SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Keppra. This scientific discussion has been updated until 1 December 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Levetiracetam is a new chemical entity, chemically related to piracetam, a nootropic drug. Initial research was directed primarily towards indications where piracetam and piracetam-like compounds had proved to be of benefit (cognition, anxiety disorders). When the particular antiepileptic profile of the drug was recognised, its development was oriented towards epilepsy as a new indication in 1991. The precise mechanism of action by which levetiracetam induces seizure protection is unknown, but it appears to be unrelated to the mechanisms identified for current drugs.

Levetiracetam, also known as ucb L059, is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. The daily dose is to be administered in two equally divided doses. As adjunctive therapy, the initial therapeutic recommended dose is 500 mg twice daily. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1500 mg twice daily.

Epilepsy is a chronic disease with a prevalence of approximately 0.35 to 1.02 % and an annual incidence of 20-80 / 100 000. It is more common in children, elderly, and black people. Epilepsy is defined as repeated seizures. Approximately 30-40% of patients (adults and children) with partial onset seizures, are refractory to treatment with a single antiepileptic drug and cannot be adequately controlled with existing antiepileptic drugs, either because of lack of efficacy or toxicity.

Most of the antiepileptic drugs currently used reduce neurone membrane excitability. The most recent drugs increase GABAergic inhibition by either decreasing the effects of excitatory amino acids or modulating the ionic channels involved in epileptogenesis. Currently, the first line anti-epileptic drugs are carbamazepine and valproate. Second line drugs include phenytoin, barbiturates and ethosuximide. New antiepileptic drugs have been approved recently (e.g., gabapentin, tiagabin, vigabatrin, lamotrigine, felbamate, topiramate). Most of them are used as adjunct therapy when first line drugs have failed.

The goal of antiepileptic drug treatment is to free the patient from seizures. However, it should be mentioned that the main endpoint used in clinical trials is usually a 50% or greater reduction in the frequency of seizures, or the absolute decrease in seizure rate. There is controversy as to the criteria, which should be used to define treatment failure. Nevertheless, from a practical standpoint, treatment failure could be defined as inadequate efficacy at the highest tolerated dose. The ideal treatment should be with a single substance devoid of adverse effects. Due to monotherapy failure, anti-epileptic drug treatment is often used in combination. Drug-drug interactions are known to occur and therefore, the drug potential for interaction is of major importance.

2. Quality

Composition

The first pharmaceutical form of Keppra to be authorised was film-coated tablets. Subsequently, an oral solution has been authorised. (See: Steps taken after authorisation). Both pharmaceutical forms contain the same active substance: levetiracetam.

- Keppra film-coated tablets contain 250, 500, 750 or 1000 mg of levetiracetam and are presented in PVC/Aluminium blisters. Excipients and pack sizes are defined in the SPC, sections 6.1 and 6.5, respectively.

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- Keppra oral solution contains 100 mg/ml of levetiracetam and is presented in amber glass bottles of 300 ml with a polypropylene white child-resistant closure. The product is delivered with a graduated syringe. Excipients and pack sizes are defined in the SPC, sections 6.1 and 6.5, respectively.

Active substance

Levetiracetam is a white to off-white crystalline powder. It has one chiral center and is the *S*-enantiomer of the pair of stereoisomers. Levetiracetam is synthesised by a route in seven stages. The synthesis and the in-process controls are satisfactorily described. The solubility, at room temperature, in several solvents, has been determined according to the criterion of the European Pharmacopoeia. Levetiracetam is very soluble in water and freely soluble in chloroform, methanol and ethanol; polymorphism has not been observed in induction studies.

Spectroscopic and other investigations confirm that levetiracetam as routinely produced by the defined method of synthesis is indeed the *S*-isomer Potential impurities are the *R*-isomer of levetiracetam and the deaminated product formed by hydrolysis of the amide group of levetiracetam. Qualification of the latter is supported by a kinetic study demonstrating that it is the major metabolite of levetiracetam. Other potential impurities evaluated during development are a residual reagent, impurityA, intermediate of step 3, impurity B, intermediate of step 4 and impurity C. The levels of impurity B and Care below 0.2 % and the level of impurity A is below 0.05 % detected by TLC. When using the HPLC method the results are below the limit of detection, 200 ppm. Therefore, in the absence of specific toxicity concerns, these impurities are considered to be not significant in the amounts found, and are not controlled in the active substance specification. Also potentially present as impurities are the residual solvents used in the last 2 steps of the synthesis.

Information on the manufacturing process has been updated according to the experience gained since the authorisation of the film-coated tablets, including an alternative route of synthesis with a chiral Multicolumn Continuous Chromatography (MCC) separation step. The capacity of this alternative route has been increased by a change in the manufacturing process. All of these updates have been evaluated and approved as variation procedures.
Batch analysis results of the active substance confirm the proposed specifications. In the long-term, accelerated and heat-stress studies there were no significant changes in any of the evaluated parameters. Therefore, the stability data support the retest period proposed by the manufacturer.

Other ingredients

The excipients for each pharmaceutical form are listed in the relevant SPC sections 6.1. Each one has been justified with reference to its established use and special function, and is of PhEur quality where applicable. Other in-house specifications where no PhEur monographs exist have been justified.

There is no significant risk of transmission of TSE arising from the use of these excipients

Film coated tablets Product development and Finished product

Keppra film-coated tablets are immediate release tablets intended for a twice-daily oral administration. The tablets are oblong and embossed with a strength-specific identification code on one side. The different strengths are identified also by their respective colour. The formulation of the cores is dose-proportional, that is to say the ratio of the ingredients is the same regardless of strength. Due to the bitter taste and the high solubility of the active substance it was decided to coat the tablets. During development a number of different finished product formulations have been used for oral administration of levetiracetam; these include tablets, capsules and an oral solution. In addition, several strengths of a parenteral formulation (in an ampoule) were also developed for use in early studies to evaluate the absolute bioavailability of levetiracetam. Oral bioavailability of capsules and oral solution relative to intravenous dose is assessed to be close to 100 %. The tablets are described as bioequivalent to capsules comparing extent and rate of absorption, so it is unlikely that small changes in the pharmaceutical variables (formulation and processing) of these tablets will significantly affect clinical performance, due to the high solubility and very high bioavailability of the active substance.

The manufacturing process and the validation of the process are satisfactorily described. The dossier includes a GMP certificate for the manufacturer of the finished product.

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Relevant control tests are applied at batch release, including assay of active substance (nonchiral,), non-chiral and chiral related substances, average mass and uniformity of mass, dissolution (PhEur paddle method), microbial contamination, etc. Dissolution comparison tests have been performed on tablets of development batches. The conclusion is that the *in-vitro* dissolution profiles are similar for the different tablet strengths and the different coating colours and are not influenced by the nature of the dissolution media used. Batch analysis results according to the specifications are presented on three industrial-scale batches for each strength and on pilot scale batches. The results are consistent between the batches and satisfy the specifications.

Stability of the product

Several large pilot-scale batches representing a selection of strengths and colours have been studied under the recommended ICH conditions for 24 months at 25ºC/60%RH and for 6 months at 40ºC/75%RH. Additionally, 12 months results at 25ºC/60%RH and 6 months results for industrial batches of the 250-mg, 500-mg and 750-mg strengths are available. Under these conditions the product appears to be stable with no significant physical changes or chemical degradation observed.

Impurity analysis revealed no new impurities, and known impurities are all below the batch release limit imposed at the time of manufacture. In general the results endorse the shelf life as proposed in the SPC. Additional stability data submitted post authorisation endorsed the storage condition: "Do not store above 25 ºC".

