lacosamide, 50mg, 100mg,150mg and 200mg tablets, 15mg/ml syrup and 10mg/ml solution for intravenous infusion (Vimpat®)

No. (532/09)

UCB Pharma Limited

09 January 2009

The Scottish Medicines Consortium (SMC) 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

lacosamide (Vimpat®) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

The proportion of responders was significantly greater with adjunctive lacosamide treatment compared to placebo. Lacosamide use is restricted to patients with refractory epilepsy and treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy.

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 patients with epilepsy aged 16 years and older.

Dosing information

The recommended starting dose is 50mg twice daily, which should be increased to an initial therapeutic dose of 100mg twice daily after one week. The maintenance dose can be increased weekly by 50mg twice daily to a maximum dose of 200mg twice daily.

Daily dose should be tapered by 200mg/week if treatment has to be discontinued.

No titration is required when converting between oral and intravenous (iv) administration.
The solution for infusion is an alternative for patients when oral administration is temporarily not feasible. It is infused over 15-60 minutes and can be administered iv without further dilution.

Product availability date

September 2008

Summary of evidence on comparative efficacy

The mechanism of action of lacosamide is considered unknown. A dual mode of action is hypothesised: it selectively enhances slow inactivation of voltage-gated sodium channels and interacts with collapsin response mediator protein-2 (CRMP-2), a protein mainly expressed in the central nervous system (CNS) and involved in neuronal differentiation and axonal outgrowth. CRMP-2 is found to be dysregulated in the brain of patients with epilepsy.

Efficacy and safety has been assessed in two phase III placebo-controlled, double-blind multicentre studies of similar design. Patients aged 16 to 70 years were observed to have simple partial-onset seizures and/or complex partial-onset seizures with or without secondary generalisation based on the 1981 International League Against Epilepsy criteria for at least two years despite prior therapy with at least two anti-epileptic drugs (AEDs). Included patients reported on average at least 4 partial-onset seizures per 28 days with seizure-free phases no longer than 21 days in the 8-week period prior to entry into the baseline phase. Patients were required to have a stable dosage regimen of 1 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation.

Both studies had an 8-week baseline phase, a 4- or 6-week (target dose-dependent) forced titration phase, a 12-week maintenance phase and either a 2-week transition for patients who chose to enrol in an open-label extension trial or a 2 or 3 week (target dose-dependent) taper phase for patients discontinuing. Lacosamide was given initially as a 100mg daily dose and patients were titrated by increments of 100mg weekly to a target dose of either 200mg or 400mg daily. Patients were allowed to back titrate 100mg/day once at the end of the titration phase if they experienced intolerable adverse events. The primary efficacy variable was the proportion of responders (at least 50% reduction in seizure frequency from baseline to maintenance phase). In general, randomised patients who also received at least one dose of study medication were included in the safety analyses and those who had at least one post-baseline efficacy assessment were included in the efficacy analysis and considered part of the Full Analysis Set (FAS).

In the first trial, 405 patients were randomised 1:2:1 to placebo, lacosamide 400mg/day or lacosamide 600mg/day and entered a 6 week titration phase. The most frequent concomitant AEDs at baseline and during treatment were levetiracetam, lamotrigine and carbamazepine. The difference in 50% responder rate for the FAS population was statistically significant for both doses compared with placebo; 18% placebo, 38% lacosamide 400mg/day, odds ratio (OR) 2.8 and 41% lacosamide 600mg/day, OR 3.2. The change in partial seizure frequency per 28 days from baseline to the maintenance phase was significant for both lacosamide treatment groups compared to placebo; a percent reduction of 22% for lacosamide 400mg/day and of 25% for lacosamide 600mg/day. A significant increase in the percentage of seizure-free days during the maintenance phase was observed for both doses compared to placebo; 0% (0/104), 2.5% (4/201) and 8.1% (5/97) patients became seizure free in the placebo, 400mg/day, and 600mg/day groups. Overall in both the Clinical Global Impression of Change (CGIC) and Patients Global Impression of Change (PGIC), a significantly greater percentage of patients in the 400mg/day and 600mg/day groups were considered improved at the end of the maintenance phase compared to patients receiving placebo. For all health outcomes assessments, the mean differences between baseline and post-baseline measurements were very small.

