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UK Medicines Information Pharmacists Group**

**NEW MEDICINES ON THE MARKET**

**Evaluated information for the NHS**

**LEVETIRACETAM**

**Summary**

- Levetiracetam is a novel, broad-spectrum antiepileptic agent licensed for adjunctive therapy for the treatment of adults with refractory simple and complex partial seizures.
- Direct comparative trials with other antiepileptic agents are not yet available, however, preliminary placebo-controlled clinical trials suggest levetiracetam significantly reduces the frequency of simple and complex partial seizures when given as adjunctive therapy. Data from preliminary monotherapy trials also look promising but additional studies are required to clarify further.
- Levetiracetam has generally been shown to be well-tolerated, the most frequent adverse events include asthenia, somnolence and dizziness.
- Potential advantages of levetiracetam include a high therapeutic index, a desirable pharmacokinetic profile (rapid and complete oral absorption, low protein binding, lack of active or toxic metabolites), minor adverse effects, and a lack of effect on serum levels of most other antiepileptic agents. It can also be initiated at a clinically effective dosage (500mg BD).
- Additional long-term studies are needed to further elucidate the therapeutic role and benefit/risk profile of levetiracetam.
- Costs appear similar to other adjunctive therapeutic alternatives.

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# LEVETIRACETAM

<b>APPROVED NAME:</b>	Levetiracetam
<b>BRAND NAME (MANUFACTURER):</b>	Keppra (UCB Pharma)
<b>PRESENTATION:</b>	Film coated tablets containing 250mg, 500mg or 1000mg levetiracetam
<b>BNF THERAPEUTIC CLASS</b>	4.8.1 Control of epilepsy
<b>LICENSED INDICATIONS</b>	Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy
<b>DOSAGE AND ADMINISTRATION</b>	Adults & adolescents older than 16yrs: 500mg twice daily (Depending upon clinical response and tolerance, the daily dose can be increased up to 1500mg twice daily. Dose changes can be made in 500mg BD increments or decrements every two to four weeks) Elderly (from 65yrs): Dose adjustment recommended if renal function impaired Children under 16yrs: Not recommended
<b>THERAPEUTIC COMMENT</b>	Levetiracetam is a new class of anticonvulsant with a novel (as yet unknown) mechanism of action. The lack of potential for drug interactions suggests it may be a useful addition to the adjunctive options available for patients with treatment-refractory partial onset seizures.
<b>SECTOR OF USE</b>	Hospital [Y] Primary Care [Y]
<b>COST AND COURSE DETAILS</b>	Levetiracetam 500mg BD £49.50 (30 days)
<b>TREATMENT ALTERNATIVES</b>	Topiramate 200-800mg /day £64.80 - £251.66
<b>[&amp; comparative costs for 30 days maintenance treatment ]</b>	Lamotrigine 100-700mg/day £31.38 - £191.38
<b>MIMS Nov 2000</b>	Gabapentin 900-2400mg/day £47.70 - £110.39 Levetiracetam 1000-3000mg/day £49.50 - £144.00

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## INTRODUCTION

Epilepsy is the most common neurological disorder, with a prevalence of 0.4-1% [1]. The condition can be subdivided into generalised, partial and unclassifiable seizures according to the International League Against Epilepsy (ILAE) classification. Generalised seizures have no anatomical localisation and no focal onset whereas partial seizures originate from a specific focal region of the brain. Complex partial seizures relate to a loss or impairment of consciousness whereas consciousness is maintained during simple partial seizures. When partial seizures become bilateral, thus involving both sides of the cortex, they are then said to be secondarily generalised [1].

The aim of epilepsy treatment is to achieve good seizure control without producing adverse events and to provide a good quality of life. Although around 50% of patients become seizure-free with a first monotherapy, approximately 30% of patients will require add-on therapy and the majority of these may even be refractory to dual therapy. Only a small percentage of refractory patients will become and remain seizure-free. Drugs of choice in patients with partial seizures with or without secondary generalisation include carbamazepine and valproic acid. Phenytoin is sometimes used when treatments have failed, however its narrow therapeutic index and toxicity potential limit its usefulness. Alternative agents include the newer drugs, gabapentin, lamotrigine, tiagabine and topiramate [1].

