Modern Approaches to Epilepsy Management

a report by
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Seizures are the symptoms of a dysfunctional brain. They manifest in myriad different epilepsy syndromes with an equally wide variety of pathophysiologies. In the developed world, the majority of patients with newly diagnosed epilepsy will be started on a prophylactic treatment with an antiepilepticdrug (AED). AEDs can only suppress seizure activity after epilepsy has developed, but none has been proven to influence the dynamic processes leading to epileptogenesis. When epilepsy remains uncontrolled, it is termed refractory or pharmacoresistant. It has long been recognised that seizures will be or will become refractory to pharmacotherapy in more than 30% of patients, and that localised related epilepsies are less likely to be controlled than the idiopathic generalised syndromes. Some of these patients will be offered epilepsy surgery or a vagal nerve stimulator. Many epilepsy sufferers will remain seizure-free on the first or second drug chosen. However, combinations of AEDs are usually prescribed in those unresponsive to monotherapy. The major dilemma inherent in this sequential approach of drug prescription lies in the imprecise understanding and definition of pharmacoresistance.

The ignorance of the neurobiological factors underlying the development of drug resistance in localisation-related epilepsy leads to an inability to individualise the prognosis. At present, it is only possible to guess at crude outcomes in patients with identified causative pathologies, such as cortical dysplasia (CD) and mesial temporal sclerosis (MTS), which often – but not always – carry a poor prognosis. Indeed, evidence of MTS has been found in patients without seizures.

Pharmacoresistance may be regarded as the flip-side of epileptogenesis. Recent research has focused on the role of multidrug transport systems, most notably P-glycoprotein (P-gp), in the pathogenesis of refractory epilepsy. P-gp is an efflux transporter, encoded by the multidrug resistance-1 (MDR1) gene, which contributes to the integrity of the blood–brain barrier and actively extrudes a wide range of pharmacological agents, including AEDs, from mammalian cells. Speculation suggests that overexpression of P-gp and other drug transport proteins in the region of epileptic foci can prevent AEDs from reaching their site of action. Elevated expression of these transporters has been reported in the region of both CD and MTS tissue. Whether drug transporters represent the cause or effect of recurrent seizures is unclear and perhaps unimportant, given that experimental seizures can induce their expression and potentially reinforce inherent or acquired intractability.

AEDs

In the past decade, nine new AEDs have been licensed, substantially widening physicians' choice, and the number of possible combinations is now almost limitless. However, a number of issues remains to be addressed:

- the number of trials of single AEDs that should be employed before the patient is treated with duo-therapy;
- the number of AEDs, either singly or in combination (and in how many combinations), that need to fail before the seizure disorder can be recognised as refractory and surgery considered;
- the stage at which epilepsy becomes pharmaco-resistant to AED treatment and what determines success or failure with AED therapy; and
- whether there are clinical features that will allow prediction of subsequent 'refractoriness'.

The responses and solutions to these issues depend on an understanding of the natural history of treated epilepsy.

Natural History of Treated Epilepsy

Epilepsy patients can be divided into two classes: easy and difficult-to-control ones. A long-term outcome study supports the hypothesis that patients with newly diagnosed epilepsy comprise two distinct populations. Approximately 60% have a good prognosis. They will become seizure-free on a modest or moderate dose of the first- or second-choice AED as monotherapy without developing intolerable side effects. Some of these will remain in remission after withdrawal of

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AED therapy. The other 30–40% have difficult-to-control epilepsy. These patients often have an underlying structural cerebral abnormality. They are more likely to have had a high number of seizures before treatment was initiated, a feature recognised increasingly as the result rather than the cause of the pathophysiological changes that later manifest as refractory epilepsy. Pharmacoresistant epilepsy may, therefore, be present *de novo* as well as evolving over time, and can be identified early when treatment with the first well-tolerated AED fails. Between these two subsets, there is a grey zone of patients who will respond to combination therapy.

