Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

eslicarbazepine acetate 800mg tablet (Zebinix) SMC No. (592/09)
Eisai Ltd

8 October 2010

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 re-submission

eslicarbazepine acetate (Zebinix) is accepted for restricted use within NHS Scotland.

Indication under review: as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

SMC restriction: patients with highly refractory epilepsy who have been heavily pre-treated and remain uncontrolled with existing anti-epileptic drugs.

Eslicarbazepine acetate reduces seizure frequency compared to placebo over a 12-week maintenance period. Direct comparative data versus other anti-epileptic drugs are unavailable, particularly comparisons with other cheaper agents with a very similar mode of action.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of eslicarbazepine acetate. This SMC advice is contingent upon the continuing availability of the PAS in Scotland.

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

400mg once daily for one to two weeks then 800mg once daily. Based on individual response the dose may be increased to 1,200mg once daily. Eslicarbazepine acetate must be added to existing anticonvulsant therapy.

Product availability date

21 April 2009 (launch date 21 October 2009)

Summary of evidence on comparative efficacy

Eslicarbazepine acetate, a dibenzazepine antiepileptic drug (AED) in the same pharmacological class as carbamazepine and oxcarbazepine, is metabolised to the active form, eslicarbazepine. Eslicarbazepine is the active metabolite of oxcarbazepine. This submission requests that SMC consider the use of eslicarbazepine acetate in patients with highly refractory epilepsy who have been heavily pre-treated with existing AED combinations.

Three phase III studies recruited adults experiencing simple or complex partial-seizures with or without secondary generalisation for at least 12 months who had at least four seizures per four-week period, despite treatment with one or two AED. The second study permitted concomitant treatment with one to three AED. After an eight-week baseline period, which was single-blind placebo-controlled in the first study and observational in the others, patients who continued to have at least four seizures per four-week period with no seizure-free interval greater than 21 days were randomised equally to double-blind treatment with eslicarbazepine acetate 400mg, 800mg or 1,200mg once daily or placebo for twelve weeks following a two-week dose titration. The third study did not include an eslicarbazepine acetate 400mg per day treatment arm. Following completion of double-blind treatment patients could enter open-label extension studies where they received eslicarbazepine acetate titrated to clinical response for one year.

In the intention-to-treat (ITT) population, which comprised all patients who received at least one dose of study drug and had at least one post-baseline seizure frequency efficacy assessment, the primary outcome, four-week seizure frequency during the 12-week maintenance period, was compared to placebo for each eslicarbazepine acetate treatment arm by analysis of covariance (ANCOVA) that modelled seizure frequency as a function of baseline seizure frequency and treatment. The results presented as least square mean (LS mean) are detailed in the table below and indicate a significant reduction in four-week seizure frequency with eslicarbazepine acetate 800mg and 1,200mg, but not 400mg, daily doses compared to placebo. ANCOVA analysis of integrated data from ITT populations of the studies indicated significant differences compared to placebo for eslicarbazepine acetate 800mg and 1,200mg daily.

Table: ANCOVA derived LS means (95% confidence intervals) seizure frequency per 28-days during 12-week maintenance within ITT population

Study	Placebo	ESL 400mg	ESL 800mg	ESL 1,200mg
A	N=102	N=99	N=98	N=98
	7.6 (6.8 to 8.6)	6.7 (6.0 to 7.7)	5.7 (5.0 to 6.5)*	5.4 (4.6 to 6.1)*
B	N=100	N=96	N=100	N=97
	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)*
C	N=84		N=84	N=77
	7.3 (6.3 to 8.5)	-	5.7 (4.9 to 6.7)**	5.5 (4.6 to 6.5)*

ESL= eslicarbazepine acetate; *significant difference versus placebo; ** p=0.048 versus placebo

Compared to placebo, the proportion of patients experiencing a response (reduction of at least 50% in seizure frequency during the 12-week maintenance period compared with baseline) was significantly greater with eslicarbazepine acetate 1,200mg in all three studies and an integrated analysis of these and was significantly greater with eslicarbazepine acetate 800mg in studies A and B and the integrated analysis. In the integrated analyses eslicarbazepine acetate 400mg, 800mg, 1,200mg and placebo were associated with response rates of 23%, 36%, 44% and 22%, respectively, and 3%, 3.8%, 8% and 2% of patients in the respective groups were seizure-free during the maintenance period.

