solution should be used.

The safety and efficacy of Levetiracetam-AFT concentrate for solution for infusion in children less than 4 years have not been established.

Monotherapy

The safety and efficacy of levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.

There are no data available.

Add-on Therapy for Children (4 to 11 years) and Adolescents (12 to 17 years) weighing less than 50 kg

Levetiracetam-AFT Oral Solution is the preferred formulation for use in children under the age of 6 years.

For children 6 years and above, Levetiracetam-AFT oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

The initial therapeutic dose is 10 mg/kg twice daily.

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.

Dose in children 50 kg or greater is the same as in adults.

Dose recommendations for children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg(1)	150 mg (1.5 ml) twice daily	450 mg (4.5 ml) twice daily
20 kg(1)	200 mg (2 ml) twice daily	600 mg (6 ml) twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg(2)	500 mg twice daily	1500 mg twice daily

(1) Children 25 kg or less should preferably start the treatment with Levetiracetam-AFT 100 mg/ml Oral Solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults.

Infants and children less than 4 years
There are insufficient data to recommend the use of Levetiracetam-AFT in children under 4 years of age.

Elderly
Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal impairment

The daily dose must be individualised according to renal function *(see section Warnings and Precautions)*. 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} in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighing 50 kg or more, using the following formula:

$$CL_{cr} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for women})$$

Then CL_{cr} is adjusted for body surface area (BSA) as follows:

$$CL_{cr}\ (\text{ml/min/1.73m2}) = \frac{CL_{cr}\ (\text{ml/min})}{\text{BSA subject } (m^2)} \times 1.73$$

Dosing adjustment for adult and adolescent patients weighing more than 50 kg with impaired renal function

Group	Creatinine clearance (ml/min/1.73m^2)	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 Levetiracetam.
(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, Levetiracetam dose needs to be adjusted based on the renal function as Levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

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 <60 ml/min/1.73m^2 *(see section Warnings and Precautions)*.

OVERDOSAGE

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.

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).

PRESENTATION AND STORAGE CONDITIONS

Not all dosage forms may be available locally

LEVETIRACETAM-AFT Oral Solution

LEVETIRACETAM-AFT oral solution is packed in 300 mL type III amber glass bottles with a child resistant closure and is available as 100 mg/mL strength. The pack also contains a 10 mL graduated oral dosing syringe and an adaptor for the syringe.

LEVETIRACETAM-AFT oral solution is stable for 2 years from date of manufacture when stored at or below 30°C in the unopened container. Once opened, store at or below 25°C, discard after 7 months.

Wash and dry the syringe after each use.

LEVETIRACETAM-AFT Concentrate Solution for Infusion

Concentrate Solution for Infusion Incompatibilities

The formation of precipitate has been observed when mixing LEVETIRACETAM-AFT Concentrate Solution for Infusion and phenytoin sodium in a polyvinyl chloride (PVC) bag.

This medicinal product must not be mixed with other medicinal products except those mentioned below.

Instructions for use and handling of the Concentrate Solution for Infusion

Table 13 provides a summary for the recommended preparation and administration of LEVETIRACETAM-AFT Concentrate Solution for Infusion to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg or 3000 mg in two divided doses:

Table 13 Preparation and administration of LEVETIRACETAM-AFT Concentrate Solution for Infusion.

Dose	Withdrawal Volume	Volume of Diluent	Infusion Time	Frequency of Administration	Total Daily Dose
250 mg	2.5 mL (half 5 mL vial)	100 mL	15 minutes	Twice daily	500 mg/day
500 mg	5 mL (5 mL vial)	100 mL	15 minutes	Twice daily	1000 mg/day
1000 mg	10 mL (two 5 mL vials)	100 mL	15 minutes	Twice daily	2000 mg/day
1500 mg	15 mL (three 5 mL vials)	100 mL	15 minutes	Twice daily	3000 mg/day

LEVETIRACETAM-AFT Concentrate Solution for Infusion is for single use in one patient only.

LEVETIRACETAM-AFT Concentrate Solution for Infusion was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15-30°C. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2 – 8 °C for not more than 24 hours OR not more than 6 hours below 25 °C.

Diluents:

- Sodium chloride (0.9 %) injection
- Lactated Ringer's injection
- Dextrose 5 % injection

Product is for single use in one patient only. Discard any residue.

One vial of LEVETIRACETAM-AFT Concentrate Solution for Infusion contains 500 mg of levetiracetam (500 mg/5 mL). The primary container is made of Type I glass closed with rubber stopper and aluminium flip cap. It is packaged in a carton containing 10 vials.

LEVETIRACETAM-AFT Concentrate Solution for Infusion is stable for 18 months from date of manufacture when stored below 30°C.

NAME AND ADDRESS OF THE PRODUCT OWNER

AFT Pharmaceuticals Ltd.
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Levetiracetam-AFT Concentrate Solution for Infusion:
SIN15436P

Levetiracetam-AFT Oral Solution:
SIN15575P

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