## PHARMACOLOGY

Levetiracetam, is a pyrrolidone derivative and a soluble analogue of the nootropic agent piracetam. It is chemically unrelated to existing anticonvulsant agents. The mechanism of action of levetiracetam is unknown, but appears to be unrelated to that of current drugs. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal

neurotransmission [2]. Various mechanisms of action have been proposed. It is thought that levetiracetam may act via a specific binding site in the brain which is present predominantly in the membranes of the CNS, as observed in a single *in vitro* study [1]. Levetiracetam has been shown to induce seizure protection in a broad range of animal models of partial and primarily generalised seizures without having a pro-convulsant effect [2,3].

## PHARMACOKINETICS

Levetiracetam is rapidly and almost completely absorbed after oral administration, with an oral bioavailability of close to 100%. Peak plasma concentrations ( $C_{max}$ ) are achieved at 1.3 hours after dosing and steady state concentrations are achieved after 2 days of continuous twice-daily administration. The volume of distribution of levetiracetam is about 0.5-0.7 litres/kg and plasma binding is minimal at <10% [3,4].

Levetiracetam has been shown not to inhibit the major human liver cytochrome P450 isoforms, glucuronyl transferase and epoxide hydroxylase activities. Renal clearance is the major route of elimination of levetiracetam; about two-thirds of an oral dose is recovered unchanged in the urine and about one-quarter is excreted as inactive metabolites. The main metabolic pathway is via enzymatic hydrolysis which occurs in a number of tissues including blood cells. It is not metabolised hepatically [1,3,4].

The plasma half-life in adults is around 7 hours and has not been shown to vary with dose, route of administration or repeated administration. In the elderly the half-life is usually increased by about 40% (10-11 hours), a consequence of the decreased renal function in this population [3,4].

## EFFICACY

The antiepileptic efficacy of levetiracetam as adjunctive therapy in treatment-refractory partial

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seizures (simple and/or complex) with or without secondary generalisation has been evaluated predominantly in 3 pivotal double-blind, randomised, placebo controlled multicentre trials [5-7]. There are currently no direct comparative trials with other antiepileptic agents. These pivotal studies were performed in a homogenous group of 904 patients with refractory partial epilepsy. Efficacy was measured over a 12-14 week evaluation period at a daily dose of between 1000 and 3000mg of levetiracetam (given as twice daily regime) or placebo. The 3 studies showed a consistent statistically significant reduction in weekly seizure frequency compared to baseline of between 18 -33% on 1000mg [5-6], 27% on 2000mg [5] and 37-40% on 3000mg [6-7] (compared to a placebo rate of 6-7%) [5-7]. In the 2 studies where doses of levetiracetam were compared, the trend was towards a larger improvement in the highest dosage groups [5,6]. The responder rate (proportion of patients that had a reduction of partial seizure frequency of at least 50%) was between 23-33% on 1000mg [5-6], 32% on 2000mg [5] and 40-42% on 3000mg [6-7], compared to placebo rates of 10-17% [5-7]. The differences were statistically significant for each dosage within each individual study when compared with placebo [5-7]. Pooled data from controlled studies show that of all patients on placebo who completed the studies, only 0.4% became completely seizure-free compared to 6.3% patients on levetiracetam therapy ( $p < 0.001$ ) [8].

Odds of achieving a 50% reduction in seizure frequency with levetiracetam were found to be 3.6 times greater than placebo [7]. The Number Needed to Treat (NNT) to obtain one responder attributable to levetiracetam effect has been calculated at 3.9, and to obtain one seizure-free patient is 13.9 [7].

Efficacy as monotherapy has been demonstrated in one of the above pivotal studies. The completed double blind placebo-controlled study [7] converted responders to add-on treatment with 3000mg levetiracetam to a monotherapy study for

a period of 3 months. Eighty-six patients were eligible for the monotherapy phase (placebo=17; levetiracetam = 69). Forty-nine of the sixty-nine patients in the active levetiracetam group were successfully down-titrated to levetiracetam monotherapy. In these patients, the average percentage reduction in seizure frequency compared with baseline was 73.8% ( $p = 0.037$ ) with a responder rate of 59.2% [7].

