Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levetiracetam Clonmel 750 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 750 mg levetiracetam.

Excipient with known effect:

Each film-coated tablet contains 0.228 mg sunset yellow FCF Aluminium salt (E110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Salmon, oblong, biconvex, film-coated tablets with a breaking notch on one side with a length of approximately 18.6 mm. The breaking notch is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levetiracetam Clonmel 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.

Levetiracetam Clonmel is indicated as adjunctive therapy

- in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month 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 adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

4.2 Posology and method of administration

Posology

Monotherapy for 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 for adults (≥18 years) and adolescents (12 to 17 years) weighing 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 tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Special populations

Elderly (65 years and older)

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

Renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighing 50 kg or more, the following formula:

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

Then CLcr is adjusted for body surface area (BSA) as follows:

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

Dosing adjustment for adult and adolescents 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 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 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.

The CLcr in ml/min/1.73 m^2 may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

$$\text{CLcr (ml/min/ 1.73 m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks = 0.45 in Term infants to 1 year old; ks = 0.55 in Children to less than 13 years and in adolescent female; ks = 0.7 in

adolescent male

Dosing adjustmentfor infants, children and adolescents patients weighing less than 50 kg with impaired renal function

Group	Creatinine clearance (ml/min/1.73m^2)	Dosage and frequency (1)	
		Infants 1 to less than 6 months	Infants 6 to 23 months, children and adolescents weighing less than 50 kg
Normal	> 80	7 to 21 mg/kg twice daily	10 to 30 mg/kg twice daily
Mild	50-79	7 to 14 mg/kg twice daily	10 to 20 mg/kg twice daily
Moderate	30-49	3.5 to 10.5 mg/kg twice daily	5 to 15 mg/kg twice daily
Severe	< 30	3.5 to 7 mg/kg twice daily	5 to 10 mg/kg twice daily
End-stage renal disease patients undergoing dialysis	--	7 to 14 mg/kg once daily (2) (4)	10 to 20 mg/kg once daily (3) (5)

(1) An oral solution should be used for doses under 125 mg and for patients unable to swallow tablets.
(2) A 10.5 mg/kg loading dose is recommended on the first day of treatment with levetiracetam.
(3) A 15 mg/kg loading dose is recommended on the first day of treatment with levetiracetam.
(4) Following dialysis, a 3.5 to 7 mg/kg supplemental dose is recommended.
(5) Following dialysis, a 5 to 10 mg/kg supplemental dose is recommended.

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/1.73 m^2.

Paediatric population

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

The tablet formulation is not adapted for use in infants and children under the age of 6 years. An 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 125 mg (half a 250 mg tablet). In all of the above cases an oral solution should be used.

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 infants aged from 6 to 23 months, Children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg

An oral solution is the preferred formulation for use in infants and children under the age of 6 years.

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 infants from 6 months of age, children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
6 kg(1)	60 mg twice daily	180 mg twice daily
10 kg(1)	100 mg twice daily	300 mg twice daily
15 kg(1)	150 mg twice daily	450 mg twice daily
20 kg(1)	200 mg twice daily	600 mg 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 oral solution.

(2) Dose in children and adolescents 50 kg or more is the same as in adults.

Add-on therapy for infants from 1 month to less than 6 months
The tablet formulation is not adapted for use in infants under the age of 6. An oral solution is the formulation to use in infants.

Method of administration

The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

4.3 Contraindications

Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Discontinuation
In accordance with current clinical practice, if Levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in infants older than 6 months, children and adolescents weighing less than 50 kg: dose decrease should not exceed 10 mg/kg twice daily every two weeks); in infants (less than 6 months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

Renal insufficiency
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 4.2).

Suicide
Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomized 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 infants and 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 childbearing potential in children remain unknown.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset seizures have been exposed in clinical studies of which only 13 were aged < 6 months.
Contains sunset yellow FCF (E110). May cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Antiepileptic medicinal products
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.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam.
A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20% higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

Probenecid
Probenecid (500 mg four times 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 medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown.

Oral contraceptives and other pharmacokinetics interactions
Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. 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 and warfarin did not influence the pharmacokinetics of levetiracetam.

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

Food and alcohol
The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.
No data on the interaction of levetiracetam with alcohol are available.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data available from the use of Levetiracetam in pregnant women. Studies in animals have shown

reproductive toxicity (see section 5.3). The potential risk for human is unknown.
Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.
As with other antiepileptic medicinal products, 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 should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

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

Fertility
No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

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 somnolence or other central nervous system related symptoms, especially 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.

4.8 Undesirable effects

Summary of the safety profile

Pooled safety data from clinical studies conducted with Levetiracetam oral formulations in adult patients with partial onset seizures showed that 46.4 % of the patients in the Levetiracetam group and 42.2 % of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 2.4% of the patients in the Levetiracetam and 2.0% of the patients in the placebo groups. The most commonly reported adverse reactions were somnolence, asthenia and dizziness. In the pooled safety analysis, there was no clear dose-response relationship but incidence and severity of the central nervous system related adverse reactions decreased over time.

In monotherapy 49.8 % of the subjects experienced at least one drug related adverse reaction. The most frequently reported adverse reactions were fatigue and somnolence.