Oral Solution

Product development and Finished productKeppra Oral Solution was developed to provide a conventional dosage form for patients who have difficulty in swallowing Keppra film-coated tablets. The development of an oral levetiracetam solution was facilitated by its high solubility in water. A sugar free formulation was produced. Adequate excipients guarantee a sufficient viscosity to aid palatability. Flavour addition was carried out to further mask the bitter taste of the drug substance . A buffer was used to ease manufacturing, ensure pH stability and protect the product from degradation. Methylparaben and propylparaben were chosen as preservatives as they are commonly used for this purpose in oral liquid solutions. Efficacy of the preservative system has been demonstrated according to the Ph Eur. No incompatibilities have been observed between levetiracetam and the individual excipients.

Product Specification
The specification includes relevant tests and justified limits for appearance, pH, deliverable volume, identification (2 HPLC methods), assay of the drug substance, assay of preservatives, chiral and achiral impurities (HPLC) and microbial quality (Ph Eur).

Batch analysis data are presented for three pilot-scale batches and three full-scale batches.

Batch analytical data indicate satisfactory compliance with specification and uniformity of the product.

Stability

18-month long-term stability data were presented for three recent pilot-scale batches and filled in the proposed commercial packaging. The samples were stored under ICH conditions 25°C/60%RH, 30°C, and 40°C. An ICH photostability conditions test was also performed. Samples are tested according to the specifications, which include validated stability indicating methods. Moreover, microbial contamination and preservative efficacy tests are performed at different test points for the long-term storage conditions. Results indicated satisfactory chemical stability, although the preservation characteristics during storage could be further optimized. These results support the shelf life and storage conditions stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance has been manufactured, characterised and controlled in an acceptable way.

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The individual pharmaceutical forms have been developed in a rational way and are also manufactured and controlled by validated methods relevant to their final use.

3. Toxico-pharmacological aspects

Pharmacodynamics

- ***In vitro* studies**

Levetiracetam did not induce a significant displacement of radioligands bound to 55 different binding sites, including $GABA_A$, $GABA_B$, glycine and glutamate (AMPA, kainic acid, NMDA) receptors.

Levetiracetam did not modulate muscimol-induced chloride flux. It had no effect on the basic electrophysiological properties of rat hippocampal CA3 neurons *in vitro*, but, at 10 µM, it produced a two-fold reduction of the increase in firing induced either by NMDA or by bicuculline.

Levetiracetam had no effect on glutamate decarboxylase and GABA transaminase *in vitro.*

Using ^{3}H-levetiracetam, specific binding sites were detected in synaptic membranes from the rat central nervous system, but not in peripheral tissues. The K_D characterising the affinity for this site was about 1 µM, whereas the affinity of the D-isomer was more than 1000-fold lower.

Since these studies, carried out for the film-coated tablets, new data has become available, derived from an *in vitro* study using Caco-2 cells.

The objective of this study was to characterise the permeation of levetiracetam through Caco-2 cell monolayers, in the presence and absence of the excipients contained in the 100 mg/ml oral solution.

No difference was observed in the levetiracetam transport under the two conditions, meaning that the excipients contained in the oral solution do not affect the levetiracetam permeation through Caco-2 cell monolayers.

- ***In vivo* studies**

At a dose of 170 mg/kg i.p., levetiracetam had a significant effect on the level of GABA and the enzymatic activities in specific regions of the brain, especially the striatum, where GABA and glutamate decarboxylase levels were decreased, while the GABA transaminase level was increased. Levetiracetam also decreased the firing rate of non-dopaminergic (presumably GABAergic) neurons in the substantia nigra pars reticulata (SNR).

Anticonvulsant activity

Levetiracetam was inactive in classical models for the detection of anticonvulsant activity. In particular, it did not protect rats and mice against convulsions induced by maximum electroshocks and high-dose pentylenetetrazol. On the contrary, it was effective in kindling models.

However, there was not always a clear-cut dichotomy between models in which levetiracetam was active and others in which it was ineffective. Levetiracetam was ineffective against the seizures induced by intracerebroventricular infusion of kainic acid in mice, whereas it decreased the severity of seizures induced by s.c. kainic acid in rats. In mice, levetiracetam did not prevent clonic seizures induced by a maximally effective dose of bicuculline, but caused up to 100% protection against submaximal doses. In rats, levetiracetam did not prevent clonic convulsions, but reduced their severity.

The discrepancy between the activity of levetiracetam in kindling models and its inactivity against seizures induced by maximal electrical or chemical stimuli differentiates levetiracetam from many antiepileptic drugs.

Experiments were also performed to determine if the protection afforded by a single dose of levetiracetam was maintained during chronic treatment. In mice, levetiracetam increased the threshold dose for i.v. DMCM to induce clonic convulsions. This effect had the same amplitude after the first

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dose and after 2 weeks of twice daily administrations, whereas the action of diazepam was clearly decreased after repeated doses.

Similarly the partial protection against bicuculline in rats (no effect on the incidence of clonic convulsions but reduction of severity) was maintained after 13 days of treatment. The feasibility of chronic treatment was also evaluated in kindling models (see next section).

Antiepileptogenic activity

In rats, levetiracetam exhibited antiepileptic activity both in the amygdala and PTZ kindling models. Daily amygdala stimulation led to seizures of progressively increasing severity score and duration. Chronic treatment with levetiracetam (54 mg/kg/day i.p.) delayed the increase in severity, but following discontinuation of the drug the severity finally reached the same level in animals treated or untreated during the kindling process. Measurement of seizure duration or of after-discharge duration led to more conclusive results. The duration remained shorter in levetiracetam-treated animals even 2 weeks after drug discontinuation. From the literature it seems that this effect of levetiracetam is rather unique. Valproate and phenobarbital delayed the increase in severity and duration during kindling, but both parameters rapidly reached control values after treatment termination.

- **General and safety pharmacology programme**

Central nervous system

In mice, levetiracetam produced dose-dependent decreases in spontaneous activity and muscular tone. In rats, performance in the rotarod test was not decreased at doses up to 1700 mg/kg, whereas chimney climbing was impaired in the 540-1700 mg/kg range. In rats the pentobarbital induced sleeping time was not affected by levetiracetam up to 1800 mg/kg orally. The doses required for protection of seizures (ED_{50}) were compared with the doses inducing rotarod performance impairment (TD_{50}) in corneally kindled mice. The safety margins (TD_{50}/ED_{50} ratio) for various antiepileptic agents were as follows: Levetiracetam 148, phenytoin 17, gabapentin 16, vigabatrin 7, lamotrigine 7, carbamazepine 6, clonazepam 3, valproate 3 and phenobarbital 2. In a related study in rats, the TD_{50} characterising the impairment of rotarod performance were similar and comparable in kindled and non-kindled animals.

Levetiracetam had no detectable analgesic action. At 300 mg/kg p.o. it slightly decreased the body temperature of rats. No sign of physical dependence was detectable in rats after stopping repeated administrations of levetiracetam after 40 days at doses up to 1800 mg/kg/day.

Cardiovascular system

In anaesthetised dogs, an i.v. bolus of levetiracetam, above a threshold dose of 100 mg/kg, produced a rapid and transient decrease in blood pressure and aortic blood flow as well as an increase in heart rate. Tachycardia and atrioventricular block were observed at doses above 1 g/kg and lethality occurred at 3.2 g/kg. In conscious dogs, levetiracetam induced short-lasting increases in heart rate and diastolic blood pressure. An increase in pulmonary artery pressure was observed after i.v. injection of 50-450 mg/kg doses.

Gastrointestinal system

Levetiracetam had no effect on the guinea pig ileum contraction induced by electrical stimulation or by various mediators. Levetiracetam had no effect on gastric secretion in rats, nor on intestinal motility in mice.

Immune function

Levetiracetam (50-1800 mg/kg/day p.o.) did not have any effects on immune function in a 4-week study in rats. No evidence of sensitisation was obtained in various tests in guinea pigs (systemic anaphylaxis, passive cutaneous anaphylaxis).

Pharmacokinetics

Absorption of oral levetiracetam was rapid (T_{max}<1 hour) and complete. The absolute bioavailability was close to 100% in all species investigated. Tissue distribution was rapid. After 1 hour, the concentrations in most organs were close to the blood concentrations. After 24 hours, the residual organ concentrations were in general higher than the blood level, especially in the brain.