Data on the efficacy of levetiracetam for the 3 pivotal studies are outlined in Table 1 [5-7].

A placebo-controlled randomised study has also evaluated the short-term effect of levetiracetam add-on therapy on health-related quality of life in the treatment of refractory partial-onset seizures [9]. 246 patients were randomised to placebo, levetiracetam 1000mg or 3000mg after a 12-week baseline period. The 31-item Quality of Life in Epilepsy (QOLIE-31) questionnaire was completed at the end of baseline and at 18-week follow-up. Clinically noticeable improvement ( $\geq 10\%$  from baseline to follow-up) was perceived by levetiracetam 3000mg responders in all areas except Emotional Wellbeing. Responders in the levetiracetam 1000mg group showed noticeable improvement in 5/9 areas, compared to 2/9 in the placebo group [9].

## PROMOTIONAL DATA

Levetiracetam's side effect profile, absence of drug interaction and convenience of use are the main features being promoted by UCB Pharma. The evidence that the recommended initiating dose for levetiracetam is effective, and the data supporting the absence of pharmacokinetic drug interactions and lack of effect on hepatic enzymes, would tend to confirm this view [4,10]. The incidence of adverse effects reported in clinical studies was high at around 46%, although not much greater than that observed with placebo (42%). However the incidence of serious undesirable effects is thought to be as low as 2% [2].

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## ADVERSE EFFECTS

Tolerability data for levetiracetam has been gathered from the 3 pivotal trials [1,5-7], and a smaller supportive trial in which tolerability was the primary endpoint [10]. In general, the overall incidence of adverse events reported with levetiracetam 1000mg (70.8 - 88.8%), 2000mg (75.5 - 83.3%) & 3000mg (55 - 89.1%) was similar to that observed with placebo (53-88.4%). No relationship between the dosage and the incidence of adverse events was observed, except for the incidence of somnolence which was highest (up to 44%) in patients receiving doses of 4000mg daily [10]. The most commonly reported adverse events occurring in >10% patients were asthenia and somnolence. Other effects reported less commonly (1-10% patients) included headache, anorexia, diarrhoea, dyspepsia, nausea, amnesia, ataxia, accidental injury, convulsions, depression, dizziness, emotional lability, hostility, insomnia, nervousness, urinary tract infections, tremor, vertigo, rash and diplopia [2,3,5-7,10]. Pooled data from the three pivotal studies showed no significant difference between patients taking placebo who terminated treatment prematurely or reduced the dose due to adverse effects (11.6%) compared with those taking levetiracetam (15.0%) [8].

## CONTRAINDICATIONS AND PRECAUTIONS

The administration of levetiracetam to patients with renal impairment may require dose adjustment. Patients with severely impaired hepatic function should have renal function assessed before dose selection [3].

Concomitant administration of levetiracetam did not affect serum concentrations of carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone [1,3], and did not bring about clinically important changes in phenytoin pharmacokinetic parameters [11]. Levetiracetam

has also not been shown to affect the pharmacokinetics of oral contraceptives (ethinyloestradiol and levonorgestrel) or levels of luteinising hormone or progesterone. Concomitant administration of levetiracetam 2000mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. The extent of absorption of levetiracetam is not altered by food, but the rate of absorption can be slightly reduced [1,3]. Levetiracetam should not be used during pregnancy unless clearly necessary. Human pregnancy data are inadequate, however some studies in animals have reported some reproductive toxicity [3]. Animal data has shown levetiracetam to be excreted into breast milk; therefore use during lactation is not recommended [3].

Due to the possibility of increased somnolence and other centrally-related symptoms, caution is recommended in these patients when performing skilled tasks e.g. driving or operating machinery [3].

