

Lacosamide: new adjunctive treatment for partial seizures

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KEY POINTS

- lacosamide (Vimpat) is a novel antiepileptic drug (AED) licensed as adjunctive treatment for partial seizures with or without secondary generalisation in patients aged 16 or older
- available as tablets – 50mg (14=£9.01), 100mg (14=£18.02, 56=£72.08), 150mg (14=£27.03, 56=£108.12) and 200mg (56=£144.16) – a syrup (15mg/ml, 200ml=£38.61) and a solution for iv administration (10mg/ml, 20ml=£29.70)
- does not appear to affect the metabolism of other AEDs but enzyme-inducing AEDs such as phenytoin may reduce plasma levels of lacosamide
- in randomised trials of 12 weeks' treatment in patients with difficult-to-control seizures, lacosamide reduced seizure frequency by about 40 per cent (vs 10-20 per cent with placebo) and increased the proportion of patients with 50 per cent reduction in seizure frequency to about 40 per cent (vs 23 per cent with placebo)
- the commonest adverse effects in clinical trials were dizziness, headache, nausea, diplopia and vomiting
- lacosamide may increase the PR interval; it is contraindicated in patients with second- or third-degree atrioventricular (AV) block and those with allergy to nuts or soya
- its place in the treatment of refractory epilepsy will become clearer when it is more widely prescribed to a broader group of patients, including those with less severe epilepsy



Lacosamide (Vimpat), which is hypothesised to have a novel dual mode of action, is a new antiepileptic drug licensed as adjunctive therapy for partial seizures. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Yvonne Hart comments on its place in treatment.

In 2004, the National Institute for Health and Clinical Excellence (NICE) recommended that seizure control in patients with epilepsy should ideally be obtained with antiepileptic drug (AED) monotherapy.¹ Adjunctive therapy was recommended when monotherapy did not achieve freedom from seizures and the treatment strategy of choice was that providing the best balance of reducing seizure frequency and maximising tolerability. Newer AEDs were recommended when older agents

such as phenytoin, valproate and carbamazepine had failed or were unsuitable.²

The use of newer AEDs has increased in recent years. In England, primary-care prescribing of newer AEDs (for all indications) increased from 27 to 38 per cent of total volume between 2004 and 2007.^{3,4} This was largely due to the introduction of pregabalin (Lyrica), which is also licensed for the treatment of pain, and increased prescribing of gabapentin, lamotrigine, levetirac-

etam (Keppra) and topiramate (Topamax).

In a recent UK study of patients with partial seizures, monotherapy with carbamazepine or newer AEDs achieved seizure freedom for one year in approximately 75 per cent of patients after five years.⁵ Older studies found that approximately half of newly-diagnosed patients became seizure free with their first or a single AED^{6,7} and a further 14 per cent did so with a second or third drug;⁶ about 70 per cent of patients were treated with monotherapy.^{6,7}

The technology

Lacosamide is an analogue of the amino acid D-serine, which modulates N-methyl D-aspartate (NMDA) receptor function. Its mechanism of action is uncertain but it may involve stabilising hyperexcitable neuronal membranes by inactivation of voltage-gated sodium channels and modulating neuronal differentiation and axonal outgrowth.

Lacosamide is licensed as adjunctive therapy of partial-onset seizures with or without secondary generalisation in patients aged 16 or over. Treatment should be initiated at a dose of 50mg twice daily and increased to 100mg twice daily after one week; the dose should be adjusted in increments of 50mg twice daily up to a maximum of 200mg twice daily.

No dose adjustment is necessary for older people or patients with mild-to-moderate renal or hepatic impairment.

Lacosamide is available as tablets and a syrup, and as a solution for intravenous administration when oral dosing is not possible.

Trials suggest that administration of lacosamide does not affect, nor is it affected by, concurrent use of carbamazepine or valproate (though pharmacokinetic modelling predicts that carbamazepine and other enzyme inducers may reduce blood levels by 25 per cent).

Lacosamide is contraindicated in patients with allergy to peanut or soya and, because it may prolong the PR interval, in those with second- or third-degree AV block. Safety during pregnancy is not known.