Of the 857 patients who completed the double-blind phases of the three phase III studies 97% entered open-label extensions and 73% of these patients completed one year's treatment with eslicarbazepine acetate median daily dose of 800mg. In the ITT population (all patients who had received at least one dose of study drug and had at least one efficacy assessment in the open-label phase), mean relative reductions from baseline in seizure frequency during weeks 41 to 52 were 41%, 39% and 58% for studies A, B and C respectively.

During the double-blind treatment phase there were no major changes in the quality of life in epilepsy inventory-31 (QUOLIE-31) mean scores from randomisation to last visit for any of the subscales or the overall score in either the placebo or eslicarbazepine acetate groups.

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

Summary of evidence on comparative safety

In the double-blind phases of the three phase III studies the incidence of treatment-emergent adverse effects increased with increasing doses of eslicarbazepine acetate 400mg, 800mg and 1,200mg: 60.7%, 62.7% and 67.5%, in the respective groups and 46.4% with placebo. The dose-dependent increase was also seen for possibly-related adverse effects (38.3%, 47.2% and 55% in the respective groups and 24.9% with placebo) and adverse effects leading to discontinuation of study medication (8.7%, 11.6%, 19.3% in the respective groups and 4.5% with placebo). There was a higher, but not dose related, incidence of serious adverse effects in the eslicarbazepine acetate groups (3.7%) compared to the placebo group (4.5%), with

incidences in the eslicarbazepine acetate 400mg, 800mg and 1,200mg groups of 4.6%, 3.5% and 3.2%, respectively.

There are no direct comparative data. However, the European Medicines Agency (EMA) review of eslicarbazepine acetate notes that in general the profile of at least possibly related treatment-emergent adverse effects appears similar to oxcarbazepine and some (e.g. headache, diplopia, nausea and vomiting) appear to occur less frequently compared to the known frequencies with oxcarbazepine. However, conclusive results could only be provided from active comparator studies.

Summary of clinical effectiveness issues

Efficacy is reported as LS mean seizure frequency during the maintenance period. The figures are derived from complex processing of seizure frequency data. In the integrated analysis of the three phase III studies median four-week seizure frequencies with placebo and eslicarbazepine acetate 400mg, 800mg and 1,200mg were 7.0, 8.0, 7.7 and 8.0, respectively, at baseline and 6.4, 5.9, 5.0 and 4.6, respectively, during the maintenance period.

The EMA noted that in responder analyses in the three phase III studies and integrated analysis patients who discontinued treatment prematurely during one of the treatment periods were still categorised as treatment responders for that particular period when their seizure frequency was reduced by 50% or more before discontinuation. Supplementary analyses in which patients who discontinued were regarded as non-responders were consistent with the original analyses. The EMA also noted that the frequency and character of the major protocol violations of study C raised doubts about the reliability of the study results. However, when it was excluded from the integrated analysis the outcomes were not significantly different from the overall integrated analysis.

The manufacturer wishes to position eslicarbazepine acetate for use in patients who have failed to respond to numerous AED. However, available efficacy data are derived from studies in which some patients may have received only one previous AED. Information on patients' lifetime previous AED use was not recorded in these studies, therefore it is not possible to estimate efficacy within the subgroup of patients who have failed to respond to numerous AEDs.

An indirect comparison was provided to support an assumption used in the economic analysis - that eslicarbazepine acetate 800mg daily is associated with a slightly higher response rate than lacosamide 400mg daily. The wide credible limits around relative risk and odds ratios indicate that it did not establish eslicarbazepine acetate or lacosamide as being more effective than the other. Of note, the indirect comparison did not adjust for differences across study populations. On average patients in the eslicarbazepine acetate studies, compared to those in the lacosamide studies, had lower baseline four-week seizures frequencies, with medians ranging from 6.7 to 9 and 9.9 to 16.5, respectively. In particular, rates of partial seizures evolving to secondarily generalised seizures were lower in the eslicarbazepine acetate studies: 33% to 41% vs. 72% to 79%, respectively. Also, patients in eslicarbazepine acetate studies received fewer concomitant AED, as shown in the table below.