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In pregnant rabbits, levetiracetam crossed the placenta. In pregnant rats, foetal levels reached the plasma level after 3 hours. A study in lactating rats showed that levetiracetam is excreted in milk, where its concentration was close to that in blood. *In vitro* binding to plasma proteins was low. The volume of distribution varied between 0.5 and 0.7 l/kg among the various species investigated.

Levetiracetam is metabolised by hydroxilation, acetamide hydrolysis and pyrrolidine opening. The acetamide hydrolysis pathway (ucb L057 production) has been evidenced in mice, rats, rabbits and dogs; it is also the major human pathway (24% of the dose). Available data indicate that hydrolysis of levetiracetam occurs by serine esterase(s) but not the cholinesterase and carboxylesterase enzymes. The reaction has a broad tissue distribution.

Levetiracetam and its metabolites were almost exclusively excreted in urine, with roughly 60% of the dose being excreted as the parent compound. In mice and dogs, similar amounts of ucb L057 and ucb K115 were excreted, as well as other metabolites. In man, ucb L057 clearly predominated over the others. Elimination half-life of levetiracetam is from 1.3 to 3.9 h in the various species studied and 7.7 h in man.

No inhibition of CYP isoforms by levetiracetam has been detected in human or rat liver microsomes. Further, it did not induce liver enzymes in rat or human hepatocytes. In the *in vivo/ex vivo* study in rat liver levetiracetam did not have any effect on the liver parameters or microsomal activities and no induction of liver enzymes was observed. However, long-term administration of L059 (> 6 months) in the rat induced signs of enzyme induction (centrilobular hypertrophy) at doses ≥ 50 mg/kg/day.

When co-administered in mice with clinically relevant AEDs, brain penetration of neither levetiracetam nor the AEDs (valproate, clonazepam, diazepam, phenobarbital, vigabatrin, phenytoin, carbamazepine and lamotrigine) was altered. However, there was a 50% decrease in levetiracetam plasma concentrations when co-administered with vigabatrin (ip 413-722 mg/kg) and a 33% reduction in valproate concentrations when co-administered at doses of 166 mg/kg

Toxicology

- Single dose toxicity:

Acute toxicity of levetiracetam is low. It was not lethal after i.v. injection of doses of up to 750 mg/kg (mice), 1000 mg/kg (rats) or 1200 mg/kg (dogs) or after oral administration of doses of up to 5000 mg/kg (rodents) or 2000 mg/kg (dog, monkey). In rodents, the main observations were decreased locomotor activity, ataxia, dyspnea, and clonic convulsions. Dogs exhibited salivation, vomiting, tachycardia and restlessness. In monkeys, nausea, vomiting and CNS depression were the most salient findings. These signs and symptoms were reversible within 24 hours.

- Repeat dose toxicity:

In rats, oral studies were performed at doses up to 4800 mg/kg (2 weeks) or 1800 mg/kg (4, 13, 26, 52 and 104 weeks).

The following target organs were identified in the rat in the repeat dose studies:

CNS

Signs of CNS disturbances were observed in the rat at high dose levels. After repeated administration by oral gavage dose dependent lethargy, rigid tail and paddling movements of the front legs were seen. The margins to clinical exposure were about 6 (Cmax) and 3 (AUC).

Liver

Centrilobular hypertrophy, increased vacuolation and fat deposition were seen after oral administration. Proliferation of the smooth endoplasmic reticulum was demonstrated in the rat at high dose levels (1800 mg/kg/day) by electron microscopy. Long-term administration (> 6 months) induced signs of enzyme induction (centrilobular hypertrophy) at doses ≥ 50 mg/kg/day. This dose level is similar to the clinical dose (20-60 mg/kg/day). In addition, increased serum enzymes (ASAT, ALAT and ALP), indicating liver toxicity were seen at high dose levels (1800 mg/kg/day) in the rat. No signs of acute cell toxicity were observed *in vitro* on primary cultures of rat hepatocytes with levetiracetam.

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Kidneys

In male rats, treatment-related accumulation of hyaline droplets in the proximal part of the kidneys was observed. Immunocytochemical investigation using a PAP technique demonstrated an increase in α_2-microglobulin. This accumulation is specific for the male rat and is considered to have no relevance for man.

In the dog, levetiracetam was administered in capsules up to 1200 mg/kg/day in the 13 and 52 – week studies. Transient restlessness and tremor were observed as well as centrally mediated salivation and vomiting. Furthermore, increased liver weights were found in the dog. Despite the increased liver weights, no histopathological changes were found in the liver, when levetiracetam was administered up to 1200 mg/kg/day during 52 weeks divided in two equal doses.

- Genotoxicity

A standard battery of genotoxicity tests was performed. These tests showed no genotoxic potential.

- Carcinogenicity:

Levetiracetam was not carcinogenic in two studies, an 80-week study in mice and a 104-week study in rats. However, the treatment regimen in the mouse study was not optimal, and the rat study was flawed by the lack of a valid control group.

- Reproduction Toxicity:

No effect on fertility was found in conventional studies performed in the rat.

The possible teratogenic effects of ucb L059 have been investigated in several studies in the rat, rabbit, and mouse.

In the rat, embryotoxicity/foetotoxicity were observed in the form of reduced skeletal ossification and skeletal anomalies (at and above 350 mg/kg/day), unossified and reduced sternebrae (at 1800 mg/kg/day), and reduced litter and foetal weight (at 1800 mg/kg/day). The NOEL was 70 mg/kg/day giving an approximate exposure level similar to the clinical exposure.

In the rabbit ucb L059 induced foetal effects (embryonic death, increased skeletal anomalies, increased malformation rate) at maternally toxic doses. The NOAEL was 200 mg/kg/day. No systemic exposure data after repeated administration are available for the rabbit. A rough comparison with single dose data gives a margin to clinical exposure at about 4 (AUC) and 5 (Cmax) to the NOAEL.

In the mice, when co-administered with valproate, levetiracetam did not increase the valproate induced neural tube defects in the offspring.

In peri/post natal studies performed in the rat, no effects were seen in maternal and foetal parameters including peri - postnatal survival and development.

- Local Tolerance:

No studies have been submitted.

- Ecotoxicity/Environmental Risk Assessment:

The predicted environmental concentrations are 0.3 µg/l in surface water, 1 ng/kg in soil and insignificant in the air.

- Impurities/Metabolites:

Ucb L057, the major metabolite of levetiracetam, was well tolerated after repeated dosing (14 days) both in the rat and the dog. Ucb L057 did not show any mutagenic potential in the Ames or mouse lymphoma assays. Of the impurities, Ucb L060, the enantiomer of levetiracetam was qualified in a 4-week repeat dose study in the rat. Ucb L060 did not show any mutagenic potential in the Ames or mouse lymphoma tests. No *in vivo* conversion to ucb L060 occurs.

- As oral tablets and oral solution are bioequivalent in man, single and repeated dose toxicity, reproduction toxicology, mutagenicity or carcinogenicity were adequate for both formulations.

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Discussion on toxico-pharmacological aspects

The anticonvulsant activity of levetiracetam was demonstrated in a number of relevant animal models of seizure disorders, mimicking complex partial and generalised tonic-clonic seizures. However, no direct interactions of levetiracetam with known receptors, re-uptake sites or second messenger systems were identified. Levetiracetam binds with an affinity, which is low but consistent with its therapeutic concentrations, to a binding site detectable only in the central nervous system; the activity associated with this site remains unknown. Overall, the high dose of levetiracetam needed to achieve anticonvulsant activity in man suggests a fairly unspecific mechanism of action.

The pharmacokinetic properties of levetiracetam are similar in the various species investigated, including man. The absolute bioavailability is nearly 100% and the volume of distribution is close to total water, which is consistent with a low binding to plasma proteins and a low accumulation in adipose tissue. Levetiracetam is the subject of several metabolic transformations, the major one being the hydrolysis of the amide group by a non-CYP enzyme. Unchanged levetiracetam and its metabolites are almost exclusively eliminated in urine.

