Scottish Medicines Consortium

levetiracetam, 250, 500, 750 amd 1000mg tablets and levetiracetam oral solution 100mg/ml (Keppra®) No. (396/07)

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

In the pivotal study, there was a significantly greater reduction in the primary generalised tonic-clonic seizure frequency in the levetiracetam group compared with the placebo group.

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 primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

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.

In adults or adolescents (12-17 years) weighing 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

August 2006

Summary of evidence on comparative efficacy

Primary generalised tonic-clonic (PGTC) seizures are a common type of seizure that are linked to several idiopathic generalised epilepsy (IGE) syndromes including childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with generalised tonic-clonic seizures only (epilepsy with grand mal seizures on awakening). The tonic-clonic seizure is considered the most debilitating seizure type within idiopathic generalised epilepsy.

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, phase III, double-blind, placebo-controlled study, randomised 164 patients (≥4-65 years) diagnosed as suffering from idiopathic generalised epilepsy, experiencing PGTC seizures and uncontrolled on at least one other anti-epileptic drug, to levetiracetam (1000 mg daily or 20mg/kg/daily) or placebo. The study comprised a 4-week up-titration period during which doses of levetiracetam were increased to 3000mg daily or 60mg/kg/daily, this was followed by a stable dose, 20-week evaluation period and finally a conversion to an open-label, follow-up study or a discontinuation down-titration period of 6 weeks. The up-titration and evaluation periods together were the treatment period.

The primary outcome was the percentage reduction per week from baseline in the PGTC seizure frequency, measured over both the treatment period in the intention to treat population. The mean percent reduction in the PGTC seizure frequency per week was significantly greater in the levetiracetam group, 56% from a mean baseline of 1.27 seizures compared with a mean reduction of 28% in the placebo group from a mean baseline of 1.20. This was supported by the results for the evaluation period.

The secondary efficacy variables supported the findings for the primary efficacy outcomes. The responder rate (defined as a ≥ 50% reduction in PGTC seizure frequency per week over the treatment period) was significantly higher in levetiracetam patients, 72%, compared with 45% in placebo patients, p<0.001. Seizure freedom was assessed over the evaluation and treatment periods. During the evaluation period, 34% of levetiracetam patients were free from PGTC seizures and 24% free from all seizure types compared with 11% and 8.3% of placebo patients (p<0.001 and p = 0.009, respectively). The results for the treatment period were significant in favour of levetiracetam for PGTC seizures but not for freedom from all seizures. Sub-analysis of efficacy within seizure type subgroups indicated no effect of levetiracetam on absence seizures, and with a greater number of patients experiencing absence seizures for the first time, however the numbers of patients were small.

Summary of evidence on comparative safety

The adverse event profile was similar to that reported previously in studies in partial seizures. A relatively high incidence of CNS-related adverse events and psychiatric adverse events was observed. No new or unexpected safety issues were reported.

Summary of clinical effectiveness issues

There is no comparative evidence for levetiracetam against other anti-epileptic drugs licensed for this indication. Sodium valproate is the treatment of choice for generalised tonic-clonic seizures while lamotrigine and topiramate are used as adjunctive treatment. Levetiracetam provided a significantly greater reduction in the primary generalised tonic-clonic seizure frequency in the levetiracetam group compared with the placebo group in both treatment and evaluation phases. It significantly improved the number of patients achieving freedom from PGTC seizures during the study period and freedom from all seizures during the evaluation period.

The selection criteria in the pivotal study included patients from the age of four. However, with only one patient under the age of six and eight under the age of twelve the Committee for Medicinal Products for Human Use (CHMP) considered that due to the limited number of children a reliable evaluation of safety and efficacy in patients with PGTC seizures in this age group was not possible. It approved the lower age limit for this indication as 12 years, restricting the new indication to adults and adolescents, consistent with the approval for levetiracetam in the treatment of myoclonic seizures.

Summary of comparative health economic evidence

The manufacturer presented a relatively straightforward 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 progressing to other adjunctive therapies.

The effectiveness of levetiracetam was drawn from the pivotal trial against placebo, while the effectiveness of topiramate was drawn from a randomised trial within the literature which also used placebo as the control. Quality of life values were taken from published literature. Dosing appears to have been based upon typical doses, rather than average doses within the trials. Other resource use was estimated using expert opinion.

Over the year only 51.3% of patients remained on topiramate as compared with 83.5% on levetiracetam. Topiramate led to more seizures than levetiracetam; 127 as against 37. Consequently, levetiracetam yielded a slight overall patient benefit of 0.008 QALYs. The levetiracetam arm cost slightly less than the topiramate arm, £57 per patient on average. As a consequence, levetiracetam was estimated as dominating topiramate (i.e. cheaper and more effective).

A number of concerns remain. The time horizon of only one year may tend to underestimate the longer term cost-effectiveness of the treatment with the lower discontinuation rate. Within the analysis this appeared to be levetiracetam, but there are uncertainties as to the validity of the indirect comparison given markedly different placebo effects within the two studies being compared. The doses that would apply in clinical practice is subject to some uncertainty. Quality of life values also did not appear to correspond to those within the cited reference but correction of this did not significantly alter the result. It also appears that the modelling may have been principally driven by withdrawals due to adverse events rather than treatment effects upon seizures. Other treatment sequences, such as levetiracetam followed by topiramate could also have been considered. However, additional evidence supplied by the manufacturer suggested that given the model structure and other inputs, other treatment sequences would still result in levetiracetam dominating.

Given these concerns, 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 (£)**
levetiracetam	**1000-3000mg daily***	**635-1861**
Topiramate	200-400mg/day	671-1247
Lamotrigine	with valproate 100-200mg/day or with enzyme inducing drugs 200-400mg/day	85-171 171-358
Sodium valproate	1000-2000mg daily	166-333
Primidone	750-1500mg daily	138-275
Phenytoin	200-500mg daily	25-61

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

Additional information: budget impact

The manufacturer estimated a cost saving net of other drug costs and net of the costs of adverse events of £19k in year 1, rising to £24k by year 3. This is based upon a market penetration among newly diagnosed patients of 7% in year 1 rising to 9% by year 3, to yield 326 patients receiving levetiracetam adjunct therapy in year 1 rising to 420 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® as adjunctive therapy in the treatment of primary generalised tonic clonic seizures (PGTCS).