A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Levetiracetam group and 30.0% of the patients in the placebo group experienced adverse reactions that were judged to be related to treatment. The most commonly reported adverse reactions were headache and somnolence. The incidence of adverse reactions in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%).

A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2 % of the patients in the Levetiracetam group and 29.8 % of the patients in the placebo group experienced adverse reactions that were judged to be related to treatment. The most commonly reported adverse reaction was fatigue.

An increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) 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 generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of

absences.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants> 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥1/100,<1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.

- Infections and infestations

Common: infection, nasopharyngitis

- Blood and lymphatic system disorders

Common: thrombocytopenia

Not known: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases)

- Metabolism and nutrition disorders

Common: anorexia, weight increase.

Not known: weight loss

- Psychiatric disorders

Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal

Not known: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

- Nervous system disorders

Very common: somnolence

Common: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment.

Not known: paraesthesia, choreoathetosis, dyskinesia

- Eye disorders

Common: diplopia, vision blurred

- Ear and labyrinth disorders

Common: vertigo

- Respiratory, thoracic and mediastinal disorders

Common: cough increased

- Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting

Not known: pancreatitis

- Hepatobiliary disorders:

Not known: hepatic failure, hepatitis, liver function test abnormal

- Skin and subcutaneous tissue disorders

Common: rash, eczema, pruritus

Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and alopecia

- Musculoskeletal and connective tissue disorders

Common: myalgia

- General disorders and administration site conditions

Very common: asthenia/fatigue

- Injury, poisoning and procedural complications

Common: accidental injury

Description of selected adverse reactions

The risk of anorexia is higher when topiramate is coadministered with levetiracetam.

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

Paediatric population

A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4 % of the patients in the Levetiracetam group and 40.2 % of the patients in the placebo group experienced adverse reactions. Serious adverse reactions were experienced in 0.0 % of the patients in the Levetiracetam group and 1.0 % of the patients in the placebo group. The most commonly reported adverse reactions were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults.

A study conducted in paediatric patients (1 month to less than 4 years) with partial onset seizures showed that 21.7 % of the patients in the Levetiracetam group and 7.1 % of the patients in the placebo group experienced adverse reactions. No Serious adverse reactions were experienced in patients in the Levetiracetam or Placebo group. During the long-term follow-up study N01148, the most frequent drug-related treatment-emergent adverse events in the 1m – <4y group were irritability (7.9%), convulsion (7.2%), somnolence (6.6%), psychomotor hyperactivity (3.3%), sleep disorder (3.3%), and aggression (3.3%). Safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years.

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 behavioral and emotional functioning indicated a worsening in Levetiracetam treated patients on aggressive behavior as measured in a standardized 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 behavior were not worse than baseline.

4.9 Overdose

Symptoms

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses.

Management of overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. 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.
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of a-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

Mechanism of action

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *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 Ca2+ levels by partial inhibition of N- type Ca2+ currents and by reducing the release of Ca2+ from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and b-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 analogs 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 medicinal product.

Pharmacodynamic effects

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive.

In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

Clinical efficacy and safety

Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy:

In adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50% or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7%, 31.6% and 41.3% for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6% for patients on placebo.

Paediatric population

In paediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing).
44.6% of the levetiracetam treated patients and 19.6% of the patients on placebo had a 50% or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4% of the patients were seizure-free for at least 6 months and 7.2% were seizure-free for at least 1 year.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six month and a dose of

25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 month to less than 4 years old, was use in this study. The total daily dose was administered b.i.d.

The primary measure of effectiveness was the responder rate (percent of patients with ≥ 50% reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6% of the levetiracetam treated patients and 19.6% of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6% of the patients were seizure-free for at least 6 months and 7.8% were seizure-free for at least 1 year.

Monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, non- inferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 - 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response.

Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 adult patients out of 69).

Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. 72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

5.2 Pharmacokinetic properties

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is 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).

Adults and adolescents

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 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 total body water volume.

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 P450 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 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 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 Levetiracetam with other substances, or *vice versa*, is unlikely.

Elimination

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 (approximately 93 % of the dose was excreted within 48 hours). Excretion *via* faeces accounted for only 0.3 % of the dose.

The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours.
The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration.
Levetiracetam elimination is correlated to creatinine clearance.

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 to adjust the maintenance daily dose of Levetiracetam, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

In anuric end-stage renal disease adult 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).

Paediatric population

Children (4 to 12 years)

Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of levetiracetam was 6.0 hours. The apparent body weight adjusted 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), 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)

Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life 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).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20% increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED.

5.3 Preclinical safety data

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

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 effects 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/m^2 or exposure basis) in parents and F1 generation.

Two embryo-fetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in fetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m^2 basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in fetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m^2 basis).
A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m^2 basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6 – 17 the MRHD on a mg/m^2 basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose,
Copovidone,
Colloidal anhydrous silica,
Magnesium stearate

Film-coating:
polyvinyl alcohol
titanium dioxide (E171)
macrogol 3350
talc
sunset yellow FCF Aluminium salt (E110)
iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs (PVC/Aluminum)

Pack sizes:
20, 30, 50, 60, 100, 150, 180 or 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd.
Waterford Road,
Clonmel,
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA126/218/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 18th November 2011

10 DATE OF REVISION OF THE TEXT