

Eslicarbazepine: new adjunctive treatment for partial epilepsy

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KEY POINTS

- eslicarbazepine acetate (Zebinix) is an antiepileptic drug licensed as adjunctive treatment for partial epilepsy, with or without secondary generalisation, in adults
- the dose for maintenance therapy is 800 or 1200mg once daily; available as 800mg tablets, 30=£154.20
- potentially clinically significant interactions have been identified with phenytoin, barbiturates and carbamazepine but not other AEDs
- in 12-week randomised trials, eslicarbazepine 800 or 1200mg per day added to treatment with one or two other AEDs reduced seizure frequency by about one-third
- approximately 30-40 per cent of patients experienced a ≥ 50 per cent reduction in seizure frequency compared with 20 per cent taking placebo
- adverse events, which include dizziness, headache, diplopia and somnolence, are more likely to cause treatment discontinuation at 1200mg per day
- initial data are encouraging for its use in refractory epilepsy, but based on small numbers of patients



Eslicarbazepine acetate (Zebinix) is a new antiepileptic drug licensed as adjunctive treatment for partial-onset seizures. In our New products review, Steve Chaplin presents the clinical data relating to efficacy and adverse effects, and Dr Andrew Kelso discusses its potential role in epilepsy treatment.

Guidance on the management of epilepsy published in 2004 and 2005 recommends that treatment with a combination of antiepileptic drugs (AEDs) should be considered when monotherapy with two AEDs does not achieve freedom from seizures; subsequent treatment then depends on the balance of benefit and risk for each individual.¹⁻³

The choice of AED depends on seizure type, concomitant medication, co-morbidity, age and sex.⁴ Current prescribing advice states that carbamazepine, lamotrigine, oxcarbazepine (Trileptal) and sodium valproate are the AEDs of choice for partial seizures.⁴ Second-line drugs include clobazam (Frisium), gabapentin,

levetiracetam (Keppra), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax) and zonisamide (Zonegran).⁴ All are used as adjunctive therapy.

The technology

Eslicarbazepine acetate (Zebinix) is a prodrug of eslicarbazepine, an active metabolite of oxcarbazepine.⁵ Like carbamazepine and oxcarbazepine, it is believed to prevent repetitive neuronal firing by blocking voltage-gated sodium channels. It is licensed as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

The recommended dose of eslicarbazepine acetate is initially

400mg once daily, increasing to 800mg once daily after one to two weeks, then if necessary to a maximum of 1200mg once daily. Experience in older people is limited and no recommendation for dose adjustment is made.

Eslicarbazepine and its metabolites are eliminated mainly in the urine; the dose should be reduced when creatinine clearance is < 60 ml per minute. No dose adjustment is required for mild to moderate hepatic impairment.

Eslicarbazepine acetate is contraindicated in patients with severe impairment of renal or hepatic function and should not be co-administered with oxcarbazepine. Its safety during pregnancy is

	Placebo	Eslicarbazepine acetate		
		400mg/day	800mg/day	1200mg/day
mean seizure frequency per 4 weeks	7.6	6.7	5.7	5.4
median relative reduction in seizure frequency vs baseline	16%	26%	36%	45%
responders (%)*	20	23	34	43
seizure free (%)	2	2	4	8
* $\geq 50\%$ reduction in seizure frequency from baseline				

Table 1. Efficacy of 12 weeks' maintenance therapy with adjunctive eslicarbazepine acetate 400mg, 800mg and 1200mg daily (after ref 7)

unknown but adverse effects were found in animal models.

Eslicarbazepine acetate inhibits CYP2C19 enzymes and weakly inhibits CYP3A4 and UDP-glucuronyl transferases. Potentially clinically significant interactions have been identified with phenytoin (increased phenytoin levels) and barbiturates and carbamazepine (reduced eslicarbazepine levels); no clinically significant interactions with lamotrigine, topiramate, valproate and levetiracetam have been identified.⁵

Eslicarbazepine acetate reduces the efficacy of combined oral contraceptives and warfarin.⁶

Clinical trials

Three randomised, double-blind, placebo-controlled trials have evaluated fixed doses of eslicarbazepine acetate (400, 800 or 1200mg per day) as adjunctive therapy in adults with partial seizures, with or without secondary generalisation, despite stable treatment with one to three AEDs.⁷⁻⁹

The primary end-point was seizure frequency per four weeks

during 12 weeks' maintenance treatment. Each study was followed by non-blinded one-year extension phases.¹⁰⁻¹²

Two trials have been published in full.^{7,9} In the first,⁷ 402 patients (mean age 37-41; mean duration of epilepsy 19-23 years) were randomised to placebo or treatment with eslicarbazepine acetate. About two-thirds were taking two other AEDs and most of the remainder took one other AED (carbamazepine, 55-60 per cent; lamotrigine and valproate, 2-30 per cent; levetiracetam 8-21 per cent).

Eighteen per cent of patients did not complete the trial, most often due to adverse events (placebo 5 per cent *vs* 4, 8 and 20 per cent with eslicarbazepine acetate 400, 800 and 1200mg per day respectively).