Acute toxicity of levetiracetam is low. The repeated dose studies revealed liver effects in both rodents and the dog. In the dog, hepatomegaly was evident, and at high doses, indications of mild degenerative changes (fatty infiltration) were seen. In the rat, liver changes indicative of an adaptive response such as increased weight, centrilobular hypertrophy, fatty infiltration and increased liver serum enzymes were observed. As the clinical relevance of this finding is unknown this information is reflected in the SPC.

In addition, kidney toxicity caused by an accumulation of α_2-microglobulin was observed in the male rat. This mechanism is not considered relevant for humans.

In reproductive toxicity studies in the rat, levetiracetam induced developmental toxicity at systemic exposure levels similar to or greater than the human exposure. In the rabbit, foetal effects were observed in the presence of maternal toxicity. The systemic exposure at the NOEL in the rabbit, was about 4 to 5 times the human exposure. As the clinical relevance of these findings are unknown this information is reflected in the SPC.

A standard battery of genotoxicity tests showed no evidence of genotoxic potential. Carcinogenicity studies did not indicate a tumourigenic response. However, a full evaluation could not be performed due to some shortcomings in the studies. An additional mouse carcinogenicity study is therefore requested, but since the available data do not raise a cause for major concern, this study can be performed as a post approval commitment.

4. Clinical aspects

Clinical pharmacology

Pharmacodynamics

Single and multiple doses (up to 21 days) up to 5000 and 3000 mg/day, respectively, have been administered to healthy volunteers. Adverse events associated with levetiracetam were primarily related to the central nervous system (CNS). In young healthy volunteers, the most frequently reported treatment-related adverse events after single doses were somnolence (28.3 % for doses < 500 mg increasing to 65 % > 2500 mg, overall 40.8 %); asthenia (15.1 %, 65.0 % and 36.7 %, respectively) and dizziness (7.5 %, 60.0 % and 28.3 %, respectively). The incidence of CNS adverse events was thus dose-dependent.

With regard to vital signs, slight decreases in systolic blood pressure (5-10 %) without changes in the heart rate were observed. No ECG abnormalities, which could be ascribed to drug treatment, were observed. During these short studies, there were no deviations in blood chemistry values. The adverse event profile in elderly patients (500 mg bid) as evaluated in one study was qualitatively similar to that observed in young volunteers. The number of elderly individuals evaluated was small, however, and it is not possible to draw any conclusions from the influence of age on the severity or incidence of adverse events from this study.

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Initial clinical data concerning epilepsy were derived from three studies that investigated the efficacy of levetiracetam in suppressing the photoparoxysmal response on the EEG induced by photic stimulation in a total of 12 patients with photosensitive epilepsy. This human epilepsy model is regarded as predictive of generalised epilepsy. A long-lasting reduction in the photoparoxysmal response was observed in some patients after oral single doses of 250 to 500 mg. At doses of 1000 mg the photoparoxysmal response was either significantly reduced or abolished in all patients. There was also a marked reduction in the frequency of myoclonic jerks in those patients (n=2) who presented them at baseline.

Pharmacokinetics

Levetiracetam is a highly soluble compound (solubility in water at room temperature is 1.04 g/ml).

Levetiracetam is rapidly absorbed after oral doses ranging from 250 to 5000 mg. Peak plasma concentrations (Cmax) are reached overall at 1.3 ± 0.7 hours after dosing. Cmax is typically 31 and 43 µg/ml following a single 1000 mg dose and repeated 1000 mg bid dose, respectively. Absolute oral bioavailability is close to 100%. The extent of absorption was dose-independent (D002, N201). When taken with food, the extent of absorption of levetiracetam was not affected (N203, N206), although the rate of absorption was slowed. Steady-state is achieved after two days of b.i.d. treatment.

No tissue distribution data are available in humans. Data available in animals have shown a rapid tissue distribution with concentrations close to those in blood, except in lens and adipose tissue (lower) and kidneys (higher). In man, neither levetiracetam nor its major metabolite are bound significantly to plasma proteins (N046, RRLE98K1501), and the volume of distribution is approximately 0.5 to 0.7 l/kg, a value close to the volume of distribution of intra-cellular and extra-cellular fluid.

Two major components, levetiracetam (66 % of the radioactive dose) and an acidic metabolite ucb L057 (24 % of the dose) were identified in the urine (N046). In addition, two minor metabolites (1.6% and 0.9% of the dose) and other unknown components (0.6% of the dose) were found. These metabolic pathways were also identified in animal species. No enantiomeric interconversion was evidenced for either levetiracetam or its major metabolite ucb L057.

The plasma half-life in adults is 7 ± 1 hours and does not vary with either the dose, route of administration or repeated administration. The mean apparent total body clearance is 0.96 ± 0.14 ml/min/kg. Pharmacokinetics are comparable in subjects of 18-39 and 40-60 years, and in Caucasians and Asians. There is no evidence of circadian variability (N128, N150).

The major route of excretion is via urine, accounting for on average 95% of the dose (N046). The renal clearance of levetiracetam is approximately 0.6 ml/min/kg indicating excretion by glomerular filtration and partial subsequent tubular reabsorption. The renal clearance of the metabolite ucb L057 is approximately 4.2 ml/min/kg (N150) indicating active tubular secretion, in addition to glomerular filtration.

The pharmacokinetic profile of levetiracetam administered following intravenous infusion, oral tablets, oral capsules and oral solution was established in the evaluation of the original Keppra film-coated tablets. The oral solution is bioequivalent to the other oral formulations, which have been extensively used in clinical trials (250 mg capsules and 500 mg tablets) and tablet formulations used in clinical trials are representative of the marketed tablet formulations.

Pharmacokinetics in special populations

Adult Patients

Pharmacokinetic data following repeated administration are available from 84 adult patients with epilepsy receiving 250 to 1500 mg bid doses (N015, N017, N018, N047, N053/123 and N143). Values for Cmax, tmax, AUC, half-life and clearance are comparable to those reported in healthy volunteers.

Children with Epilepsy

Pharmacokinetic data are available for single oral dose administration (N151) in 24 patients (6-12 years. Values for Cmax and AUC adjusted to body weight (one mg/kg dose) are approximately 30-40% lower than in adults. The half-life is 6.0 ± 1.1 hours and is gender independent. The apparent body clearance is 1.43 ± 0.6 ml/min/kg (n=24).

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Elderly

In elderly subjects (n=16), there was an increase in half-life up to 10-11 h following a single dose of 500 mg or multiple doses of 500 mg bid given for 10 days (N083). The longer half-life in the elderly is partly due to the decline in renal function. As levetiracetam is eliminated almost exclusively by renal excretion, the dose of levetiracetam should be adjusted for elderly patients with compromised renal function.

Renal Impairment

The apparent total body clearance of levetiracetam was decreased in subjects with renal impairment (N137, N145 and N152). The renal clearance of both levetiracetam and ucb L057 was directly proportional to the creatinine clearance. Based on this evidence, a reduction in daily maintenance dose is recommended for patients with moderate and severe renal impairment. In anuric subjects (N152), the half-life of levetiracetam was approximately 25 and 3.1 hours during inter- and intra-dialytic periods, respectively. Both levetiracetam and ucb L057 were readily removed from plasma during haemodialysis. Therefore, an initial loading dose equivalent to 1.5 times the daily maintenance dose is recommended in anuric subjects, whereas on dialysis days, 30 to 50% of the daily dose should be supplemented after dialysis.

Hepatic Impairment

In subjects with mild and moderate impairment, there was no relevant modification of the clearances of levetiracetam and ucb L057 (N139). This is consistent with the limited role, if any, of the liver in the metabolism of levetiracetam. However, in most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50%, probably due to a concomitant renal impairment (hepato-renal syndrome). No dose adjustment is required in patients with isolated hepatic impairment. Monitoring of renal function in patients with severe hepatic impairment is recommended before dose selection.

