Scottish Medicines Consortium

levetiracetam, 250, 500, 750 and 1000mg tablets and levetiracetam oral solution 100mg/ml (Keppra®) No. (395/07)

UCB Pharma Limited

10 August 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

levetiracetam (Keppra®) is not recommended for use within NHS Scotland as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.

In the pivotal study, significantly more patients treated with levetiracetam than with placebo had a ≥50% reduction in the weekly number of myoclonic seizure days in both treatment and evaluation periods.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy (JME).

Dosing information

In adolescents (12-17 years) weighing less than 50kg, initially, 10 mg/kg twice daily, then depending on response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

Dosage in adults or adolescents (12-17 years) 50 kg or greater, initially, 500 mg twice daily, then depending on response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Product availability date

April 2006

Summary of evidence on comparative efficacy

Juvenile myoclonic epilepsy (JME) accounts for 5-10% of all epilepsies and is one of the idiopathic generalised epilepsies, with onset usually around the age of 12-18 years. A key feature of JME is the presence of myoclonic seizures which are very brief, uncontrollable, shock-like movements, typically involving the arms, legs or trunk on awakening. Unlike other childhood epilepsy syndromes, JME does not usually remit in adulthood and therefore lifelong therapy is required as relapse off-treatment is common.

Levetiracetam is an anti-epileptic, chemically unrelated to other anti-epileptic drugs, which has a different mode of action, the precise mechanism of which is not fully understood. It has linear pharmacokinetics and is minimally metabolised.

The pivotal, placebo-controlled, double-blind study to support this licence extension randomised 122 adolescents and adults (≥ 12 and ≤ 65 years), suffering from idiopathic generalised epilepsies (IGE) with myoclonic seizures uncontrolled on one or two concomitant anti-epileptic therapies, to levetiracetam 1000mg daily (n=62) or placebo (n=60). The study comprised a 4-week up-titration period during which doses of levetiracetam were increased to 3000mg daily, followed by a stable dose phase, the 12-week evaluation period, and finally conversion to an open-label, follow-up study or a discontinuation down-titration period for 6 weeks. The up-titration and evaluation periods together were the treatment period.

The primary outcome measure was the responder rate for myoclonic seizure days per week over the treatment period in the intention to treat population. A responder was defined as a patient with ≥ 50% reduction in the weekly number of myoclonic seizure days measured from baseline over the treatment period. Significantly more patients in the levetiracetam group were responders compared with placebo (58% (35/60) vs 23% (14/60).

The odds ratio for levetiracetam versus placebo response for the treatment period (using logistic regression and adjusting for baseline myoclonic seizure days per week) was 4.77 (95% confidence interval (CI): 2.12 to 10.77, p=0.0002).

A sensitivity analysis of the primary efficacy variable, limiting the period to the evaluation period only, also demonstrated a significant difference in responder rates between the levetiracetam and placebo groups (67% vs 35%), with an odds ratio for response of 4.29 (95%CI:1.93 to 9.54, p=0.0003).

Secondary outcome variables also showed significant benefit for levetiracetam over placebo. For seizure freedom recorded during the evaluation period, 25% of patients treated with levetiracetam had complete freedom from myoclonic seizures compared with 6.9% of placebo patients (p = 0.0039) and freedom from all seizure types, was recorded by 22% of patients receiving levetiracetam compared with 3.4% on placebo (p < 0.001).

Summary of evidence on comparative safety

No new safety issues were reported in this study, which confirmed a safety profile for levetiracetam observed in previous studies for partial onset seizures.

Summary of clinical effectiveness issues

The choice of anti-epileptic treatment is crucial in the treatment of JME as some anti-epileptic drugs are associated with seizure exacerbation. Sodium valproate is considered the treatment of choice, and in the above study an equal number of patients in both groups were treated concomitantly with sodium valproate (57%). Levetiracetam did not seem to be associated with seizure worsening in this patient population, although patient numbers are limited. There is no comparative evidence for levetiracetam against other anti-epileptic drugs licensed for this indication.

In November 2000 a Committee for Medical Products for Human Use (CHMP) guidance note, 'For guidance on clinical investigation of medicinal products in the treatment of epileptic disorders' stated that: the analysis of efficacy should be based on the period when patients are established on a fixed dose of either the study product or placebo/comparator. Finalisation of the protocol for the pivotal study pre-dated the finalisation of this guidance note, and the primary outcome was reported over the treatment period including both the titration and evaluation phases. To conform to this guidance the company undertook the sensitivity analysis limiting the assessment of treatment to the evaluation phase, the results of which supported the primary outcome.

