Scottish Medicines Consortium

levetiracetam, 250, 500, 750 and 1000mg tablets and levetiracetam oral solution 100mg/ml (Keppra®) No. (394/07)

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 partial onset seizures with or without secondary generalisation in children from 4 years of age with epilepsy.

In the pivotal study, levetiracetam reduced partial seizure frequency compared to placebo in both the treatment and evaluation phases.

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 partial onset seizures with or without secondary generalisation in children from 4 years of age with epilepsy.

Dosing information

In children and adolescents 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 children or adolescents 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

September 2006

Summary of evidence on comparative efficacy

Half of epilepsies begin before the age of 20 and a quarter of these are intractable, having severe and cognitive consequences. Epilepsy in childhood differs from epilepsy in adults especially by the occurrence of seizures in a structurally and functionally maturing brain. Partial seizures are the most common seizure type in children.

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. Levetiracetam has a licence as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age. The basis of this submission is the extension of that indication to include children from the age of 4 years. There is one pivotal, phase lll study of efficacy and tolerability and an open-label extension study of long-term efficacy and safety.

The pivotal study was a randomised, placebo-controlled, double-blind study in children (aged 4 to 16 years inclusive), with refractory partial onset seizures (including the subtypes of simple, complex, and partial seizures evolving to secondarily generalised seizures) that at the time of enrolment were inadequately controlled with one or two concomitant anti-epileptic drugs. Patients were randomised to either levetiracetam 20mg/kg/day (n=101) or placebo (n=97). The study comprised a 4-week up-titration period during which doses of levetiracetam were increased up to 60mg/kg/day and this was followed by a stable dose, 10-week evaluation period. The up-titration and evaluation periods together were the treatment period.

The primary efficacy variable was partial seizure frequency per week during the treatment period versus baseline in the intention-to-treat population. The median percent reduction of partial seizure frequency from baseline was 43% in the levetiracetam group compared with 16% in the placebo group and the difference between the groups was statistically significant, equivalent to a 27% (95% CI: 14 to 38%, p=0.0002) reduction in partial seizure frequency per week for levetiracetam over placebo. The results for the evaluation period only were similar to those of the treatment period (44% vs 23%, p<0.01). The primary outcome was supported by the following secondary efficacy variables. The responder rate, defined as the proportion of patients experiencing a ≥ 50% reduction from baseline in partial seizure frequency per week during the treatment period, was significantly greater for levetiracetam than for placebo (45% vs 20%; p=0.0002); the median absolute reduction from baseline in partial seizure frequency per week in the treatment period was -1.6 in the levetiracetam group and -0.7 in the placebo group; and seven patients (6.9%) on levetiracetam were seizure-free during the treatment period compared with one patient (1.0%) on placebo.

In the open-label extension study, most patients remained on treatment for more than a year and the rate of attrition was relatively low. The efficacy of levetiracetam was maintained.

Summary of evidence on comparative safety

The adverse event profile of levetiracetam in children was similar to that reported in adults. At least one treatment-emergent adverse event was experienced by 88% (89/101) of levetiracetam and 92% (89/97) of placebo patients and in 55% of levetiracetam-treated patients and 40% of placebo-treated patients these were considered related to study drug. Discontinuations due to adverse events in the key study were small, occurring in five patients receiving levetiracetam (5.0%) compared with nine patients in the placebo group (9.3%).

In the pivotal study, the incidence of CNS-related adverse events of disturbances of behaviour and/or mood was significant (39%). To ascertain if the risk was greater in children, the relative risk of psychiatric/behavioural events between levetiracetam and placebo in the pivotal study was compared with adult data. In adults treated with levetiracetam the corresponding incidence was lower (19%), however due to the higher incidence of these events in children treated with placebo when compared as relative risk over placebo, it was concluded that the relative risk for psychiatric and behavioural events was only modestly elevated in children treated with levetiracetam compared with adults. The majority of the adverse events in children are in the category of non-psychotic mood/anxiety/behaviour symptoms and those with the greatest relative risk include agitation, nervousness, depression and hostility.

The Committee for Medical Products for Human Use (CHMP) considered that, with regard to prolonged adverse events, it was difficult to determine from the pivotal study which effects would persist. Further analysis from the manufacturer suggested that agitation, hostility, hyperkinesia, nervousness and personality disorder could be present for prolonged periods while somnolence was more common at the beginning of treatment. The CHMP concluded that the safety data were reassuring in terms of duration of adverse events, reversibility and lack of a clear dose-relationship for any effect (with possible exceptions for nervousness, agitation and emotional liability).