Interactions

The findings from studies conducted both in vitro, in healthy volunteers and in patients with epilepsy suggest, that drug interactions are in general unlikely. Levetiracetam is highly soluble and permeable, and has a high pH-independent intrinsic dissolution rate. Neither levetiracetam nor its major metabolite are significantly protein bound (<10%) (N046, RRLE98K1501), and the drug is not metabolised extensively in the liver. Interactions at the level of protein binding or hepatic metabolism would therefore not be expected. However, it has been shown that drugs excreted by tubular secretion can inhibit the urinary excretion of the acidic major metabolite ucb L057, but not that of levetiracetam.

In Vitro Studies

An in vitro programme has been conducted to assess the inhibition potential of levetiracetam and its metabolite with major human liver CYP450 (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1, 1A2), glucuronyl transferase (UGT1*6, UGT*1, UGT [pI6.2]) and with epoxide hydrolase. All results showed no inhibition, even at high concentrations (=170 µg/ml). In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. In human hepatocytes in culture, levetiracetam did not cause enzyme induction.

In Vivo Interactions with Antiepileptic Drugs (AED)

An exploratory study in epilepsy patients (N017) suggested a possible interaction of levetiracetam with phenytoin. However, in two further studies (N143 and N047), no consistent changes in the pharmacokinetic parameters of phenytoin were observed when levetiracetam was added to phenytoin therapy. In four randomised, placebo-controlled studies (N051, N052, N132, N138), levetiracetam did not alter the mean plasma concentrations of carbamazepine, phenytoin, valproate, lamotrigine, phenobarbital, primidone or gabapentin in patients with stable doses of AEDs. The evaluation was inconclusive for vigabatrin only, due to paucity of data. However, the AUC of levetiracetam was increased by 24% in patients taking valproate only. The relevance of this finding is not clear, and the data available do not suggest that a dose adjustment of levetiracetam is needed when valproate is taken concomitantly.

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In Vivo Interactions with Other Drugs

No interactions between levetiracetam and R or S-warfarin (N146), digoxin (N144) or the oral contraceptives ethinylestradiol and levonorgestrel (N135) have been demonstrated. In addition, endocrine parameters (LH and progesterone) (N135) and prothrombin times (N146) were not modified by the co-administration of levetiracetam. Levetiracetam and its major metabolite are excreted in urine by glomerular filtration and active tubular secretion, respectively. The renal clearance of the metabolite ucb L057 was reduced by probenecid (N150). The pharmacokinetic parameters of levetiracetam were not affected.

Clinical efficacy

A total of 904 patients were randomised to the 3 pivotal studies. All patients were to be on a stable dose of maximum 2 (N051 and N132) or 1 (N138) classic anti epileptic drugs (AED) before randomisation. The inclusion criteria stipulated a baseline seizure frequency of at least 1 partial onset seizure per week for studies N051 and N132, whereas N138 required patients with at least 1 complex partial seizure per fortnight. Demographic characteristics were comparable across these studies. Studies N132 and N138 were parallel group studies. Study N138 had an initial parallel group evaluation period (part I). The standard AED was then down titrated to provide a monotherapy evaluation period (part II). Study N051 was a crossover trial designed as a double blind, two-period and three-treatment crossover. The first study period (period A) was powered to be evaluated as a parallel group study with 3 treatment arms receiving either placebo, 1000 or 2000 mg/day of levetiracetam for 12 weeks. A b.i.d. regimen was used in all pivotal studies.

All efficacy analysis was performed on the Intent-To-Treat population defined as all patients randomised to treatment who had at least 1 seizure count available during the evaluation period. The primary efficacy parameter was the weekly partial onset seizure frequency calculated over the entire evaluation period. Among secondary efficacy parameters were [1] responder rate (patients experiencing a 50 % reduction in partial onset frequency); [2] the proportion of seizure-free patients; [3] response to treatment (percent reduction in partial onset seizure frequency during evaluation period compared to baseline period graded in six improvement classes); [4] percentage reduction in seizure frequency from baseline.

Dose-response studies and main clinical studies

- Dose response studies

The evaluation of a dose-effect relationship was not the primary objective of the three pivotal studies. Two of the studies had, however, parallel groups randomised to placebo and different doses of levetiracetam; 1000 and 2000 mg/day; and 1000 and 3000 mg/day, respectively. The results therefore give an indication of a dose-effect relationship.

- Main studies

Study N051

Design: This trial was performed as a double blind, two-period and three-treatment crossover study. The study drug was given as add-on to a stable antiepileptic drug (AED) treatment. The study began with a baseline period of 12 weeks. Patients who were found eligible after this period were randomised. Study treatment began by a 4-week transition period A (week 13-16), during which the study drug was titrated to the dose required for evaluation period A. Evaluation period A had duration of 12 weeks (week 17-28). During evaluation period A, two doses of levetiracetam, 1 g/day and 2 g/day, were evaluated against placebo. After completion of period A, the patients entered period B. There was a 4-week transition period B (week 29-32) during which there was a gradual transfer from the evaluation period A treatment to evaluation period B treatment. During evaluation period B, two doses of levetiracetam, 1 g/day and 2 g/day, were again evaluated against placebo.

After completion of evaluation period B, the patients could either enter a study drug withdrawal period (week 45 - 48) or enter follow-up study N133.

Inclusion criteria: Patients (male or female) with refractory epilepsy, experiencing only or predominantly partial onset seizures for at least two years. Patients were on a stable dose regimen of a

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maximum of two AEDs. Patients had at laest four partial onset seizures per each four weeks during the baseline period. Age 16-65 years.

Efficacy variables: The primary efficacy variable was partial seizure frequency per week over evaluation period A and B. Secondary efficacy variables were

[1] Responder rate (patents experiencing a 50 % reduction in partial onset frequency)

[2] Response to treatment (percent reduction in partial onset seizure frequency during evaluation period compared to baseline period graded in six improvement classes)

[3] Percentage reduction in seizure frequency from baseline

[4] Seizure frequency by seizure subtype

[5] The proportion of seizure-free patients

[6] Quality of life assessments

Treatment: Of 324 patients randomised at baseline, 278 (86 %) completed the evaluation period A. In period A, more patients prematurely terminated the study in the levetiracetam 2 g group (18%) compared to the placebo (13 %) and the levetiracetam 1 g group (11 %). The number of patients that completed evaluation period B was 232 (83 % of 278).

Efficacy results: For the primary efficacy variable (partial seizure frequency per week over evaluation period A and B), there was a statistically significant reduction in the active groups (least squares mean percentage reduction over placebo was 16.9 % for levetiracetam 1 g and 18.5 % for 2 g, $p<0.001$ for both dose groups compared to placebo). No significant differences were seen between the two levetiracetam groups. The responder rate was 26.2 % for the 1-g/day group and 34.3 % for the 2-g/day group (placebo 12.2 %).

When partial onset seizure frequency was analysed during evaluation period A only, similar results were obtained. During the entire evaluation period A, five patients (5.0 %) on levetiracetam 1 g and two patients (2.0 %) on 2 g were completely seizure-free compared to one patient (0.9 %) in the placebo group. Comparable proportions of seizure-free patients were reported during evaluation phase B, five patients (5.4%) on levetiracetam 1 g and eight patients (8.8 %) on 2 g compared to one patient on placebo (1.2 %). With regard to quality of life scores, no statistically significant changes were found in the levetiracetam groups compared to placebo. The difference in efficacy estimates between levetiracetam 1 g and 2g reached statistical significance only for the responder rate in the crossover analysis.

Study N132

Design: A multicentre, randomised, add-on, double blind, placebo controlled, parallel group study in adult patients with partial seizures that were refractory to standard AED therapy.