The aim of the study was to demonstrate the effect of levetiracetam on myoclonic seizures in patients with idiopathic generalised epilepsy. However, as nearly all of the study patients (93%) were diagnosed with JME, the present extension of the indication is limited to JME.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility Markov model with quarterly cycles over a one year time horizon. This modelled the use of adjunctive levetiracetam mainly against adjunctive topiramate. Patients could discontinue due to either inadequate seizure control or adverse events, those doing so crossing over to adjunctive topiramate or adjunctive levetiracetam. Failure on these led to the use of adjunctive lamotrigine.

The effectiveness of levetiracetam was drawn from the pivotal trial against placebo. Since the literature review did not identify any relevant studies for topiramate, the effectiveness of topiramate was assumed to be the same as levetiracetam.

Quality of life values were stated as having been drawn from the literature. Dosing appears to have been based upon typical doses, rather than average doses within the trials. Other resource use was estimated through expert opinion.

Given the assumption of equal clinical effectiveness, over the year the same percentage of patients (81.4%) was found to remain on levetiracetam as remained on topiramate, with each arm experiencing 72 seizures on average.

The levetiracetam arm cost slightly more than the topiramate arm, £5 per patient on average, and as a consequence equivalent cost-effectiveness between levetiracetam and topiramate was concluded.

Some concerns remain around these estimates. There is obvious uncertainty around relative clinical effectiveness. However, the estimates of clinical effectiveness within the PGTCS indication, which encompasses JME, while also subject to uncertainty may indicate some superiority of levetiracetam over topiramate. Dosing did not appear to reflect trial experience, and the dosing that would apply in clinical practice is subject to some uncertainty. It also appears that the modelling may have been principally driven by withdrawals due to adverse events rather than treatment effects upon seizures. In addition, no sensitivity analysis was provided.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guideline Network (SIGN) Guideline no.81: Diagnosis and management of Epilepsies in Children and Young People, April 2005. This guideline states: there is a paucity of studies on the comparative efficacy of anti-epileptic drugs in specific epilepsy syndromes; that when indicated the choice of the first anti-epileptic drug should be determined by syndrome diagnosis and potential adverse events. In drug-resistant idiopathic generalised epilepsies, topiramate, lamotrigine and clobazam are effective as add-on treatments.

SIGN Guideline no.70: Diagnosis and management of epilepsy in adults, April 2003 updated in October 2005 states that for drug-resistant idiopathic generalised epilepsy, lamotrigine, topiramate, levetiracetam and sodium valproate have a wide spectrum of activity that includes most types of generalised seizures. The choice of drugs in combination should be matched to the patient's seizure type(s) and should be limited to two or at most three anti-epileptic drugs.

Additional information: previous SMC advice

In January 2005, following two abbreviated submissions the SMC recommended that levetiracetam 100mg oral solution and 750mg tablets were accepted for restricted use in NHS Scotland as an additional dosage forms for adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients for whom therapy is appropriate. Its use should be initiated by physicians who have appropriate experience in the treatment of epilepsy. The budget impact for NHS Scotland is likely to be small.

Additional information: comparators

Other anti-epileptic drugs

Cost of relevant comparators

Drug	**Dose regimen for usual maintenance dose often given in divided doses**	**Cost per year (£) Cost per course (£)**
levetiracetam	**1000-3000mg daily***	**635-1861**
Lamotrigine	with valproate 100-200mg/day or with enzyme inducing drugs 200-400mg/day	85-171 171-358
Primidone	750mg-1500mg daily	138-275
Topiramate	200-400mg/day	671-1247
Sodium valproate	1000-2000mg/day	166-333
Clobazam	20-30mg/day	236-355

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 June 2007. *This is the maximum dose range for levetiracetam. **These costs are for a 40kg patient. Costs are presented for adults, not including patients <50kg, and are for general comparison only.

Additional information: budget impact

The manufacturer estimated a cost net of other drug costs and net of the costs of adverse events of £156 in year 1, rising to £698 by year 3. This is based upon a market penetration among newly diagnosed patients of 20% in year 1 rising to 40% by year 3, to yield 28 patients receiving levetiracetam adjunct therapy in year 1 rising to 126 by year 3.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 July 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The reference below, shaded grey, is additional to information supplied with the submission.

European Medicines Agency (EMEA). European public assessment report (EPAR) for Keppra® [a]s adjunctive therapy in the treatment of myoclonic seizures in subjects with Juvenile Myoclonic Epilepsy (JME). www.emea.eu.int