The mean seizure frequency per four weeks was 7.6 with placebo and 5.7 and 5.4 with eslicarbazepine 800 and 1200mg per day respectively (see Table 1). Responder rates (proportion of patients experiencing at least a 50 per cent reduction in seizure fre-

quency from baseline) were 20, 34 and 43 per cent respectively. All differences from placebo were statistically significant. Few patients became free of seizures (2, 4 and 8 per cent respectively).

Responder rates were similar with eslicarbazepine acetate but lower with placebo in the subgroup of patients taking carbamazepine.

There appeared to be no clear differences in response according to type of seizure (simple, complex or generalising partial seizures).

Seizure exacerbation by ≥ 25 per cent occurred in fewer than 12 per cent of patients taking eslicarbazepine acetate and 22 per cent with placebo.

In the second trial,⁹ 253 patients (mean age 36-38; mean duration of epilepsy 22-24 years) were randomised to eslicarbazepine acetate 800 or 1200mg per day or placebo. About three-quarters were taking two other AEDs and one-fifth were taking one (carbamazepine 56 per cent, valproate 31 per cent). Twenty-three per cent of patients discontinued treatment, due to adverse effects in about one-third of cases.

Over 12 weeks, mean seizure frequency per four weeks was significantly lower with eslicarbazepine acetate than placebo (5.7 and 5.5 *vs* 7.3). The responder rate was significantly higher than with placebo (23 per cent) for eslicarbazepine acetate 1200mg per day (38 per cent) but not 800mg per day (35 per cent).

The proportions of patients seizure free were not significantly different (placebo, 1.2 per cent; eslicarbazepine acetate 800mg per day and 1200mg per day, 4.8 and 3.9 per cent).

Seizure exacerbation was reported by 23 per cent of patients taking placebo and 17 and 13 per cent of those taking eslicarbazepine acetate.

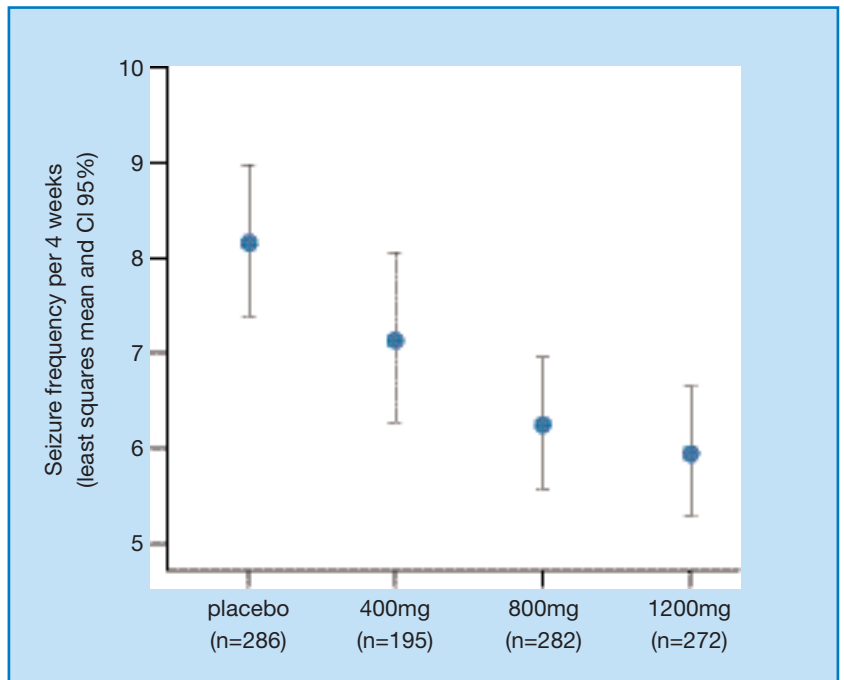


Figure 1. Efficacy of 12 weeks' treatment with eslicarbazepine acetate in a pooled analysis of three randomised trials (after ref 13)

A separate analysis by concomitant AED was not reported.

These findings are consistent with the limited data available from the unpublished trial (n=393)⁸ and a pooled analysis of all three trials (see Figure 1).¹³

In the nonblinded phase of these trials (n=314, 325 and 194),¹⁰⁻¹² 70-80 per cent of patients completed a year's treatment. The mean dose of eslicarbazepine acetate was 877-917mg per day; 65-82 per cent of patients were taking two other AEDs and 18-34 per cent were taking one other AED.

The median relative reduction in seizure frequency over the last 12 weeks was approximately 40 per cent^{10,11} or, averaged over the entire year, 58 per cent.¹² Responder rates were 38-56 per cent and the proportion of patients who were free of seizures was 11-18 per cent.

These trials also reported significant improvements in quality-of-life scores and a reduction in scores of depression after one year

compared with baseline (but lacked a placebo comparator).¹⁴⁻¹⁶

Adverse effects

In the published trials,^{7,9} the overall frequency of adverse events was 31-39 per cent with placebo and approximately 44, 50 and 61 per cent with eslicarbazepine acetate 400, 800 and 1200mg per day.

