Scottish Medicines Consortium

eslicarbazepine acetate 800mg tablets (Zebinix®) No. (592/09)
Eisai Ltd.

04 December 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

eslicarbazepine acetate (Zebinix®) is not recommended for use within NHS Scotland for adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

The efficacy of eslicarbazepine acetate in terms of the reduction in standardised seizure frequency was demonstrated in three 12-week placebo-controlled studies. There are no clinical studies comparing eslicarbazepine acetate to other anti-epileptic drugs, and a mixed-treatment indirect comparison was undertaken to show equivalent efficacy of eslicarbazepine acetate and a single other anti-epileptic drug.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

Dosing information

The recommended starting dose is eslicarbazepine acetate 400mg once daily which should be increased to 800mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1,200mg once daily.

Product availability date

26 October 2009

Summary of evidence on comparative efficacy

Eslicarbazepine acetate is a new member of the dibenzazepine family of antiepileptic drugs (AEDs) that includes carbamazepine (first generation) and oxcarbazepine (second generation).

The submitting company has requested that the Scottish Medicines Consortium consider the use of this product in a sub-set of the licensed indication, as a treatment option in patients who are highly refractory and heavily pre-treated who remain uncontrolled on existing AED combination options.

Three phase III randomised placebo-controlled studies have been conducted in adult patients with simple or complex partial seizures with or without secondary generalisation for at least 12 months before screening. In addition patients had to be receiving one to two AEDs (one to three in the second study), on a stable dose regimen for at least two months before screening and to have had at least four partial-onset seizures over the two four-week periods of the baseline phase, with no seizure-free interval greater than 21 consecutive days. The studies included an eight-week baseline phase (which was single-blind, placebo controlled in the first study and observational in the other studies) followed by the double-blind phase, which included a two-week titration phase, when eslicarbazepine acetate was titrated to the randomised dose, and a 12-week maintenance phase. Two studies included a four-week tapering-off phase.

Patients were randomised equally to placebo, eslicarbazepine acetate 400mg (in the first and second studies only), 800mg or 1,200mg in addition to their usual AED treatment regimen. Oxcarbazepine was not permitted as a concomitant AED as it has common metabolites with eslicarbazepine acetate. The primary endpoint was seizure frequency over the 12-week maintenance period standardised to frequency per four weeks. Secondary endpoints included responder rate (proportion of patients with ≥50% reduction in seizure frequency), seizure freedom (proportion of patients with 100% reduction in seizure frequency) and retention rate (proportion of patients remaining on treatment). The primary efficacy analysis was carried out for the intention to treat (ITT) population defined as all randomised patients who received at least one dose of study medication and at least one post-baseline seizure frequency assessment. Seizure frequency, the primary endpoint, was compared among the treatment groups using an analysis of covariance (ANCOVA) that modelled seizure frequency as a function of baseline seizure frequency and treatment.

In all studies eslicarbazepine acetate 800mg and 1,200mg was significantly superior to placebo in reducing the standardised seizure frequency over the 12-week maintenance period compared to the baseline period. Results of the primary endpoint for all studies are included in the table below.

Table: Primary endpoint (seizure frequency, standardised to frequency over 4 weeks)

	Placebo	**Eslicarbazepine acetate**		
		400mg	**800mg**	**1,200mg**
Study 1				
N (ITT)	102	99	98	98
Mean baseline seizure frequency	12.4	11.4	11.2	11.6
LS mean (95% CI) seizure frequency on treatment	7.64 (6.78 to 8.58)	6.73 (5.93 to 7.60)	5.66 (4.92 to 6.45)	5.35 (4.63 to 6.12)
P-value vs. placebo	-	NS	0.0028	0.0003
Study 2				
N (ITT)	100	96	100	97
Mean baseline seizure frequency	13.3	14.4	15.5	15.9
LS mean (95% CI) seizure frequency on treatment	9.8 (8.7 to 11.1)	8.7 (7.7 to 9.9)	7.1 (6.2 to 8.2)	7.0 (6.0 to 8.1)
P-value vs. placebo	-	NS	0.002	0.001
Study 3				
N (ITT)	84		84	77
Mean baseline seizure frequency	12.6		12.8	11.7
LS mean (95% CI) seizure frequency on treatment	7.3 (6.3 to 8.5)		5.7 (4.9 to 6.7)	5.5 (4.6 to 6.5)
P-value vs. placebo	-		0.048	0.021

LS=least square, CI=confidence interval, NS=not significant.