Combination Therapy

Combining AEDs requires an understanding of their pharmacology, particularly their mechanisms of action. Other issues that need to be considered in planning a treatment schedule for the individual patient include spectrum of efficacy, side effect profile and propensity for adverse interactions. Although the mechanisms of action of all AEDs are not fully understood, they fall into a number of general categories. Drugs such as phenytoin, carbamazepine and lamotrigine act primarily by limiting sustained repetitive firing via blockade of voltage-gated sodium channels. This property is shared by some of the newer AEDs, such as oxcarbazepine and zonisamide. Ethosuximide uniquely reduces low-threshold T-calcium currents. A number of AEDs, such as the barbiturates and the benzodiazepines vigabatrin and tiagabine enhance the inhibitory action of γ-aminobutyric acid. Effects on calcium and potassium channels and reduction of glutamate-mediated excitation also contribute to the antiepileptic properties of many drugs. Many of the newer AEDs, especially gabapentin, topiramate, felbamate, zonisamide and probably also lamotrigine and levetiracetam, have multiple pharmacological effects.

Theoretically, seizure freedom can be achieved by combining drugs with different, overlapping or similar mechanisms of actions, with the aim of finding a complementary formula for the individual patient. In patients with multiple-seizure types or difficult-to-control epilepsy, AEDs with differing pharmacological properties should be chosen. Patients with a single-seizure type may, in addition, respond to a pairing that influences an individual ion channel or neurotransmitter system in different ways. Although robust data evaluating the effectiveness of AED combinations are scarce, some regimens, such as sodium valproate with ethosuximide for absence seizures, sodium valproate with lamotrigine for partial-onset and generalised seizures and lamotrigine with topiramate for a range of seizure types, have been suggested in clinical and laboratory studies to have additive or even synergistic effects. There is emerging evidence that a wide range of combinations of two or perhaps three AEDs can be effective in some patients with difficult-to-control epilepsy.

Epilepsy Management – Practical and Theoretical Considerations

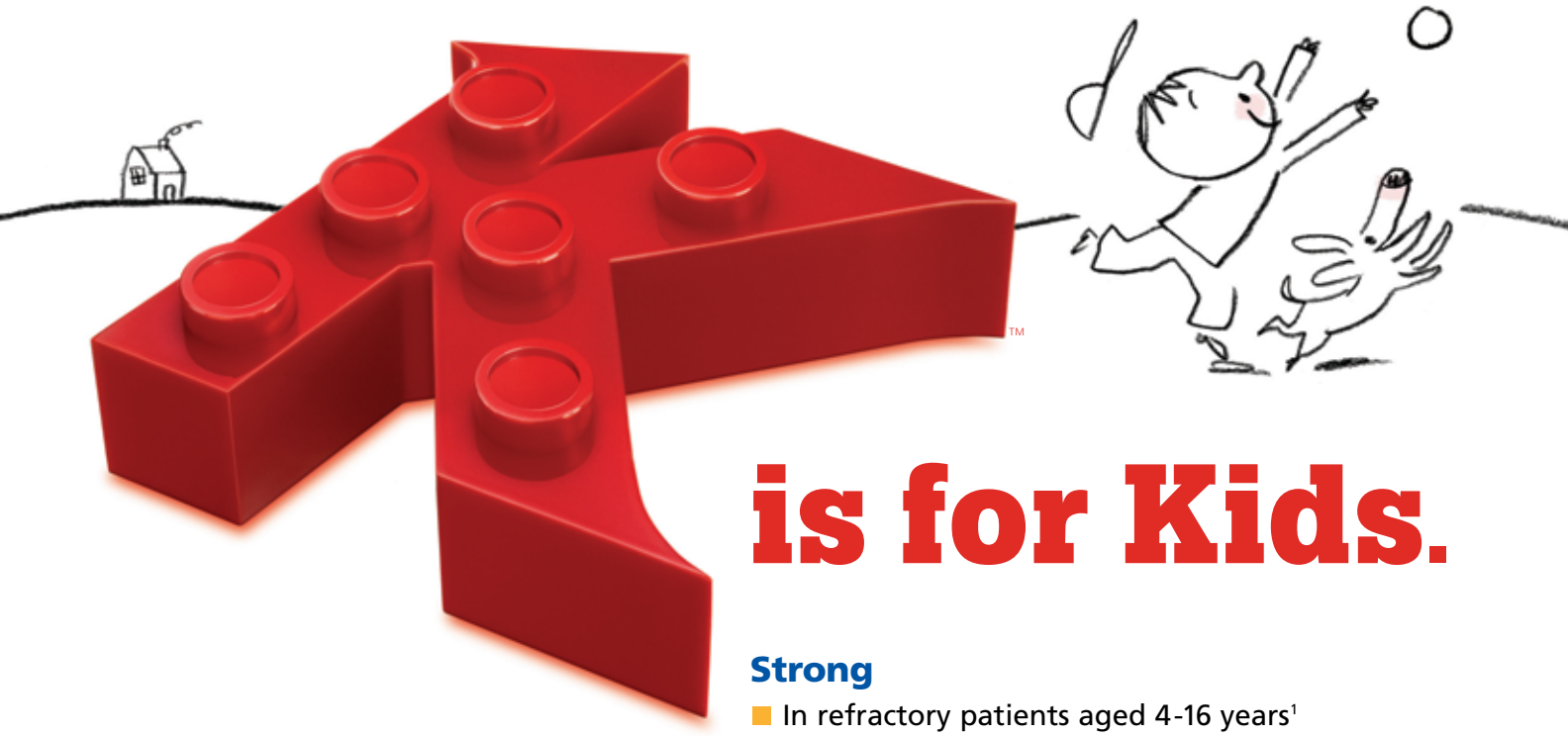
The most suitable AED for each patient should be chosen to maximise the chance of remission without producing side effects, given that life-long treatment may be required in a patient with often mild epilepsy. Failure on the first AED due to lack of efficacy implies refractoriness, as only 11% of such patients subsequently become seizure-free. It is unclear whether substituting or adding another AED is a more effective strategy in this situation. For practical purposes, a patient may be regarded as having refractory epilepsy when no seizure control is obtained with consecutive trials of two AEDs. The challenge facing the clinician is to improve the outcome for patients not responding to monotherapy by combining more appropriately modern AEDs with complementary modes of action or offering them early resective surgery. If a structural abnormality, such as MTS, can be identified on brain imaging, surgery should be considered. For most patients in whom epilepsy cannot be 'cured' by surgery, combination therapy should be employed early in the management process.

