Scottish Medicines Consortium

levetiracetam 250, 500, 750 and 1000mg tablets and levetiracetam oral solution 100mg/ml (Keppra®) No. (397/07)

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 monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Levetiracetam has been shown to be non-inferior to carbamazepine controlled-release, the first choice anti-epileptic drug for partial seizures.

However, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and they did not present a sufficiently robust economic analysis.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As monotherapy, in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Dosing information

Starting dose 250 mg twice daily increased to 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending on clinical response. Maximum dose 1500 mg twice daily. Tablets must be swallowed with a sufficient quantity of liquid and may be taken with or without food.

Product availability date

August 2006

Summary of evidence on comparative efficacy

Monotherapy is considered the ideal management for epilepsy, although this is not always achievable. Following initial licensing for adjunctive therapy, levetiracetam is now approved for monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. This extended licence indication is the basis of this submission.

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 lll, randomised, double-blind, active comparator study was designed to demonstrate the non-inferiority of levetiracetam monotherapy to carbamazepine controlled release (CR) monotherapy in newly diagnosed epilepsy patients with partial onset or generalised tonic-clonic seizures. The study comprised a titration phase, a 6-month evaluation phase and a 6-month maintenance phase. Patients were randomised and titrated to the first target dose of levetiracetam 500mg twice daily (n=285) or carbamazepine CR 200mg twice daily (n=291) and following stabilisation entered the evaluation phase. If a seizure occurred during the evaluation phase, patients were titrated to a second target dose (levetiracetam 1000mg twice daily or carbamazepine CR 400mg twice daily) and following stabilisation, re-entered the 6-month evaluation period. The same procedure was undertaken if a seizure occurred during the evaluation period at the second dose level with escalation to the third target daily dose (levetiracetam 1500mg twice daily or carbamazepine CR 600mg twice daily). Discontinuation due to lack of efficacy was only allowed at dose level three. Patients with poor tolerability at target dose levels two or three could down-titrate once to a lower dose.

The primary efficacy outcome was the proportion of patients in the per-protocol (PP) population with 6-month seizure freedom at the last evaluated dose. The PP population was defined as those patients who had no major protocol deviations affecting the efficacy variables; equating to 237 patients in the levetiracetam group and 235 patients in the carbamazepine CR group at 6 months. The non-inferiority margin, a pre-specified threshold, was calculated as a 15% absolute difference in seizure freedom rates between treatments. A logistic regression model was used to analyse the data. Secondary efficacy endpoints included 6-month (in the intention to treat (ITT) population) and one year (in the PP and ITT populations) seizure freedom rates, at last evaluated dose and by dose level.

Two thirds of randomised patients completed the 6-month evaluation period. The percentage of patients seizure free after six months was 73% (173/237) in the levetiracetam group and 72.8% (171/235) in the carbamazepine CR group, giving an adjusted absolute difference using the logistic regression model of 0.2% (95% CI, -7.8%, 8.2%). The observed lower limit of the confidence interval was -7.8%, well above the –15% threshold, thus levetiracetam was statistically non-inferior to carbamazepine CR. The PP results were supported by the results in the ITT population, with 67% (190/285 and 194/291) of patients in each group respectively seizure free at six months. Results at one year were similar for both the PP and ITT populations, although a non-inferiority limit was not defined for one year seizure freedom.

Summary of evidence on comparative safety

No new adverse events were reported. The pivotal study provided comparative safety data in 576 patients; 426 of whom were exposed to the study drugs for at least 6 months. Most adverse events in both groups were mild to moderate. Significantly fewer patients in the levetiracetam group discontinued or had their dose reduced due to adverse events (16% vs 23%, p=0.046).

The adverse event profile differed between levetiracetam and carbamazepine, with a greater frequency of psychiatric adverse events (including depression, nervousness and insomnia) in the levetiracetam group and a greater frequency of skin reactions and some gastrointestinal events (including rash, pruritus, nausea, vomiting) in the carbamazepine group.

Summary of clinical effectiveness issues

Anti-epileptic treatment is dependent on the epilepsy seizure type and syndrome; treatment choices should be made on an individual patient basis with consideration for co-morbidities and any concomitant medication. Carbamazepine is the first choice anti-epileptic drug for partial seizures and the CR dosage form is the best tolerated. In terms of efficacy, levetiracetam has been shown to be non-inferior to carbamazepine CR. The advantages for levetiracetam include low intra- and inter- subject variability and fewer drug-drug interactions. The manufacturer anticipates that levetiracetam will be used after the trial of other generic anti-epileptic monotherapy.

Levetiracetam has a significant adverse event profile, although different from carbamazepine. Further to Committee for Medical Products for Human Use (CHMP) request, the manufacturer’s review of suicidal ideation as an adverse event in patients exposed to levetiracetam in the monotherapy studies has not provided evidence that, in this limited population, an increased incidence of depression, sleep disturbances or irritability is linked to increased suicide ideation in patients treated with levetiracetam.