The frequency of the commonest adverse events with 800 and 1200mg doses was similar, but the higher dose was associated with more events leading to discontinuation (8 *vs* 11 and 20 per cent).

The commonest adverse events at maintenance doses were dizziness (14-30 per cent), headache (about 10 per cent), diplopia (4-11 per cent) and somnolence (9-14 per cent). No cardiovascular effects were reported.

In the pooled analysis, four patients (all also taking carbamazepine) developed hyponatraemia and three developed hypernatraemia.¹³

The commonest adverse events were approximately twice as frequent in the open-label phase of one trial,¹¹ but no new adverse events were reported. The rates of discontinuation due to adverse events were 3.5,¹⁰ 4.6¹² and 11¹¹ per cent.

References

1. NICE. *The epilepsies*. CG20. October 2004.
2. NICE. *Newer drugs for epilepsy in adults*. TA76. March 2004.
3. SIGN. *Diagnosis and management of epilepsy in adults*. Guideline No. 70. April 2003 (updated 2005).

4. Joint Formulary Committee. Control of epilepsy. In: *British national formulary*. 58th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; September 2009 <http://bnf.org/bnf/bnf/current/3575.htm>.
5. European Medicines Agency. *Zebinix European public assessment report*. February 2009. www.emea.europa.eu/humandocs/PDFs/EPAR/zebinix/H-988-en6.pdf.
6. Eisai Ltd. *Zebinix summary of product characteristics*. October 2009.
7. Elger C, et al. *Epilepsia* 2009;50:454-3.
8. Hufnagel A, et al. *Epilepsia* 2009;50:suppl 4:104.
9. Gil-Nagel A, et al. *Acta Neurologica*

- Scand* 2009;120:281-7.
10. Halász P, et al. *Epilepsia* 2008;49 suppl 7:s435-6.
11. Gabbai AA, et al. *Epilepsia* 2008;49 suppl 7:s432-3.
12. Lopes-Lima J, et al. *Epilepsia* 2008;49 suppl 7:s441-2.
13. Elger C, et al. *Epilepsia* 2008;49 suppl 7:s428.
14. Cramer J, et al. *Epilepsia* 2008;49 suppl 7:s426-7.
15. Soares-da-Silva P, et al. *Epilepsia* 2008;49 suppl 7:s455-6.
16. Pereira H, et al. *Epilepsia* 2008;49 suppl 7:s446-8.

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Place in therapy

Current data show that 30-40 per cent of patients with epilepsy have seizures that remain uncontrolled by medication. Once seizures have failed to come under control with two AEDs in monotherapy, the chance of any subsequent AED achieving seizure freedom is extremely small.¹ Epilepsy has established mortality² and patients with refractory seizures can have poor quality of life.³

The advantages and disadvantages

Eslicarbazepine acetate (according to prelicensing data) can be titrated quickly and easily.⁴ Any monotherapy has obvious theoretical and practical benefits. Preliminary data indicate that it has good retention (up to 78 per cent after one year) and rash and hyponatraemia seem to have a low incidence, although they still occur.

In terms of seizure control, it is better than placebo in refractory patients, with seizure reduction data comparable to those of other agents⁴ and quality of life improvements.⁵

There are still reports of dizziness, somnolence and nausea, also

observed with many other AEDs. The apparently low incidence of rash and hyponatraemia needs active monitoring, as the numbers of patients treated, and reported cases, are still small.

Although eslicarbazepine is said to have fewer drug interactions than other AEDs, decreased effectiveness of warfarin is reported, which could have potentially fatal consequences. Therefore, vigilance regarding drug interactions is still important.

What is its place in our choice of AEDs?

Eslicarbazepine acetate may have a place in the treatment of refractory epilepsy (and ultimately in monotherapy), but further experience is essential before widespread use can be recommended. The initial data are encouraging, but based on small numbers of patients (around 1000). However, none of the medications currently available have changed the proportion of drug-refractory patients, and quality-of-life factors have rarely been considered to date.

Potential opportunities for this medication, based upon the prelicensing data, might include patients who have unacceptable

side-effects on carbamazepine, patients overly sensitive to rarer side-effects, eg hyponatraemia in older patients, and patients with poor compliance or quality-of-life gains.

However, further specific evidence of benefit in these subgroups is necessary before these recommendations can be substantiated, either from postmarketing surveillance or – based on the Standard and New Antiepileptic Drugs (SANAD) trial model – specifically designed pragmatic trials.

References

1. Kwan P, et al. *New England Journal of Medicine* 2000;342:314-9.
2. Forsgren L, et al. *Epilepsia* 2005;46 (s11):18-27.
3. Birbeck GL, et al. *Epilepsia* 2002;43: 535-8.
4. Elger C, et al. *Epilepsia* 2009;50(3): 454-63.
5. Cramer J, et al. *Epilepsia* 2008;49 (Suppl 7):s426-7.

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