In the second trial, 485 patients were randomised 1:1:1 to placebo, lacosamide 200mg/day and lacosamide 400mg/day and entered a 4 week titration phase. The most frequent concomitant AEDs at baseline and during treatment were carbamazepine, valproate and lamotrigine. At baseline in the FAS population, 13%, 50%, and 37% took 1, 2 or 3 concomitant AEDs; 30%, 33%, and 37% had taken 1 to 3, 4 to 6, and 7 or more lifetime AEDs respectively and median seizure frequency was 10, 12, and 10 in the placebo, 200mg/day and 400mg/day groups. The difference in 50% responder rate for the FAS population was not significant for the 200mg/day dose but was statistically significant for lacosamide 400mg/day dose compared with placebo; 26% placebo, 35% lacosamide 200mg/day, OR 1.6 (CI: 1.0 to 2.6) and 41% lacosamide 400mg/day, OR 2.0 (CI:1.2 to 3.2). The change in partial seizure frequency per 28 days from baseline to the maintenance phase was significant for both lacosamide treatment groups compared to placebo; a percent reduction of 14% (CI: 2.2 to 25.1) for lacosamide 200mg/day and of 15% (CI:1.4 to 26.8) for lacosamide 400mg/day. A significant increase in the percentage of seizure-free days during the maintenance phase was observed for the lacosamide 400mg/day group but not for the lacosamide 200mg/day group; 2.1% (3/96), 3.6% (5/107), and 2.4% (3/107) became seizure free in the placebo, 200mg/day, and 400mg/day groups. Overall in both the CGIC and PGIC, although not statistically significant, a greater percentage of patients in the 400mg/day group were considered improved compared with placebo. For all health outcomes assessments, the mean differences between baseline and post-baseline measurements were very small and similar across treatment groups.

Long-term tolerability and efficacy were assessed in a phase II open-label extension trial. A total of 370 patients were enrolled who had previously received lacosamide as adjunctive therapy and completed a trial for the treatment of partial seizures. Investigators could change the dose of up to three concomitant AEDs and/or lacosamide to optimise tolerability and seizure reduction and additionally could taper and discontinue concomitant AEDs to achieve lacosamide monotherapy. During their lifetime 18% of patients had previously tried 1-3 AEDs, 30% had a lifetime use of 4-6 AEDs, and 52% of patients had tried at least seven AEDs. The efficacy of lacosamide in the interim analysis was assessed based on the percentage change from baseline in 28-day seizure frequency and responder rates. A subject was considered a responder if he/she experienced a ≥ 50% reduction in 28-day seizure frequency. The median percentage change from baseline in 28-day seizure frequency for >6 to12 months, >18 to 24 months, and for the treatment period was -48%, -62%, and -46%, respectively. The percentage of patients with ≥50% response to treatment for >6 to 12 months, >18 to 24 months, and for the treatment period was 48%, 61%, and

47%, respectively. Over the entire treatment period there was a similar 50% responder rate across the modal doses ≥200mg/day.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In both pivotal studies adverse events (AEs) among all treatment groups most commonly affected the central and peripheral nervous system and the gastrointestinal system. Dose related AEs included dizziness, nausea, fatigue, ataxia, vision abnormal, diplopia, vertigo and nystagmus. Adverse events were reported to be of mild or moderate intensity and were generally higher in the forced titration phase compared to the maintenance phase.

Lacosamide had no effect on laboratory, vital signs or body weight variables in either trial and the incidence of AEs including somnolence, rash, cognitive impairment and behaviour abnormalities typical of many AEDs was low. The rate of early treatment discontinuation due to AEs in patients treated was 15% with lacosamide versus 5% with placebo. There were two deaths, one in each trial, both unrelated to lacosamide. Evaluation of ECG data showed that increasing plasma concentrations of lacosamide were associated with a small prolongation of the PR interval.