Summary of clinical effectiveness issues

There is no comparative evidence for levetiracetam relative to other anti-epileptic drugs licensed for this indication in children.

In November 2000 a 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. However, it should be noted that the median reduction of partial seizure frequency from baseline for the evaluation period alone was also significantly better than placebo (44% vs 23%, $p<0.01$).

The protocol for the pivotal study prescribed a maximum dose titration, for all patients, to 60mg/kg/day over four weeks. However, efficacy was noted even at the lowest dose, 20mg/kg/day. Dose titration in practice is unlikely to follow such a rigid titration as that in the pivotal study and patients may not necessarily titrate to the maximum dose but, it is recommended, should remain on the lowest effective dose. A lower dose and more gradual dose titration may affect the overall tolerability.

There are still some outstanding safety issues to be resolved in post-marketing surveillance.

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 and those doing so progressed to other adjunctive therapies.

The effectiveness of levetiracetam was drawn from the pivotal trial against placebo coupled with a literature value used for withdrawal rates. The effectiveness of topiramate was drawn from a published randomised trial within the literature which also used placebo as the control.

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.

Over the year 96.5% of patients remained on topiramate as compared with 93.2% on levetiracetam. Topiramate also led to fewer seizures than levetiracetam; 38 as against 61. Consequently, topiramate yielded a very slight overall patient benefit of 0.002 QALYs. The levetiracetam arm cost very slightly less than the topiramate arm, £36 per patient on average, to yield an overall cost effectiveness of £17,374 per QALY. However, this cost-effectiveness ratio may require careful interpretation as it relies on an assessment of society's preferences regarding their willingness to accept health losses (the intervention being cheaper but less effective).

Some concerns remain around this, in that the time horizon of one year may have underestimated the benefit of the lower discontinuation rate for topiramate and consequently lower number of patients undesirably progressing though other adjunctive therapies. It was also unclear to what extent the main clinical input in terms of withdrawal rates was drawn from the trial results as reported within the clinical effectiveness section. It also appears that dosing and drug costs may not have reflected the clinical trial, with there being some uncertainty as to what dosing would apply in clinical practice. The dosing for topiramate may also have been too low. Quality of life values also did not appear to correspond to those within the cited reference. 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 although additional information from the manufacturer suggests that this would not markedly affect the estimate of cost effectiveness given the model structure and other inputs.

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; the potential adverse events of anti-epileptic drugs should be a major determinant of the choice of drug in the individual child.

National Institute for Health and Clinical Excellence (NICE) Technology Appraisal no.79. Newer Drugs for Epilepsy in Children, May 2004. This was planned for review in December 2006. No details are at present available. The May 2004 appraisal recommended gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate and vigabatrin (as an adjunctive for partial seizures) for the management of epilepsy in children who have not benefited from treatment with the older 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, as detailed below

Cost of relevant comparators

Drug	Dose regimen for usual maintenance dose often given in divided doses	Cost per year (£)
levetiracetam	**20-60mg/kg/day***	**517-1555[A]**
Carbamazepine CR	400mg-1000mg daily	68-168[B]
Gabapentin	900mg daily	176[B]
Lamotrigine	with valproate: 1-5mg/kg/day with enzyme inducers: 5-15mg/kg/day	83-132[C] 132-450[B]
Primidone	500mg-1500mg daily	92-275[B]
Phenytoin	4-8mg/kg/day	56-112[A]
Topiramate	5-9mg/kg/day	694-982[B]
Sodium valproate	20-30mg/kg/day	108-157[B]
Oxcarbazepine	30mg/kg/day	437[B]

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4th June 2007. *This is the maximum dose range for levetiracetam. Costs were calculated for a 30kg patient for general comparison.

[A] These costs were calculated using a liquid preparation of the exact dose

[B] These costs were calculated using twice daily dosing and solid dosage forms. It was not always possible for the morning and evening doses to be equally divided or the exactly calculated dose to be administered. The closest estimation has been made.

[C] This cost was calculated on once daily dosing

Additional information: budget impact

The manufacturer estimated a cost net of other drug costs and net of the costs of adverse events of £91 in year 1, rising to £382 by year 3. This is based upon a market penetration among newly diagnosed patients of 5% in year 1 rising to 9% by year 3, to yield 2 patients receiving levetiracetam adjunct therapy in year 1 rising to 9 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 undernoted reference was supplied with the submission.

Glauser TA, Ayala R, Elterman RD et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in paediatric partial seizures. Neurology 2006; 66:1654-1660.