Conclusions

If clinical, molecular or genetic markers can be identified that will refine prediction of outcome, compounds can start to be developed that do not just prevent seizures, but will also hinder or reverse the insidious processes underlying the genesis of refractory epilepsy. In addition, certain proteins are providing scope for pharmacological exploitation, and the recent identification of polymorphism-related P-gp expression may aid prediction of a patient's innate drug resistance. This is, however, the tip of the iceberg.

Many genes influence the disposition of and response to AEDs. It is unlikely that a single polymorphism in the MDR1 gene alone will be predictive of outcome. By characterising polymorphisms in all genes that encode proteins that influence AED pharmacokinetics or pharmacodynamics, it may be possible to predict efficacy and acceptable tolerability with a specific drug in a designated patient with a defined epilepsy syndrome. This may in turn advance the understanding of epileptogenesis itself. Hopefully, the many decades of trial and error in choosing AED therapy will slowly give way to a more scientific rationale in the choice of antiseizure drugs for people with localisation-related epilepsy and antiepileptogenic agents for those at risk of developing it. ■

new
indication!



is for Kids.

Strong

- In refractory patients aged 4-16 years[1]
  - — 7% of patients achieved seizure freedom
  - — 45% of patients achieved ≥50% seizure reduction

Simple

- Flexible dosing options
  - — Available in tablets and oral solution
- Starting dose is 20 mg/kg/day (10 mg/kg bid)

Secure

- Favourable tolerability profile[2]
- No known clinically significant drug interactions[2]

Keppra® (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy.

References: 1. Glauser TA, Gauer LJ, Chen L, et al. Multicenter, double-blind, placebo-controlled trial of adjunctive levetiracetam (Keppra®) therapy (up to 60 mg/kg/day) in pediatric patients with refractory partial epilepsy. *Epilepsia.* 2004;45(suppl):186.
2. Data on file, UCB Pharma, Inc.

Keppra®

A powerful foundation for life

ABBREVIATED PRODUCT INFORMATION

NAME OF THE MEDICINAL PRODUCT: Keppra® (levetiracetam) film-coated tablets and oral solution. QUALITATIVE AND QUANTITATIVE COMPOSITION: Each film-coated tablet contains 250 mg, 500 mg, 750 mg or 1000 mg levetiracetam. Each ml of oral solution contains 100 mg levetiracetam.
PHARMACEUTICAL FORM: Film-coated tablet and oral solution. CLINICAL PARTICULARS: Therapeutic indications: Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy. Posology and 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 oral solution may be diluted in a glass of water and may be taken with or without food. A graduated oral syringe and instructions for use in the package leaflet are provided with Keppra. The daily dose is administered in two equally divided doses. Adults (≥18 years) and adolescents (12 to 17 years) of 50 kg or more: The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. Elderly (65 years and older): Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Patients with renal impairment" below). Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg: 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 increments or decrements of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. Dosage in children 50 kg or greater is the same as in adults. The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Dosage recommendations for children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg (1)	150 mg 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 20 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.