Inclusion criteria: Patients with epilepsy who had experienced uncontrolled simple and/or complex partial seizures with or without secondary generalisation for at least 2 years, who had been exposed to at least two classical AEDs either simultaneously or consecutively, were eligible for study.

Treatment: Eligible patients entered a 12-week baseline period taking a maximum of two classical AEDs and single blind placebo. A total of 294 patients (178 male, 116 female, aged from 16 to 70 years) were randomised to treatment. Data from 294 patients were used for intent-to-treat (ITT) analysis and data from 243 patients were used for per-protocol (PP) analysis. 26 patients discontinued the study prematurely and titrated off study medication. 268 patients completed the study, 266 of whom enrolled directly in the follow-up study (N140). Treatment groups were balanced with respect to age, sex, and ethnicity and also with respect to medical history and concurrent disorders. Patients who continued to qualify at the end of the baseline period were then randomised into one of three treatment groups: levetiracetam 1 g/day (n = 98), levetiracetam 3 g/day (n = 101), or placebo (n = 95). Treatment duration was 18 weeks and included a 6-week titration period and a 12-week evaluation period. The last 2 weeks of the titration period were included in the efficacy data analysis.

Efficacy variables: The primary variable was the mean number of partial onset seizures per week (seizure frequency) over the entire 14-week evaluation period adjusted for baseline. The following secondary parameters were evaluated: Responder rate (the incidence of patients with ≥ 50% reduction

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from baseline in partial onset seizure frequency), response to treatment (the percentage of reductions in the mean number of partial onset seizures during the evaluation period compared to the baseline period), the incidence of seizure-free patients, absolute and percentage change in partial onset seizure frequency during the evaluation period compared to the baseline period, mean number of seizures per week at each visit during the evaluation period, by type (simple partial, complex partial, partial secondarily generalised, simple + complex partial, and generalised), and quality of life assessments.

Efficacy results: For the primary efficacy variable, significantly lower seizure frequencies were shown for the two levetiracetam groups compared to the placebo group ($p<0.001$ for both active groups). There was a trend towards a lower seizure frequency in the 3000 mg group compared to the 1000 mg group, but no statistically significant difference between the two doses was observed. The percentage of responders (≥ 50 % reduction in partial onset seizure frequency) was 33 % in the levetiracetam 1000 mg group and 39.8 % in the 3000 mg group compared to 10.8 % for the placebo group. Both differences were statistically significant for the ITT population. 11/199 patients on active treatment and none of 95 patients on placebo were seizure free during the entire 14-week evaluation period. Health-related QOL was not improved in the active groups.

Study N 138

Design: The study had a monotherapy outpatient withdrawal design. The study was multicentre, double blind, placebo-controlled and with parallel groups (part I: add-on treatment; part II: monotherapy).

Inclusion criteria: Male or female patients, aged 18-60 years who had experienced uncontrolled partial onset seizures (classifiable according to the International Classification of Epileptic Seizures) for at least 1 year, despite medical treatment with at least one standard AED, were included. Only patients who experienced at least two complex partial seizures (whether or not secondarily generalised) per every 4 weeks during the 12-week baseline were eligible. Patients had to be taking one standard AED at stable, optimal dose for at least 4 weeks preceding study entry.

Treatment: A total of 343 patients were enrolled and 286 patients were randomised in a 1:2 ratio to either placebo or to 3000 mg/day levetiracetam. Up-titration occurred at increments of 1000 mg. The evaluation period for efficacy of levetiracetam as adjunctive treatment lasted 14 weeks (part I). Only patients who responded to levetiracetam or placebo (according to specified responder selection criteria) entered the monotherapy part of the study (part II). A subsequent down-titration of standard AEDs occurred over a transition period of 12 weeks, and efficacy was then evaluated as monotherapy in a further evaluation period of 12 weeks (part II). 239 patients completed part I, and 46 patients completed part II. Levetiracetam was administered in a dose of 1500 mg b.i.d. The treatment duration for part I (all patients) was: 30 weeks (12 weeks baseline, 4 weeks up-titration, 12 weeks add-on evaluation, 2 weeks responder selection).

The primary efficacy variable was defined separately for the two parts of the trial.

- Part I: weekly mean number of partial onset seizures during the add-on evaluation period.
- Whole study (part I + part II): proportion of patients who completed the monotherapy period compared to the number of patients randomised to part I (ITT population)

The secondary efficacy variables were:

Part I: Type of seizures; seizure severity; visual analogue scale measures

Part II: Number of seizures per month (change from baseline and change from add-on period) for patients having completed the monotherapy evaluation period; types of seizures; seizure severity; visual analogue scale measures.

Efficacy results:

Part I + Part II: 36/181 patients (19.9 %) randomised to levetiracetam completed the whole study compared to 10/105 (9.5 %) placebo patients ($p=0.029$).

Part I, add-on: The frequency of partial onset seizures was statistically significantly lower in the levetiracetam group than in the placebo group ($p<0.001$). The median percent reduction in partial

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onset seizure frequency from baseline to add-on evaluation was 7.2 % for placebo and 39.9 % for levetiracetam. The responder rate in the levetiracetam group was 42.1 % compared to 16.7 % in the placebo group ($p<0.001$). Response to treatment (using six classes of improvement) was statistically significantly greater in the levetiracetam 3-g group than in the placebo group ($p<0.001$).

The mean absolute change in visual analogue scores for everyday life from baseline to the add-on evaluation period was 0.30 for the placebo group and 0.72 for the levetiracetam group ($p=0.051$).

Part II, monotherapy: During the monotherapy evaluation period, the median percent reduction in seizure frequency from baseline was 73.8 % for the levetiracetam 3 g/day group (n=49), which was statistically significant. The responder rate (≥ 50 % reduction in partial seizure frequency from baseline) during the monotherapy evaluation period was 59.2 % in the levetiracetam 3 g/day group.

Nine of 36 patients (25 %) in the levetiracetam 3-g group who completed part II of the study remained seizure-free throughout the monotherapy evaluation period (12 weeks). The mean absolute change in scores from baseline to the monotherapy evaluation period was 1.37 for everyday life scores and 2.33 for seizure control (n=48). These changes were statistically significant ($p=0.004$ for everyday life scores and $p<0.01$ for seizure control). An overview of the primary efficacy variable and some secondary variables in pivotal studies is shown in Table 1.

Table 1. Overview of primary efficacy variable and some secondary variables in pivotal studies

	Placebo	**1000 mg**	**2000 mg**	**3000 mg**
N051				
Seizure Frequency at Baseline*	2.5	2.82	2.58	
Seizure Frequency Evaluation**	2.58	2.00	1.85	
LSM^	1.453	1.274	1.258	
% reduction from Baseline[#]	6.1	17.7	26.5	
Response rate (%)[$]	10.4	22.8	31.6	
N132				
Seizure Frequency at Baseline*	1.77	2.53		2.08
Seizure Frequency Evaluation**	1.73	1.77		1.29
LSM^	1.366	1.131		1.041
% reduction from Baseline[#]	6.8	32.5		37.1
Response rate (%)[$]	10.8	33.0		39.8
N138				
Seizure Frequency at Baseline*	1.75			1.69
Seizure Frequency Evaluation**	1.75			1.06
LSM^	1.150			0.899
% reduction from Baseline[#]	7.2			39.9
Response rate (%)[$]	16.7			42.1

* Median seizure frequency, ITT population

** Median seizure frequency, inferential ITT population

^ LSM: least square mean of the log transformed seizure frequency, derived from analysis of covariance. p value for comparison with placebo group: $p< 0.001$ for both doses in N132 and for 3 gram in N138; $p = 0.006$ and 0.003 for the 1 and 2 gram group in N051, respectively.

Median reduction from baseline including patients with data both at baseline and during evaluation period

$ p value for comparison with placebo: $p<0.001$ for N132 (both doses), N138 and 2 gram group in N051; $p= 0.019$ in N051 for the 1 gram group.

