Resubmission

levetiracetam 250,500,750 and 1000mg tablets and levetiracetam oral solution 100mg/1ml (Keppra®) (No. 397/07)

UCB Pharma Ltd

11 January 2008

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 resubmission

*levetiracetam (Keppra®)* is accepted for restricted 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 an older first choice anti-epileptic drug for partial seizures.

Levetiracetam is significantly more expensive than traditional drugs so its use is restricted to patients for whom the range of traditional drugs normally used for first-line treatment are ineffective or unsuitable.

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 antiepileptic, chemically unrelated to other antiepileptic 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, 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 six months. A logistic regression model was used to analyse the data, and the absolute difference between treatments in seizure freedom rates was calculated. The margin for non-inferiority was set at −15% for the lower bound of the two-sided 95% confidence intervals for this difference. 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.
About two-thirds of randomised patients completed the 6-month evaluation period. The percentage of patients seizure free after six months was 73% in both the levetiracetam and carbamazepine CR groups (n=173/237 and n=171/235 respectively), giving an adjusted absolute difference using the logistic regression model of 0.2% (95% CI: -7.8% to 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% (n=190/285 and n=194/291) of patients in each group respectively seizure free at six months. Results for seizure freedom at one year were also similar between groups for both the PP and ITT populations, although a non-inferiority limit was not defined for this endpoint.

### 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 differs between levetiracetam and carbamazepine, with a more frequent occurrence of psychiatric adverse events (including depression, nervousness and insomnia) in the levetiracetam group and a more frequent occurrence 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 and 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 pharmacokinetic variability and fewer drug-drug interactions. The company anticipates that levetiracetam will be used after a trial of other generic anti-epileptic monotherapy.

Levetiracetam still has a significant adverse event profile, although different from carbamazepine. Further to a request from the Committee for Medical Products for Human Use (CHMP), 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 because of adverse events in the carbamazepine group (19%, n=56/291) than in the levetiracetam group (14%, n=41/285) while more patients discontinued the study because of lack of efficacy in the levetiracetam group (18%, n=50/285) than in the carbamazepine group (10%, n=29/291). The fairly rapid up titration of carbamazepine CR may have contributed to the adverse events in this group.

The study design conforms to the European Medicines Agency (EMEA) guidelines for both the clinical investigation of medicinal products in the treatment of epileptic disorders and for the conduct of non-inferiority studies. Although in the scientific discussion the EMEA states
that the choice of –15% set for the non-inferiority margin might be considered too high, 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 analysis with a 2-year time horizon comparing levetiracetam monotherapy with a 'no change in therapy' option in a cohort of newly diagnosed patients. The no change comparator involved continuing on a basket of anti-epileptic drugs (AEDs, consisting of 51% carbamazepine, 41% lamotrigine, and 8% topiramate) that newly diagnosed patients have tried but are achieving only limited seizure control with (i.e. considered treatment-refractory). This represented a specific positioning for levetiracetam after all other AED monotherapy options have been tried.

The effectiveness of levetiracetam in preventing or reducing seizures was derived from the pivotal clinical trial of levetiracetam monotherapy in newly diagnosed patients, which reported 66% probability of seizure freedom at 6 months, and 75% at one year. Patients not responding or experiencing adverse events were withdrawn from levetiracetam but continued to receive other AEDs. The reduction in the relative efficacy for the comparator was based on the difference in seizure occurrence for patients receiving AEDs compared to those not, derived from a single published study in high-risk epilepsy patients. The efficacy in year 2 for levetiracetam responders was assumed to be the same as in year 1. Efficacy for comparator patients not responding in year 1 was reduced arbitrarily by 10%.

For a cohort of 1000 patients the incremental costs of levetiracetam were estimated as £134,000 with a reduction in 28,000 seizures and a gain of 325 QALYs over a 2 year time horizon, resulting in an incremental cost per QALY gained of £413.

The manufacturer’s submission suffered from a lack of transparency and clarity. The main weaknesses concerned a limited indirect comparison to derive the relative efficacy of the comparator, arbitrary assumptions for year 2 efficacy, and a lack of clarity concerning the derivation of cost savings from a reduction in seizure frequency. There were some concerns over the high utility estimates applied for seizure freedom and seizure reduction. A response from the manufacturer clarified some issues and provided additional sensitivity analyses that provided reassurance that, under a variety of different assumptions and scenarios, levetiracetam is a cost-effective choice in patients whose seizures are not adequately controlled by other anti-epileptic drugs.

**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

After review of a full submission, the Scottish Medicines Consortium issued advice on 10th August 2007 that levetiracetam 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.

After review of a full submission, the Scottish Medicines Consortium issued advice on 12th January 2004 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.

After review of two abbreviated submissions, the Scottish Medicines Consortium issued advice on 10th January 2005 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen for usual maintenance dose often given in divided doses</th>
<th>Cost per year (£)</th>
</tr>
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<tbody>
<tr>
<td>levetiracetam</td>
<td>1000-3000mg daily*</td>
<td>635-2162</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>600-2400mg daily</td>
<td>289-1134</td>
</tr>
<tr>
<td>gabapentin</td>
<td>900-1200mg daily</td>
<td>294-351</td>
</tr>
<tr>
<td>topiramate</td>
<td>100mg daily</td>
<td>336</td>
</tr>
<tr>
<td>sodium valproate</td>
<td>1000-2000mg daily</td>
<td>142-285</td>
</tr>
<tr>
<td>carbamazepine CR</td>
<td>400-1200mg daily</td>
<td>63-188</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>100-200mg daily</td>
<td>36-82</td>
</tr>
<tr>
<td>phenytoin</td>
<td>200-500mg daily</td>
<td>25-61</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs were from eVadis accessed on 24th October 2007. *This is the maximum dose range for levetiracetam

Additional information: budget impact

The net drug budget impact was estimated by the manufacturer as £65k in 2007 (year 1), £142k in 2008 (year 2) and £229k in 2008 (year 3), based on an estimate of 6%, 7% and 8% respectively of newly diagnosed patients with partial onset seizures with or without generalised seizures treated with levetiracetam. Experts considered that this may however be a significant underestimate.
**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 16th November 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, 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**