Table: Concomitant antiepileptic drugs (AEDs)

Study	1 AED	2AED	3AED	4AED
Eslicarbazepine study A	36%	64%	0.5%	
Eslicarbazepine study B	19%	72%	8.4%	0.8%
Eslicarbazepine study C	20%	74%	5.5%	0.4%
Lacosamide study SP667	16%	84%		
Lacosamide study SP755	13%	50%	37%	7.8%
Lacosamide study SP754	18%	55%	27%	

In the phase III studies, 58% of randomised patients were already receiving carbamazepine, which is in the same pharmacological class as eslicarbazepine acetate. Post-hoc sub-group analysis of pooled data from the three pivotal trials was conducted to gain an understanding of the efficacy of eslicarbazepine when combined with carbamazepine, similar efficacy results were observed in patients who received the combination compared to the overall study population.

The majority of AEDs are taken in two to three daily doses whereas eslicarbazepine acetate and zonisamide can be taken once daily.

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 in a subset of patients who are highly refractory, heavily pre-treated and remained uncontrolled on existing AED treatments. Four periods of six months were modelled.

In the first period patients could respond or not respond, with response rates (reduction of at least 50% in seizure frequency during the 12-week maintenance period compared to baseline) drawn from the mixed treatment comparison described above. The mixed treatment comparison included the three phase III studies for eslicarbazepine acetate, coupled with the results of a phase IIb study and a phase III study for lacosamide taken 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, with the values used showing reasonable correspondence with those of the 2005 HTA monograph on the cost effectiveness of epilepsy treatments.

Price parity 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.

The base case estimated an average gain of 0.004 quality adjusted life years (QALYs) at an average cost of £75 to yield a cost effectiveness estimate of £16,099 per QALY. Applying dose escalation as observed within the one-year open-label study for eslicarbazepine acetate and an interim analysis of a lacosamide open-label extension of up to 5.5 years patient exposure resulted in the net cost rising to £92 resulting in a cost effectiveness estimate of £22,487 per QALY. A patient access scheme (PAS) was submitted by the manufacturer and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount would be applied to the price of eslicarbazepine acetate. With the PAS, eslicarbazepine acetate would yield a cost saving of £108, and thus dominate lacosamide (i.e. cheaper and more effective). When the PAS was applied to the dose escalation scenario, eslicarbazepine acetate was also the dominant treatment.

Sensitivity analysis showed that the results were sensitive to the relative efficacy of eslicarbazepine and lacosamide with the potential for negative QALY gain if the relative response for eslicarbazepine was reduced.

Other issues that were noted included:

- concern around the comparability of populations in eslicarbazepine acetate and lacosamide studies, with more patients in lacosamide studies having dual or triple therapy at baseline and this not being adequately controlled for within the mixed treatment comparison. Lacosamide studies also showed higher baseline seizure frequencies and higher numbers of patients experiencing partial seizures that evolved to secondary generalized seizures indicating more severe epilepsy although meta regression over the small number of studies did not indicate a link between the number of concomitant AEDs and response rates;
- increasing the eslicarbazepine response rate from 37% to 62% worsened the cost-effectiveness of eslicarbazepine due to an increase in the net treatment cost but small QALY gains.

Despite these issues, the economic case was considered demonstrated when the effect of the PAS was included.

Summary of patient and public involvement

A Patient Interest Group submission was received from Epilepsy Scotland.
A Patient Interest Group letter of support was received from Epilepsy Action.