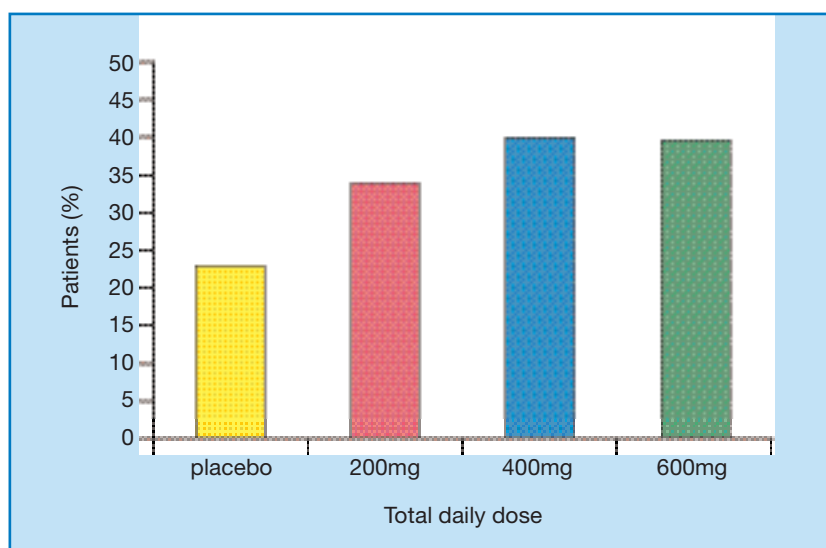


Figure 1. Proportion of patients with 50 per cent reduction in seizure frequency (pooled analysis of key trials)⁸

Clinical trials

Three placebo-controlled trials involving a total of 944 patients provide key efficacy data for oral lacosamide,⁸ of which one has been published.⁹ These trials were of similar design and included adults with difficult-to-control simple-partial or complex-partial seizures with or without secondary generalisation of at least two years' duration despite treatment with at least two AEDs.

In addition, patients were required to have at least four partial seizures per 28 days in the eight weeks before treatment and no seizure-free interval exceeding 21 days while on stable treatment with up to three AEDs.

Treatment with lacosamide was initiated at a dose of 50mg twice daily and increased in increments of 50mg twice daily to target doses of 100, 200 or 600mg twice daily;

the dose could be reduced by 100mg per day in the event of adverse effects.

The primary end-point was the proportion of patients with a 50 per cent reduction in seizure frequency at the end of a 12-week treatment period.

In a pooled analysis of these trials, all doses of lacosamide were significantly superior to placebo in increasing the proportion of patients with 50 per cent reduction in seizure frequency, but there was no difference between 200mg and 300mg twice-daily doses (see Figure 1).

Lacosamide did not increase the proportion of patients seizure free during maintenance treatment (3.6 per cent at 200mg per day, 2.4 per cent at 400 mg per day *vs* 2.1 per cent with placebo). The highest dose was also associated with more adverse effects and has therefore



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not been approved. Median seizure frequency was reduced by approximately 40 per cent.

The response to treatment was not affected by the number of AEDs previously used. Simple-partial seizures were not significantly reduced by lacosamide, perhaps because complex-partial and generalised seizures were converted to simple-partial seizures.⁸

Adverse effects

Safety data pooled from double-blind placebo-controlled trials of lacosamide show that the frequency of adverse effects was dose related and greatest during the dose-titration phase.⁸ The commonest were dizziness (placebo, 8 per cent; 100mg twice daily, 16 per cent; 200mg twice daily, 30 per cent), headache (9, 11 and 14 per cent respectively), nausea (4, 7 and 11 per cent), diplopia (2, 6 and 10 per cent) and vomiting (3, 6 and 9 per cent).

Overall, 17 per cent of patients discontinued lacosamide due to adverse effects compared with 5 per cent taking placebo.

First-degree AV block was reported in 0.7 per cent of patients treated with 100mg twice daily but not at a dose of 200mg twice daily; the incidence of syncope was similar to that among patients taking placebo (0.1 vs 0.3 per cent).¹⁰ Chest pain was reported rarely but more frequently with lacosamide than placebo; its aetiology was unknown. The long-term tolerability of lacosamide is being evaluated in several extension trials.⁸

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Place in therapy

Lacosamide, which is licensed as adjunctive treatment for partial seizures with or without secondary generalisation in patients aged 16 or over, is hypothesised to have a novel dual mode of action: selectively enhancing slow inactivation of voltage-gated sodium channels and interacting with CRMP-2 (collapsin response mediator protein-2), which is involved in neuronal differentiation and axonal outgrowth.

The literature suggests that the chance of someone with partial epilepsy that has failed to respond to the first two or three AEDs becoming seizure free with the introduction of the next is small, possibly of the order of 4 per cent,⁴ and the value of marketing yet

more novel antiepileptic drugs is sometimes questioned. The justification is two-fold.

Firstly, some patients do have a dramatic response to the next AED, and for those individuals who become seizure free after years of multiple daily seizures, the change to their lives is immeasurable.

Secondly, the side-effects of medication play a significant role in determining its acceptability to patients, and weight gain, weight loss, altered thinking, depression, tiredness and dizziness are all reasons for patients discontinuing medication that is effective in terms of seizure control. Prescribing for many patients with refractory epilepsy then becomes very much a matter of tailoring a drug to the particular patient.

Prelicensing regulatory trials, carried out in patients with severe

partial epilepsy, suggest that the efficacy of lacosamide is similar to that of other new AEDs, with the commonest adverse effects being dizziness, headache, nausea, vomiting and double vision.

The true test will come when it is more widely prescribed to a broader group of patients, including those with less severe epilepsy than those taking part in the preliminary trials, and both its efficacy and the real extent of its adverse effects will determine its place in the armamentarium of drugs for treating refractory epilepsy.

Reference

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