MTRAC
Midlands Therapeutics Review and Advisory Committee

VERDICT & SUMMARY

Lacosamide

(Vimpat®▼)

As add-on therapy for the treatment of partial-onset seizures

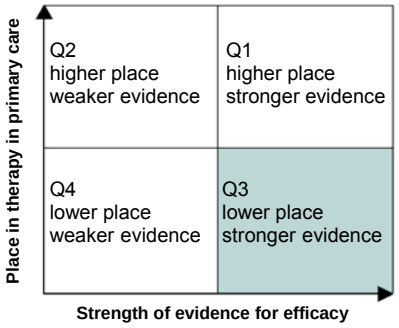
Committee's Verdict: CATEGORY B (Q3) **BNF: 4.8.1**

Treatment with lacosamide should be initiated and stabilised within secondary care. It is then appropriate for GPs to prescribe lacosamide over the longer term.

***Category B**: suitable for restricted prescribing under defined conditions*

Q3 rating: The evidence for the efficacy of lacosamide was considered to be relatively strong, based on three double-blind, randomised controlled trials (RCTs) comparing lacosamide with placebo. Compared with placebo, treatment with lacosamide 400 mg/day was associated with a greater decrease in seizure frequency, with a higher proportion of patients experiencing at least a 50% decrease in seizure frequency; evidence for efficacy was weaker for the 200 mg/day dose. As a number of established alternative therapies exist, lacosamide is considered to have a relatively low place in therapy.

The Q rating relates to the drug's position on the effectiveness indicator grid. *The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.*



MTRAC reviewed lacosamide because it is a new product with potential for prescribing in primary care.

Licensed indication

Lacosamide is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.[1]

Background information

Epilepsy is one of the most common neurologic disorders, characterised by recurrent, spontaneous seizures, caused by an abnormal excessive or synchronous neuronal activity in the brain.[2]

Epileptic syndromes fall into two broad categories: generalised and partial-onset (or focal) seizures. Generalised seizures begin simultaneously in both cerebral hemispheres. In contrast, partial-onset seizures originate in one or more localised foci.[3] During a simple partial-onset seizure, consciousness is unimpaired. If discharge spreads and affects larger areas of the brain, consciousness may be impaired or lost, and this type of seizure is known as a complex partial-onset seizure. In partial-onset seizures, epileptic activity may also become secondarily generalised, spreading through the brain.

The National Institute for Health and Clinical Excellence (NICE) guideline on the management of epilepsy quoted a UK prevalence figure for active epilepsy of five to ten cases per 1,000.[4] Partial-onset seizures are the most common type of epilepsy, representing approximately 60% of cases.[5]

NICE guidance from 2004, which predates the introduction of lacosamide, recommended that newer anti-epileptic drugs (AEDs) should be used in patients refractory to treatment with older AEDs or for whom older drugs are contraindicated.[6]

It is estimated that approximately 70% of patients diagnosed with epilepsy achieve complete seizure control with a single AED, the remaining 30% often requiring combinations of AEDs.[6] The following newer AEDs are licensed for use as adjunctive agents in the treatment of partial-onset seizures: pregabalin, tiagabine, vigabatrin, zonisamide and lacosamide.[7]

Clinical efficacy

Two published RCTs have investigated adjunctive therapy with lacosamide in patients with uncontrolled partial-onset seizures. Lacosamide was compared with placebo when added to either one or two AEDs (trial SP667, n = 418)[8] or one to three AEDs (trial SP755, n = 485).[9] In both trials, patients entered an eight-week baseline phase, followed by randomisation to treatment with placebo, lacosamide 200 mg/day, 400 mg/day or 600 mg/day (an unlicensed dose, trial SP667 only). Following titration, the target dose was administered during a 12-week, fixed-dose phase. Two primary outcomes were measured, both based on the change in seizure frequency: 1) the median

percentage change in partial-onset seizure frequency from the baseline period to the fixed-dose period and 2) the 50% responder rate (the percentage of patients with ≥ 50% decrease in seizure frequency during the fixed-dose period compared with the baseline period).

In both trials, treatment with 400 mg/day lacosamide (the maximum recommended dose) resulted in a significantly greater reduction from baseline in seizure frequency during the fixed-dose period compared with placebo ($p \leq 0.05$; median reductions of 36% to 39% with lacosamide 400 mg/day *vs.* 10% to 21% with placebo). The 50% responder rate was significantly higher with lacosamide 400 mg/day in both trials compared with placebo ($p \leq 0.01$). At a dose of 200 mg/day, a significantly greater reduction in seizure frequency was reported in one of the two trials ($p \leq 0.05$).[9] In neither trial was the 50% responder rate significantly higher than with placebo at this dose of lacosamide (although a significantly higher 50% responder rate was reported in an analysis of pooled data from the two trials).[5]

Statistical significance for both of these primary outcomes was also demonstrated for the 400 mg/day dose in a third, as yet, unpublished trial of similar design.[5,10]

In both published trials, patients in the lacosamide 400 mg/day group experienced a greater number of seizure-free days during the fixed-dose phase compared with the placebo group ($p \leq 0.01$), and the 75% responder rate was significantly greater in the one trial reporting this outcome ($p = 0.002$).[8]

Adverse effects

Dose-related adverse events (AEs) in the published RCTs included dizziness, nausea, vomiting, fatigue, ataxia, abnormal vision, diplopia and nystagmus.[8,9] The Summary of Product Characteristics (SPC) cites dizziness as the most common AE leading to treatment withdrawal. See the SPC for further information on adverse events.[1]

Additional information

- Oral lacosamide should be initiated at 50 mg twice daily, increasing to 100 mg twice daily after one week. The dose may be incrementally increased up to 200 mg twice daily. Discontinuation should be performed gradually.
- Lacosamide is contraindicated with patients with known second- or third-degree atrioventricular block. Prolongations in the PR interval have been observed in clinical studies. As with other AEDs, patients should be monitored for signs of suicidal ideation and behaviour.
- At current prices, one year's treatment with lacosamide 100 mg and 200 mg twice daily costs £940 and £1,879 respectively.

References

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Launch date: September 2008 *Manufacturer: UCB Pharma Ltd* *EU/1/08/470/001,4,5,7,8,11,14*

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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NO GUIDANCE WAS AVAILABLE FROM NICE FOR LACOSAMIDE AT THE TIME OF ISSUE OF THIS VERDICT

Date: September 2009

VS09/11