In the long term extension trial, of the 370 patients in the safety set, 88%, 77%, and 61% patients had more than 6, 12, or 24 months of exposure to lacosamide respectively. The most common AEs were dizziness (37%), headache (18%), and abnormal co-ordination (13%). There were 4 deaths; none were considered related to lacosamide. Serious AEs reported in more than 1% of patients included convulsion (4.6%) and status epilepticus (1.6%). A total of 33 patients (8.9%) discontinued treatment due to AEs.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

There is no comparative evidence for lacosamide against other anti-epileptic drugs licensed as adjunctive therapy for this indication.

Despite patients having a high level of pre-treatment and high frequency of baseline seizures (both predictors of a poor response), addition of lacosamide to standard treatment achieved significantly higher 50% responder rates versus addition of placebo for both the 400mg/day and 600mg/day doses and a significantly greater reduction in seizure frequency from baseline to maintenance phase in 200mg/day, 400mg/day, and 600mg/day doses. The European Medicines Agency (EMEA) noted that the effects of lacosamide on these outcome measures were similar across the range of lacosamide doses used as well as for the lifetime levels of pre-treatment with different AEDs.

From the interim results of the extension trial, primarily a safety trial, the overall percentage of patients with ≥50% response to treatment and the overall median percentage change from baseline in 28-day seizure frequency were maintained over time for patients completing >24 months. Lacosamide was generally well tolerated with <10% discontinuing treatment over approximately 5.5 years.

Pivotal trials involved the use of a 600mg/day dose; this showed similar efficacy to the 400mg/day dose but an inferior safety profile; the 600mg/day dose was withdrawn from the licensing application.

Dizziness was the most common AE in both pivotal trials, particularly in the titration phases, and in the extension trial. The Summary of Product Characteristics (SPC) notes that the occurrence of accidental injury or falls can increase and patients should exercise caution until they are familiar with the effects of lacosamide. Adverse events were more frequent in the titration phase in the studies but the titration technique used may not reflect clinical practice where titration is dependent on response and tolerability.

The SPC notes that lacosamide should be used with caution in patients with known cardiac conduction problems or severe cardiac disease or when lacosamide is used in combination with products known to be associated with PR prolongation.

The SPC notes that lacosamide generally has a low interaction potential. Caution is needed when starting or stopping potent enzyme inducers in patients on lacosamide. There are no drug-drug interactions with ethinyloestradiol, levonorgestrel and progesterone.

The EMEA noted that the risk management plan approved by the Committee for Medicinal Products for Human Use (CHMP) for lacosamide will include monitoring of cardiac and psychiatric events. Enhanced pharmacovigilance measures will be applied to cardiovascular events related to PR prolongation. The EMEA noted that a post approval safety study will be conducted.

Lacosamide solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The SPC states that conversion between oral and intravenous administration can be done directly without titration.

Clinical experts have advised that they expect lacosamide to have a useful role in patients with refractory epilepsy.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing adjunctive treatment with lacosamide with standard AED therapy in patients with refractory epilepsy. This is a niche proposed by the manufacturer within the licensed indication. A decision tree model was used to estimate costs and benefits over a two year time horizon and used clinical data based on a pooled analysis of the two pivotal trials. In the base case, the manufacturer estimated a cost per Quality Adjusted Life Year (QALY) of £20,017 based on an increased cost of £757 and a QALY gain of 0.038. The cost per seizure avoided was estimated to be £112.

The economic model used was relatively simple and was a suitable way of modelling the disease. The time horizon was appropriate and avoids extensive extrapolation from the clinical trial results over a long time horizon, although it was still necessary to extrapolate beyond the end of the trial. Standard AED therapy was the appropriate comparator given the niche proposed and responses from SMC clinical experts confirmed this.

The utility values used in the analysis may overestimate the utility gain associated with a 50% reduction in seizure frequency when compared with values in the literature for comparable health states. This may bias the analysis in favour of the more effective treatment, which is lacosamide. The sensitivity analysis highlighted the utility values for

seizure reduction and withdrawal health states as being important drivers of the model and showed that when the seizure reduction utility value was reduced by 10%, the cost per QALY increased to around £29,000. However, the utility values used in the model have been accepted in previous epilepsy submissions to SMC.