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**Table 1. Efficacy studies for levetiracetam**

Ref No	Design of Study	Treatments Assessed	Major Outcome Measures	Results and Comments
Shorvon et al [5]	Multicentre, randomised, double blind, placebo-controlled study. Levetiracetam was given as add-on to a stable antiepileptic drug (AED) treatment. <u>Inclusion criteria:</u> 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 2 classical AEDs either simultaneously or consecutively	Levetiracetam (LEV) 500mg BD Levetiracetam 1000mg BD Placebo  Baseline period of 8 or 12wks. 4 wk titration period. 12 wk evaluation period	<u>Primary outcome measure :</u> Weekly partial onset seizure frequency calculated over entire evaluation period. <u>Secondary Outcome measures:</u> Responder rates (patients experiencing a 50% reduction in partial onset frequency) Proportion of seizure-free patients Percentage reduction in seizure frequency from baseline Seizure frequency by seizure subtype	324 patients randomised at baseline, 278 (86%) completed evaluation During evaluation period, 18% of pts on 2g LEV dropped out of study, compared with 13% on placebo and 11% on 1g LEV. <u>Primary efficacy variable (partial seizure frequency per week)</u> Percentage reduction over placebo: 16.4% 1g LEV, 17.7% 2g LEV (p<0.001) Responder Rate: 22.8% 1g LEV; 31.6% 2g LEV; 10.4% placebo. Seizure-free: 1g LEV (5%) (n=5), 2g LEV ( 2%) (n=2), placebo (0.9% ) (n=1)
Cereghino et al [6]	Multicentre, randomised, add-on, double blind, placebo controlled, parallel group study. Levetiracetam was given as add-on to a stable antiepileptic drug treatment. <u>Inclusion criteria:</u> As for reference [5]	Levetiracetam 500mg BD Levetiracetam 1500mg BD Placebo  Baseline period of 12 wk. 4wk titration period. 14 wk evaluation period	<u>Primary Outcome measure:</u> As for reference [5] <u>Secondary Outcome measures:</u> As for reference [5] Response to treatment (percent reduction in partial onset seizure frequency during evaluation period compared to baseline period graded in six improvement classes) Quality of Life (QOL) assessments	294 pts randomised, 268 pt completed study (91%). Drop outs from study included 12.2% LEV 1g, 7.9% LEV 3g and 6.3% placebo. <u>Primary efficacy variable (partial seizure frequency per week)</u> Percentage reduction over placebo : 20.9% LEV 1g and 27.7% LEV 3g (p<0.001) Responder rate: 33% LEV 1g; 39.8% LEV 3g ; 10.8% placebo (p=0.004) Seizure-free: 1g LEV (3%) (3pts) (not signif), 3g LEV (8%) (8pts) (p=0.01) c.f none on placebo during 14 week period. QOL scores – no statistically significant difference observed
Ben-Menachem et al [7]	Multicentre double-blind placebo-controlled parallel group study. Two part study:- Part I – adjunctive therapy Part II – monotherapy <u>Inclusion Criteria</u> Pts with epilepsy who had experienced partial onset seizures for >1yr despite medical treatment with 1 standard AED. Only pts who experienced $\geq 2$ complex partial seizures per 4wk period during 12wk baseline period were included	Levetiracetam 1500mg BD Placebo  Part I Baseline period 12wks 4wk titration period 12wk add-on evaluation 2wk responder selection Part II 12wk down titration of standard AED 12 wk monotherapy evaluation	<u>Primary Outcome measure:</u> As for reference [5] <u>Secondary Outcome measures:</u> <u>Part I</u> Type of seizure Seizure severity Visual analogue scale measures <u>Part II</u> As for Part I and :- No. seizures per month (change from baseline and change from add-on)	286 pts randomised, 239 pts completed Part I 46 completed Part II (36(19.9% LEV ) c.f 10 (9.5%) placebo , p=0.029) Drop outs from study were 18% LEV c.f 15% placebo. <u>Primary efficacy variable (partial seizure frequency per week)</u> Percent reduction of seizure frequency from baseline = 39.9% LEV c.f 7.2% placebo (p<0.001) Responder rate: 42.1% LEV c.f 16.7% placebo (p<0.001) <u>Monotherapy</u> 86 pts entered Part II (LEV n=69 & placebo n=17). Of these 49 were successfully titrated to LEV monotherapy. Median percent reduction in seizure frequency from baseline :- 73.8% LEV (p=0.037) Responder rate: 59.2% LEV Seizure-free: 9 pts (25%) who completed Part II