Responder rates, a secondary endpoint, were significantly higher than placebo for eslicarbazepine acetate 1,200mg in all studies and for eslicarbazepine acetate 800mg in two studies. In pooled analysis of the three phase III studies, responder rates were 22%, 23%, 36% and 44% for placebo, eslicarbazepine acetate 400mg, 800mg and 1,200mg respectively. In all studies, more patients became seizure free during the 12-week maintenance period in the eslicarbazepine acetate 800mg and 1,200mg groups than in the placebo group although differences versus placebo were statistically significant for eslicarbazepine acetate 1,200mg in the first study only.

All studies included an optional one-year open-label extension for patients who had completed the placebo-controlled period and 97% (831/857) entered the open label studies. Patients were treated with eslicarbazepine acetate 800mg once daily for four weeks after which the dose could be titrated up or down by 400mg increments. Doses of concomitant AEDs were kept stable. The median dose of eslicarbazepine acetate was 800mg/day. Standardised seizure frequency was significantly reduced at the final reporting period (weeks 41 to 52) of the open-label phase compared to the baseline period of the double-blind study in all three studies; median relative reductions in seizure frequency were 56%, 39% and 58% for the studies, respectively. Retention rates during the one-year open label period were high for all studies (76%, 69% and 77%, respectively). Quality of life was assessed using the Quality of Life in Epilepsy (QOLIE)-31 scale which includes seven subscales; seizure worry, emotional well-being, cognitive effects, medication effects, overall quality of life, energy/fatigue and social function. There were increases in all subscales of

the QOLIE-31, with statistical significance shown in most cases, and the overall QOLIE-31 score was significantly improved over one year of eslicarbazepine acetate treatment in all three studies.

Summary of evidence on comparative safety

In the pooled analysis of the phase III studies, the rates of possibly treatment-related emergent adverse events (TEAE) were 25% for placebo and 38%, 47% and 55% for eslicarbazepine acetate 400mg, 800mg and 1,200mg respectively. The proportions of TEAEs that led to study discontinuation were 12% and 19% for patients on eslicarbazepine acetate 800mg and eslicarbazepine acetate 1,200mg respectively, compared to 4.5% on placebo.

The majority of TEAEs associated with eslicarbazepine acetate treatment were central nervous system related; the incidence rates for dizziness, somnolence and headache during the 12-week maintenance period for patients treated with eslicarbazepine acetate 800mg were 21%, 13% and 10%, respectively and for eslicarbazepine acetate 1,200mg were 29%, 15% and 14%. The most common non-CNS TEAEs associated with eslicarbazepine acetate treatment during the 12-week maintenance period were gastrointestinal; in the eslicarbazepine acetate 800mg treatment group, 7.4%, 6.7% and 4.2% experienced nausea, vomiting and diarrhoea, respectively compared to 10%, 7.1% and 2.1% in the eslicarbazepine acetate 1,200mg group. TEAEs occurred mainly during the first 6 weeks of treatment.

Serious AEs occurred in a higher percentage of patients on eslicarbazepine acetate (3.7%) compared to placebo (1.4%) although appeared not to be dose related. Hyponatraemia was reported as a serious TEAE in one patient on eslicarbazepine acetate 800mg in the pooled phase III study population.

In the open-label extensions, between 51% and 83% of patients experienced at least one TEAE, with most being of mild to moderate severity. Between 3.5% and 11% patients discontinued treatment due to TEAEs.