More patients discontinued the study due to adverse events in the carbamazepine group (56/291, 19%) than in the levetiracetam group (41/285, 14%) while more patients discontinued the study due to lack of efficacy in the levetiracetam group (50/285, 18%) than in the carbamazepine group (29/291, 10%). The fairly rapid up-titration of carbamazepine CR dosing may have contributed to the adverse events in this group.

The study design conforms to the European Medicines Agency guidelines (i.e. both the new guideline for the clinical investigation of medicinal products in the treatment of epileptic disorders and the guideline for the conduct of non-inferiority studies). In the scientific discussion within the EPAR it was noted that the choice of –15% set for the non-inferiority margin might be considered too high but the observed lower limit of the confidence interval, at –7.8%, was well above this.

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 levetiracetam first-line monotherapy against topiramate first-line monotherapy. Patients could discontinue due to either seizure or adverse events, those doing so progressing to second-line carbamazepine. Failure on this would lead to adjunctive therapy using lamotrigine, with failure on this leading to the use of adjunctive oxcarbazapine.

The effectiveness of levetiracetam was drawn from the pivotal trial against carbamazepine, while the effectiveness of topiramate was drawn from a randomised trial within the literature which also used carbamazepine as the control. Quality of life values were drawn from the literature. Dosing was based upon typical doses, rather than average doses within the trials. Other resource use was estimated through expert opinion, valued using the tariff schedule for England and Wales.

Over the year 66.0% of patients remained on topiramate as compared with 63.5% on levetiracetam. Despite this and possibly perversely, modelling anticipated more seizures overall in the topiramate arm than in the levetiracetam arm; 187 as against 155. Consequently, levetiracetam yielded a slight overall patient benefit of 0.004 QALYs. The levetiracetam arm cost on average £220 more than the topiramate arm, to yield an overall cost effectiveness of £48,455 per QALY.

There were a number of concerns around the modelling. The one year time horizon may have tended to favour the treatment with the poorer continuation rate (i.e. levetiracetam). Given that levetiracetam and topiramate are only likely to be used subsequent to other drugs such as carbamazepine, sodium valproate and lamotrigine unless these are contraindicated, effectiveness may not be as high as in the trials where they were used first-line, although there is a lack of data in this area . Similarly, the modelling of carbamazepine monotherapy subsequent to both levetiracetam monotherapy and topiramate monotherapy is questionable.

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 data supplied by the manufacturer suggested that cost effectiveness estimates would remain similar.

The manufacturer’s justification of the treatment’s cost in relation to its health benefits was not sufficient to gain acceptance by SMC and they did not present a sufficiently robust economic analysis.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

National Institute of Health and Clinical Excellence (NICE) Clinical Guideline no 20 The epilepsies: the diagnosis and management of epilepsies in adults and children in primary and secondary care (October 2004) states that it is recommended that individuals should be treated with a single antiepileptic drug (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. NICE plans to review this epilepsy clinical guideline in October 2008 and is expected to include levetiracetam.

There are two Technology Appraisals from NICE: Newer drugs for epilepsy in adults (no.76) (March 2004) and in children (no.79) (April 2004). Review of these guidelines was planned for December 2006.

The Scottish Intercollegiate Guidelines Network (SIGN) Guideline no.70: Diagnosis and Management of Epilepsy in Adults. April 2003, updated October 2005. This states that: carbamazepine, sodium valproate, lamotrigine and oxcarbazepine can all be regarded as first-line treatments for partial and secondary generalised seizures. All anti-epileptic drugs licensed for monotherapy have similar efficacy in newly-diagnosed epilepsy and the side effect and interaction profiles should direct the choice of drug for the individual patient.

Additional information: previous SMC advice

In January 2004, following a full submission, the SMC recommended that, topiramate was accepted for restricted use within NHS Scotland for its extended (monotherapy) indication. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

Topiramate should be used principally in patients who have not benefited from treatment with an older anti-convulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contraindications, interactions or poor tolerance. Its use for second-line therapy in epilepsy is unaffected by this recommendation.

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	100mg daily	336
Oxcarbazepine	600-2400mg daily	291-1165
Gabapentin	900-1200mg daily	176-294
Primidone	Up to 1500mg daily	Up to 275
Sodium valproate	1000-2000mg daily	166-333
Carbamazepine CR	400-1200mg daily	68-203
Lamotrigine	100-200mg daily	85-171
Phenytoin	200-500mg daily	25-61

Doses are for general comparison and do not imply therapeutic equivalence. Costs were from eVadis accessed on 4th June2007. *This is the maximum dose range for levetiracetam

Additional information: budget impact

The manufacturer estimated a cost net of other drug costs and net of the costs of adverse events of £14k in year 1, rising to £50k by year 3. This is based upon a market penetration among newly diagnosed patients of 6% in year 1 rising to 8% by year 3, to yield 64 patients receiving levetiracetam monotherapy in year 1 rising to 224 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 references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

European Medicines Agency (EMEA). European public assessment report (EPAR) for Keppra® as monotherapy. www.emea.eu.int

Brodie M, Perucca E, Ryvlin P et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology 2007;68:402-408