(2) Dosage in children and adolescents 50 kg or more is the same as in adults. The graduated oral syringe contains up to 1,000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0.25 ml).
Infants and children less than 4 years: There are insufficient data to recommend the use of levetiracetam in children under 4 years of age.
Patients with 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 using the following formula:

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

Dosing adjustment for adult patients with impaired renal function:

Group	Creatinine clearance (ml/min)	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.
Patients with hepatic impairment: No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <70 ml/min. Contraindications: Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients. Special warnings and special precautions for use: In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults: 500 mg twice daily decrements every two to four weeks; in children: dose decrease should not exceed decrements of 10 mg/kg twice daily every two weeks). 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). 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. An increase in seizure frequency of more than 25% was reported in 14% of levetiracetam treated adult and paediatric patients, whereas it was reported in 26% and 21% of placebo treated adult and paediatric patients, respectively. The administration of Keppra 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 "Posology" above). Keppra 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed). It also includes maltitol; patients with rare hereditary problems of fructose intolerance should not take this medicine. Interaction with other medicinal products and other forms of interaction: Pre-marketing data from clinical studies in adults indicate that Keppra 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 Keppra. Consistent with formal pharmacokinetic studies in adults, there has been no clear 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 levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested that enzyme-inducing antiepileptic medicinal products increase levetiracetam clearance by 22%. Dosage adjustment is not required. 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. 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. No data on the influence of antacids on the absorption of levetiracetam are available. 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. Pregnancy and lactation: There are no adequate data from the use of Keppra in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for human is unknown. Keppra should not be used during pregnancy unless clearly necessary. Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. 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, 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. Undesirable effects: Pooled safety data from clinical studies conducted in adult patients showed that 46.4% of the patients in the Keppra 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 Keppra and 2.0% of the patients in the placebo groups. The most commonly reported undesirable effects 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 undesirable effects decreased over time. A study conducted in paediatric patients (4 to 16 years) showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects 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. The following undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common: >10%; common: >1 - 10%; uncommon: >0.1% - 1%; rare: 0.01% - 0.1%; very rare: <0.01%, including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated.
Very common undesirable effects (>10%). Body as a whole: asthenia; Nervous system: somnolence.
Common undesirable effects (>1% - ≤10%). Nervous system: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor; Psychiatric disorders: agitation, depression, emotional lability, hostility, insomnia, nervousness, personality disorders, thinking abnormal; Post-marketing experience: abnormal behaviour, aggression, anger, anxiety, confusion, hallucination, irritability, psychotic disorder, suicide, suicide attempt and suicidal ideation; Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, vomiting; Metabolism and nutrition disorders: anorexia; Ear and labyrinth disorders: vertigo; Eye disorders: diplopia; Injury, poisoning and procedural complications: accidental injury; Infections and infestations: infection; Respiratory, thoracic and mediastinal disorders: cough increased; Skin and subcutaneous tissue disorders: rash. Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued; Blood and lymphatic system disorders: Post-marketing experience: leukopenia, neutropenia, pancytopenia, thrombocytopenia. Overdose: Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Keppra overdoses. 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. PHARMACOLOGICAL PROPERTIES: Pharmacotherapeutic group: antiepileptics, ATC code: N03AX14. The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. 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: 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%). Biotransformation: Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P_{450} isoforms. Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive. 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. 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. Children: (4 to 12 years) Following single 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. PHARMACEUTICAL PARTICULARS: Nature and contents of container: Keppra film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing film-coated tablets of 250, 500, 750 or 1000 mg. Keppra oral solution is packaged in 300 ml amber glass bottles (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a graduated oral syringe (polyethylene, polystyrene) and a patient information leaflet. Not all pack sizes may be marketed in each EU country.

MARKETING AUTHORISATION HOLDER: UCB S.A. Allée de la Recherche 60 B-1070 Bruxelles Belgium.

NUMBERS IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS: EU / 1 / 00 / 146 / 001-029

LEGAL CATEGORY: PRESCRIPTION ONLY MEDICINE.

DATE OF PREPARATION: October 2005

FULL PRESCRIBING INFORMATION including Summary of Product Characteristics is available from UCB S.A.