The European Medicines Agency (EMEA) commented that the rates of at least possibly-related TEAEs in the clinical trial programme appear to be similar to oxcarbazepine and some TEAEs (e.g. headache, diplopia, nausea and vomiting) appear to occur less frequently compared to the known frequencies for oxcarbazepine. However, conclusive results could only be provided by active comparator studies.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium consider the use of eslicarbazepine acetate in a sub-set of the licensed indication, as a treatment option in patients who are highly refractory and heavily pre-treated and who remain uncontrolled on existing AED combination options. The inclusion criteria of the pivotal studies did not specifically detail recruitment of highly refractory and heavily pre-treated patients; in the pooled analysis of the phase III studies 27% and 69% of patients were on one and two concomitant AEDs respectively and the mean duration of epilepsy was 22 years. Therefore there are limited data to support the efficacy of eslicarbazepine acetate in the proposed sub-set of the licensed indication.

Data to demonstrate the efficacy for eslicarbazepine acetate versus placebo are from three randomised placebo-controlled studies all of which had open label extensions. When added to concomitant anti-epileptic drugs eslicarbazepine acetate decreased the standardised median frequency of seizures per month from 7.7 to 5.0 for eslicarbazepine acetate 800mg and from 8.0 to 4.6 for eslicarbazepine acetate 1,200mg, compared to a decrease from 7.0 to 6.4 seizures for placebo. Also the proportion of responders was improved by eslicarbazepine acetate (36% to 44%) compared to 22% in the placebo group. Furthermore the EMEA commented that, taking the results of the three open-label extension-studies together, it appears the therapeutic effect of eslicarbazepine acetate is maintained over time.

The EMEA noted that 35% (85/245) of patients had protocol violations in the third study and doubts were raised regarding the reliability of the study results. However the EMEA concluded that, although the drop-out rate in the study was relatively high, the overall results did not change after excluding this study from an integrated analysis.

There are no controlled comparative data versus other AEDs used as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. A mixed treatment indirect comparison versus lacosamide was included in the company's submission. However limitations of the indirect comparison included heterogeneity between studies and an unconvincing probability of superiority of eslicarbazepine acetate over lacosamide.

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

Summary of comparative health economic evidence

The manufacturer submitted a two year cost-utility decision tree analysis, which compared adjunctive eslicarbazepine acetate 800mg with adjunctive lacosamide 400mg. Four periods of six months were modelled.

In the first period patients could respond or not respond, with response rates being drawn from a mixed treatment comparison. The mixed treatment comparison estimated >50% responder rates at the end of the trials' maintenance period. This was based on the results of three phase III trials of eslicarbazepine acetate, coupled with the results of a phase IIb trial and a phase III trial for lacosamide as drawn from the literature. Eslicarbazepine acetate was estimated to have a 1.09 relative risk of response compared to lacosamide, and a 60% probability of being superior to lacosamide in terms of response rates.

Transition probabilities for subsequent periods were taken from the literature, and were common to both arms. Those responding could maintain response in the next period or enter the non-responding state. Those not responding entered a 6-month switch state during which adjunctive therapy was down-titrated. Those having switched moved to no adjunctive therapy thereafter.

Utility values were drawn from the literature, but given uncertainty around the values for responders, optimistic and pessimistic analyses were performed. The pessimistic values corresponded more closely with those of the 2005 HTA monograph on the cost-effectiveness of epilepsy treatments.

Price equilvalence was assumed for eslicarbazepine acetate and lacosamide. Other resource use was estimated from the literature and related to health states within the model, the main distinctions being additional GP visits, neurology visits and electroencephalograms for those when switching therapy.

Applying the optimistic utility values, the base case estimated an average gain of 0.008 QALYs at an average cost of £74.61 to yield a cost effectiveness estimate of £8,510 per QALY. The more pessimistic utility values resulted in a smaller average gain of 0.004 QALYs to yield a cost effectiveness estimate of £16,099 per QALY.