The pooled analysis was performed also by age, gender and concomitant AED. In all these analyses, levetiracetam was superior to placebo. A trend towards a higher response rate in males was observed. With regard to seizure-free patients, 1 of 276 (0.4 %) patients on placebo who completed the studies became completely seizure-free, whereas 32 out of 509 (6.3 %) patients on levetiracetam became free of seizures.

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Magnitude of effect

The relative risk, i.e. the relative probability to be a responder (a responder is a patient with a ≥ 50 reduction from baseline in partial seizure frequency) and number needed to treat for the responder rate have been computed for the three pivotal studies (N051 period A, N132 and N138). In the N051, N132 and N138 studies, the placebo responses were similar, excepted for the N138: the placebo responder rate was respectively of 10.4 %, 10.8 % and 16.7 %.

Clinical studies in special populations

Supportive study

Study N052

Design: A multi-centre, double blind, parallel group, add-on study to compare the tolerability and efficacy of 2 daily doses of levetiracetam (2 g and 4 g daily) with placebo as add-on treatment in refractory epilepsy. The two doses of levetiracetam were evaluated against placebo treatment followed by a 24 weeks open-label active treatment.

Study: A total of 119 patients were randomised to receive double-blind treatment (39 patients in the placebo group, 42 patients in the levetiracetam 2g group, and 38 patients in the levetiracetam 4 g group). There were 17 screening failures, and 51 patients dropped out after randomisation. The patients first had a Screening Visit and then followed a 4 week Baseline Period. If the patients met the entry criteria at the Baseline Visit they were randomised into 3 parallel groups and entered the 24 week double-blind Randomised Treatment Period.

Inclusion criteria: Well-characterised refractory epilepsy presenting any type of seizure, which was classifiable according to the International Classification of Epileptic Seizures. Patients were on 1-3 AEDs and experienced at least 4 seizures in the 24 weeks prior to entry into the study. During the 4-week Baseline Period, 16 patients (13.4 %) of the ITT population were seizure free (6 placebo; 4 levetiracetam 2 g and 6 patients levetiracetam 4 g). Of those patients who had at least one seizure reported over the baseline period, 58 (48.7 %) had partial onset seizures, and 50 (42.0 %) had generalised seizures.

Efficacy variables: The protocol originally defined the responder rate and the CGI severity as the primary efficacy variables. However, the analysis focused on one primary endpoint, the responder rate up to 24 weeks of treatment. A responder was defined by a decrease from the baseline visit of at least 50% of the weekly seizure frequency. Among the secondary efficacy variables were: 1)Responder rate over the overall double-blind period, 2)Responder rate up to 4 and 12 weeks of treatment, 3)Clinical Global Impression (CGI) score (restricted to Severity of Illness, 7 scores from normal to extremely ill), 4)Seizure frequency by seizure type, 5)Seizure-free intervals and 6)QOL score.

Efficacy results: The results for the primary efficacy variable showed that the responder rate (for all seizures, after 24 weeks of treatment) was 16.1 % in the placebo group, 48.1% in the 2 g group, and 28.6 % in the 4 g group. The difference between placebo and the 2 g group was statistically significant (p=0.011), whereas the difference between placebo and the 4 g group was not (p=0.27). With regard to the CGI for the overall double-blind period 18.4% of the patients in the placebo group improved versus 29.3% in the levetiracetam 2g/day group, and 29.7% in the levetiracetam 4 g/day group. The differences were not statistically significant relative to placebo (p=0.264 and p=0.252, respectively). For the overall open-label period, the responder rates were 44.0%, 46.2%, and 39.3% for patients who had been randomised to placebo, levetiracetam 2 g/day, and levetiracetam 4 g/day while on double-blind treatment, respectively. The proportion of patients with an improvement in severity of illness was 34.6%, 42.9%, and 46.4%, respectively.

Clinical safety

Patient exposure:

The safety database of levetiracetam covers a total of 1231 patients included in epilepsy studies (short- and long-term). Of these 1231 patients, 1023 patients (772 levetiracetam, 351 placebo) participated in

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the 4 placebo-controlled epilepsy studies. Safety data from studies in other indications include 1577 additional patients exposed to levetiracetam.

Only events considered serious, deaths, pregnancies and laboratory evaluations, are discussed for these patients, since dose and duration of exposure, use of concomitant medication, age of patients, methods for collection of data, and other parameters are different from the studies in epilepsy.

With regard to duration of exposure, 780 patients were treated with levetiracetam for more than 6 months, 592 for more than 1 year, 366 for more than 2 years and 185 for more than 3 years. A high percentage of patients completed the studies (86.0 % in the levetiracetam group versus 88.8 % in the placebo group).

Adverse events and serious adverse event/deaths:

(a) Deaths

The overall mortality rate (expressed as number per 1000 patient-years of exposure, ‰) in epilepsy and non-epilepsy studies was 13.3 ‰, 13.4 ‰ for levetiracetam and 12.5‰ for placebo. The mortality rate in all epilepsy studies was 10.8 ‰ (n=20) in levetiracetam-treated patients and 13.5 ‰ (n=2) in placebo-treated patients. Ten cases of sudden unexpected death in epilepsy (SUDEP) were reported (nine being treatment-emergent), which makes SUDEP the most common cause of death in the clinical studies. The overall SUDEP rate was 4.5‰ for all epilepsy studies, and 3.6 ‰ and 7 ‰ for levetiracetam and placebo, respectively, in the controlled studies. These rates are similar to those reported in the literature among patients with severe epilepsy.

(b) Serious adverse events

Most SAEs occurred during open label extension studies on longer-term treatment. The much longer exposure explains the difference in frequency of SAEs in the placebo and levetiracetam-treated patients in the "all epilepsy studies" group.

(c) Other clinical adverse events

The most affected body systems in the placebo-controlled studies in epilepsy (n=672) were Body as a Whole and the Nervous System. For Body as a Whole, the incidence of AEs for levetiracetam was 49% versus 49.3% for placebo. AEs in the Nervous System were more frequent in the levetiracetam group (45.4%) than in the placebo group (35.3%). Of the other body systems, only the Respiratory System displayed a clinically relevantly higher incidence of AEs (13.8% vs 10.5% on placebo). This difference was due to a slightly higher incidence of Pharyngitis (5.7% vs 3.7%), Rhinitis (4.3 vs 2.6 %) and Sinusitis (2.1 vs. 0.9%) in the levetiracetam group. Table 2 shows treatment-emergent AEs occurring in at least 3% of the patients and with a difference in incidence between the levetiracetam group and the placebo group of at least 3%. Treatment-emergent AEs (TAES) were defined as those with onset dates on or after the first day of investigational treatment.

Table 2. Treatment-emergent AEs occurring in at least 3% of the patients and with a difference in incidence between the levetiracetam group and the placebo group of at least 3%.

Adverse events	**Levetiracetam**					**Placebo**
	1g/day (n=204)	2g/day (n=148)	3g/day (n=282)	4g/day (n=38)	Overall (n=672)	(n=351)
Accidental injury	16.2%	9.5%	6.0%	13.2%	10.3%	16.5%
Asthenia	12.3%	18.2%	13.5%	13.2%	14.1%	9.7%
Infection	17.6%	5.4%	13.8%	15.8%	13.2%	7.4%
Dizziness	10.8%	6.1%	9.6%	10.5%	9.2%	4.3%
Somnolence	14.7%	15.5%	10.6%	44.7%	14.9%	9.7%

The most frequent CNS-related AEs were asthenia, somnolence and dizziness. The use of smaller dose increments (333 mg in the 1000 mg group of study N132) only to a limited extent reduced the frequency of these AEs compared to studies where 1000 mg increments were used.

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A higher incidence of infections was observed in the active group. In 93 % of the cases, this term comprises the investigator reports of common colds and upper respiratory tract infections.

No increases in the incidence of other infections were observed, and there was no correlation to changes in white blood cell and neutrophil counts.

The proportion of patients terminating the treatment prematurely or reducing the dose due to AEs was 15.0 % for levetiracetam and 11.6 % for patients on placebo.