Overall, despite the concerns about the utility values, the economic case has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Epilepsy UK

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN); Guideline No.70. Diagnosis and Management of Epilepsy in Adults, published April 2003. SIGN states that the side effect and interaction profiles should direct the choice of drug for the individual patient. When two AEDs have failed as monotherapy improvement in seizure control may be obtained by combining two or at most three AEDs. For drug-resistant focal epilepsy, vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine and levetiracetam were recommended as equally effective adjunctive therapies, although the development of concentric visual field defects with vigabatrin were highlighted as a safety concern.

National Institute for Health and Clinical Excellence (NICE); Clinical Guideline 20. The Epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care; published October 2004. This was planned for review in October 2008. NICE recommends that treatment should be individualised to achieve the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.

NICE; Technology Appraisal 76. Newer drugs for epilepsy in adults; published March 2004 and Clinical Guideline 20 both state that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. The newer AEDs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin are recommended for patients who have not benefited from or are unsuitable for treatment with older AEDs such as carbamazepine or sodium valproate.

Additional information: previous SMC advice

Following an abbreviated submission, the Scottish Medicines Consortium issued advice in October 2006: levetiracetam 500mg/5ml concentrate for infusion is accepted for use in NHS Scotland as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy. It is an alternative when oral administration is temporarily not feasible in patients for whom levetiracetam is an appropriate anticonvulsant.

Following a full submission, the Scottish Medicines Consortium issued advice in December 2005 that zonisamide (hard capsules; 25mg, 50mg and 100mg) is accepted for restricted use within NHS Scotland as adjuctive therapy in adult patients with partial seizures, with or without secondary generalisation. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and 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 contra-indications, interaction or poor tolerance.

Following a full submission, the Scottish Medicines Consortium issued advice in January 2005: pregabalin (capsules; all strengths) is accepted for restricted use within NHS Scotland as adjunctive therapy in adults with partial seizures with or without secondary generalisation. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and 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 contra-indications, interaction or poor tolerance.

Following two abbreviated submissions, the Scottish Medicines Consortium issued advice in January 2005: levetiracetam 100mg oral solution and 750mg tablets are accepted for restricted use in NHS Scotland as 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 antiepileptic drugs, as listed below.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
lacosamide	**400mg daily orally**	**1,874**
topiramate	800mg daily orally	2,839
zonisamide	500mg daily orally	2,038
levetiracetam	3000mg daily orally	1,861
tiagabine	^45mg daily orally with enzyme inducer	1,421
	30mg daily orally without enzyme inducer	947
oxcarbazepine	2400mg daily orally	1,134
gabapentin	^3600mg daily orally	1,011
pregabalin	600mg daily orally	837
clobazam	60mg daily orally	709
carbamazepine	*30mg/kg daily orally	206
sodium valproate	^^2.5g daily	137
lamotrigine	200mg daily orally with valproate	71
	400mg daily orally, without valproate; with addition of inducers of lamotrigine glucuronidation	122
phenytoin	^^^500mg daily	61

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21 October 2008. Costs are calculated for the maximum recommended maintenance dose using twice /^three times daily dosing and solid dosage forms. It was not always possible for the morning and evening doses to be equally divided; ^^the 2.5 g dose was split 1.5g am and 1.0g pm; ^^^ the 500mg dose was split 300mg am and 200mg pm. *costs calculated for a 70kg adult.

Additional information: budget impact

The manufacturer estimated a net drug budget impact of £9k in year 1 rising to £371k in year 3. The number of eligible patients was estimated to be 10,256 in year 1 rising to 10,318 in year 3. Market share was estimated to be 0.2% in year 1 rising to 3.6% in 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 14 November 2008.

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.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted reference was supplied with the submission.

European Medicines Agency (EMEA). European Public Assessment Report (EPAR) for lacosamide (Vimpat). Published.17.09.08. http://www.emea.europa.eu/humandocs/Humans/EPAR/vimpat/vimpat.htm