Weaknesses included:

- questionable comparability between eslicarbazepine acetate and lacosamide trials, with more patients in lacosamide trials having dual or triple therapy at baseline, although this was partly controlled for within the mixed treatment comparison by adopting a random effects approach;
- the switch health state being distinct from the no-response health state and of questionable duration;
- assuming a flat dosing schedule for eslicarbazepine acetate and long term equivalence of direct drug costs when the open label trials indicated a substantial number of patients receiving the more costly 1200mg daily dose by trial end; and
- cost-effectiveness results which were unaffected by response rates due to the assumed parity in direct drug costs, which as noted above, may not be realistic .

As a consequence, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN); Guideline No. 70; Diagnosis and Management of Epilepsy in Adults (2003). The guideline notes that when two AEDs have failed as monotherapy an 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 are recommended as equally effective adjunctive therapies, although the development of concentric visual field defects with vigabatrin were highlighted as a safety concern. A consultation to ascertain whether a review of the guideline is warranted was published in 2007. The consensus was that the guideline should be reviewed either in its entirety or selected elements. No date is available for the completion of this.

National Institute for Health and Clinical Excellence (NICE); Clinical Guideline (CG) 20; The Epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (2004). This guideline is currently being reviewed with an anticipated publication date of November 2010.

NICE; Technology Appraisal (TA) 76. Newer drugs for epilepsy in adults (2004).

The NICE TA76 and CG20 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: comparators

The SIGN guideline recommends, vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine and levetiracetam as equally effective adjunctive therapies for drug-resistant focal epilepsy. Lacosamide was accepted for restricted use by SMC in January 2009. Vigabatrin is only used in patients in whom all other combinations are inadequate or are not tolerated and therefore is not included in the table below.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Eslicarbazepine acetate	**800mg to 1,200mg once daily**	**1,870 to 2,806**
topiramate	400mg twice daily	2,729
zonisamide	250mg twice daily	2,242
levetiracetam	1.5g twice daily	2,162
lacosamide	200mg twice daily	1,874
tiagabine	15mg twice to three times daily*	910 to 1,365
pregabalin	200mg three times daily	1,256
oxcarbazepine	1.2g twice daily	1,159
clobazam	60mg once daily	341
gabapentin	1.2g three times daily	242
lamotrigine	100mg to 200mg twice daily**	73 to 124

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on date 29 September 2009.
Costs are based on maximum recommended maintenance doses using solid dosage forms
* dose dependent on co-administration with enzyme inducer.
** dose dependent on co-administration of other AEDs.

Additional information: budget impact

Based upon an eligible patient population of around 8000 and a 3.4% penetration for lacosamide, the manufacturer estimated that in the first year eslicarbazepine acetate would take 50% of the lacosamide market share: 136 patients. Given a growth of market penetration for the two drugs to 10% by the fifth year, the manufacturer estimated that both would have 423 patients.

This resulted in a gross budget impact of £256k in year 1 for eslicarbazepine acetate, rising to £796k by year 5. The net impact was estimated as being budget neutral due to price parity with lacosamide.

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 13 November 2009.

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 references were supplied with the submission. The references shaded grey are additional to those supplied with the submission.

Elger C, Halász P, Maia J, Almeida L, Soares-da-Silva P, on behalf of the BIA-2093-301 Investigators Study Group (2009). Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: A randomized, double-blind, placebo-controlled, parallel-group phase III study. Epilepsia; 50: 454–463.

Hufnagel A, et al. (2008). Efficacy and safety of eslicarbazepine acetate as add-on treatment in adults with refractory partial-onset seizures: BIA-2093-302. Poster presented at the European Congress on Epilepsy 2008. 21-25 September, Berlin, Germany

Lopes-Lima J, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in adults with refractory partial-onset seizures: BIA-2093-303. Poster presented at the European Congress on Epilepsy 2008, 21-25 September, Berlin, Germany

The European Medicines Agency (EMEA) European Public Assessment Report. Eslicarbazepine (Zebinix®). 19/02/2009, EMEA/304525/2009. www.emea.europa.eu.

Bial Portela & C. Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial. Clinical Study Report (BIA-2093-302). 14 June 2007

Bial Portela & C. Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial. Clinical Study Report (BIA-2093-303). 14 June 2007