The adverse event profile in all epilepsy studies, controlled and uncontrolled (n=1162), did not differ from that observed in the placebo-controlled studies. Events that caused a dose reduction or discontinuation were recorded in 349 (30%) of patients. The most frequently reported adverse events that resulted in a dose reduction or discontinuation were convulsion (6.5%), somnolence (6%), asthenia (2.9%), dizziness (2.7%), nervousness (1.5%), ataxia (1.5%), headache (1.4%), depression (1.3%) and accidental injuries (1.1%).

Laboratory findings

For clinical laboratory data, a descriptive analysis of change from baseline to final visit is provided for the placebo-controlled epilepsy studies (all studies pooled, all durations, n=769 for the levetiracetam group and n=439 for the placebo group). P-values are provided for the changes from baseline to final visit in the active and placebo groups, and for the change between groups. No statistically significant differences were observed between treatment groups, except for a slight reduction in haemoglobin, haematocrit and red blood cells. The differences were small, however, and are not likely to be of clinical significance. For haemoglobin, there was a reduction in mean concentration from 13.97 to 13.87 g/dl for the active group, versus a reduction from 13.87 to 13.86 g/dl for the placebo group [p=0.0092 for the difference between groups]. In some of the open extension studies, abnormal values were reported for haematology parameters with slight decreases in haematocrit and haemoglobin levels, decreases in WBC counts and increases in eosinophil counts. For blood chemistry, elevations in GGT were common, as well as increases in potassium levels and cholesterol levels.

Postmarketing

During post-marketing surveillance cases of pancytopenia, thrombocytopenia, and neutropenia have been reported. The assessment of the cumulative reports concluded that as levetiracetam is used as adjunct therapy, it is not possible to reliably establish a causal relationship. However, the cases showed a temporal association with the introduction of levetiracetam and the product information was updated through a Type II variation to include the terms neutropenia, pancytopenia and thrombocytopenia." In order to adequately reflect the safety profile, the SPC was also amended to include ‘abnormal behaviour’, ‘aggression’, ‘anger’, ‘anxiety’, ‘confusion’, ‘hallucination’, ‘irritability’ and ‘psychiatric disorders’.

New data showing that levetiracetam is excreted in human breast milk have become available and the “Lactation” section of the Summary of Product Characteristics of both the oral solution and film-coated tablets (update through a type II variation) has become *“Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.”*

5. Overall Conclusion and benefit/risk assessment

Keppra 250, 500, 750 or 1000 mg film coated tablets

- **Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

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- **Preclinical pharmacology and toxicology**

Overall, the primary pharmacodynamic studies provided adequate evidence that levetiracetam has anticonvulsant activity in a large number of relevant animal models of seizure disorders, mimicking complex partial and generalised tonic-clonic seizures. The high dose of levetiracetam needed to achieve anticonvulsant activity in man suggests a fairly unspecific mechanism of action. The pharmacokinetic properties of levetiracetam are similar in the various species investigated, including man.

Overall, the toxicology programme revealed that the acute toxicity of levetiracetam is low.

In repeated dose toxicity studies, liver effects were observed in both rodents and dogs. In the dog, hepatomegaly was evident and at high dose-levels, indications of mild degenerative changes (fatty infiltration) were seen. In the rat, signs of liver changes (increased liver weights, centrilobular hypertrophy, fatty infiltration, increased liver enzymes in serum) were observed. Similar effects, but to a lesser extent, were observed in the mouse. Proliferation of smooth endoplasmic reticulum was confirmed in the rat. The cause for this has not been established. After long-term repeat dosing in the rat, effects were observed at dose/exposure levels similar to the clinical exposure and dose. The possible relevance of the observed liver changes for man is unknown and is therefore reflected in the SPC.

Levetiracetam induced developmental toxicity at exposure levels similar to or greater than in humans. In the rat and mouse, signs of developmental toxicity without maternal effects were observed in spite of a discontinuous drug exposure. In the rabbit, an increased incidence of malformations was observed. This was only observed in one strain and at a dose level inducing marked maternal toxicity. However, different strain sensitivities are well known for anticonvulsants such as phenytoin, phenobarbital and valproic acid for which the effects have been shown to be relevant for humans. The developmental effects of levetiracetam observed in the available studies are reflected in the SPC.

The carcinogenic potential of levetiracetam can not be fully assessed since the treatment regimen in the mouse study does was not optimal, and the rat study is flawed by the lack of a valid control group. However, levetiracetam is not genotoxic and did not elicit a tumourigenic response in the two submitted carcinogenicity studies. An additional mouse carcinogenicity study is requested, but since the available data do not raise a cause for major concern, this study could be performed as a post approval commitment. The Applicant is planning this additional carcinogenicity study and is currently in preparation of a dose-range finding study in mice.

In conclusion, the Applicant should be required to conduct a new mouse carcinogenicity study as a post approval commitment follow-up measure.

- **Efficacy**

The clinical studies in the application have demonstrated efficacy of levetiracetam as add-on treatment in refractory partial epilepsy. Levetiracetam as add-on medication in daily doses of 1000 to 3000 mg significantly reduces seizure frequency in patients with refractory partial epilepsy when compared to placebo. In the three pivotal studies, doses of 1000 to 3000 mg/day resulted in a reduction of seizure frequency of approximately 17 to 40% from baseline compared to 6-7% for placebo. The response rate in the active groups (all doses) varied from 22% to 42% (placebo 10 to 16%). Higher doses did not increase efficacy but increased the rate of side effects. Although the clinical data are judged to be adequate to permit the use of levetiracetam as add-on treatment in partial seizures, data are insufficient to justify the use of levetiracetam as monotherapy.

- **Safety**

The safety profile of levetiracetam is in accordance with that expected from pre-clinical studies. The most frequent adverse events were CNS-related. No major safety concerns have emerged in the clinical studies.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Keppra used as adjunctive therapy in the treatment of partial onset

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seizures with or without secondary generalisation in patients with epilepsy was favourable and therefore recommended the granting of the marketing authorisation.

Keppra 100 mg/ml Oral Solution

- **Quality**

The important quality characteristics of the active substance are well-defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic for this new pharmaceutical form application. The specifications and batch analytical results indicate a consistent product with uniform clinical performance from batch to batch. At the time of the CPMP Opinion on the application for Marketing Authorisation, there were some outstanding quality issues, which, however, did not have a negative impact on the benefit/risk balance. The applicant therefore committed to provide the necessary information (as follow up measures) within an agreed timeframe, and to submit variations if required following the evaluation of this additional information. The MAH committed not to market the product until resolution of the outstanding issues. .

- Preclinical pharmacology and toxicology

The pharmacological and toxicological profile of levetiracetam has already been established and therefore no additional data have been submitted or considered necessary for Keppra Oral solution by the CPMP.

- **Efficacy**

No new information has been submitted since assessment of the original marketing authorisation application dossier for Keppra film-coated tablets. These data were acceptable to CPMP, and no additional information is considered necessary for Keppra Oral Solution by the CPMP.

- **Safety**

There is no known risk of therapeutic inequivalence.

6. Benefit/risk assessment

The overall benefit/risk assessment is considered to be positive considering that

- no new indication or population is claimed, reference is made to the original Keppra film-coated tablets application for the benefits and risks of levetiracetam indicated as adjunctive therapy the treatment of partial onset seizures with or without generalization, in adult patients with epilepsy.

- specifically to this new pharmaceutical form, benefits include the availability of levetiracetam as a liquid form for patients with swallowing difficulties. Keppra 100 mg/ml oral solution has also been developed for clinical studies in children and future pediatric application.

- in the opinion of CPMP, there are no specific efficacy or safety issues related to this new oral pharmaceutical form, bioequivalent to the already approved Keppra film-coated tablets.

Based on the review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Keppra 100 mg/ml Oral Solution as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy was favourable and therefore recommended the granting of the marketing authorisation for the Oral Solution.

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