Additional information: guidelines and protocols

In April 2003 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 70 on diagnosis and management of epilepsy in adults. This recommends that carbamazepine, sodium valproate, lamotrigine and oxcarbazepine can all be regarded as first line treatments for partial and secondary generalised seizure. Combination therapy should be considered when treatment with two first line AEDs has failed or when the first well tolerated drug substantially improves seizure control but fails to produce seizure-freedom at maximal dosage. The choice of

drugs in combination should be matched to the patient's seizure type(s) and should be limited to two or at most three AEDs. In relation to drug-resistant focal epilepsy, the guideline notes that seven AEDs have been licensed in the last decade. These are in chronological order, vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine and levetiracetam. Systematic reviews have confirmed the efficacy and tolerability of all of these agents as adjunctive therapy for patients with drug-resistant focal epilepsy. The development of concentric visual field effects with vigabatrin has substantially limited its clinical use. In 2007 a review consultation report indicated that the entire guideline or elements of it should be reviewed. No date is available for publication of the updated guideline.

In March 2004 the National Institute for Health and Clinical Excellence (NICE) published technology appraisal number 76 on newer drugs for epilepsy in adults and in October 2004 NICE published clinical guideline number 20 on the epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Both of these recommend that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with anti-epileptic drugs have not resulted in seizure freedom. The newer antiepileptic drugs, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin are recommended for patients who have not benefited from or are unsuitable for treatment with older anti-epileptics such as carbamazepine or sodium valproate. The clinical guideline is currently being reviewed with an anticipated publication date of March 2011.

Additional information: comparators

The majority of AED can be used within their licensed indications as adjunctive treatment for partial seizures with or without secondary generalization. In practice the older drugs (e.g. carbamazepine and sodium valproate) tend to be used as first-line treatments, with the newer AED used as adjunctive therapy in patients not controlled with monotherapy.

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Year (£)
Eslicarbazepine acetate	**800mg to 1,200mg daily**	**1,871 to 2,806**
Zonisamide	300mg to 500mg daily	1,223 to 2,038
Lacosamide	200mg to 400mg daily	1,124 to 1,874
Levetiracetam	1,000mg to 3,000mg daily	635 to 1,862
Tiagabine	15mg to 45mg daily*	446 to 1,339
Oxcarbazepine	600mg to 2,400mg daily	295 to 1,176
Pregabalin	150mg to 600mg daily	837
Topiramate	200mg to 800mg daily	184 to 631
Gabapentin	900mg to 3,600mg daily	42 to 168
Lamotrigine	100mg to 400mg daily*	50 to 126

Doses are for general comparison and do not imply therapeutic equivalence. The above total daily doses are taken as two or three divided doses, except for eslicarbazepine and zonisamide, which may be taken once daily. Costs from eVadis on 15 July 2010.
* maximum dose dependent upon concomitant use of enzyme inducing drugs.

Additional information: budget impact

Based upon an estimated 880 patients currently receiving lacosamide being eligible for eslicarbazepine acetate and given a market share estimate of 50%, the manufacturer estimated a gross annual drug cost of £1.7m without the PAS. Due to the assumed price parity with lacosamide 400mg per day and retaining the assumption of a flat dosing schedule (i.e. no dose escalation on eslicarbazepine acetate), the manufacturer estimated a zero net drug cost.

With the patient access scheme, the manufacturer estimated a gross annual drug cost of £1.6m, and a net annual drug cost saving of £83k.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Elger C, Halász P, Maia J et al. 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 2009; 50: 454–463

Ben-Menachem E, Gabbai AA, Hufnagel A et al. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. Epilepsy Res 2010; 89: 278-85

Gil-Nagel A, Lopes-Lima J, Almeida L et al. Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures. Acta Neurol Scand 2009: 120: 281–287

Guekht A, Elger C, Halász P et al. Long-Term Treatment of Partial Epilepsy with Eslicarbazepine Acetate (ESL): Results of a 1-year Open-Label Extension to Study. Poster presented at the American Epilepsy Society (AES) Congress, 5-9 December 2008, Seattle, WA, USA.

Gabbai AA, Ben-Menachem E, Maia J et al. (2008). Long-Term Treatment of Partial Epilepsy with Eslicarbazepine Acetate (ESL): Results of a One-Year Open-Label Extension to Study BIA-2093-302. Poster presented at the American Epilepsy Society (AES) Congress, 5-9 December 2008, Seattle, WA, USA.

Lope-Lima J, Gil-Nagel A, Maia J et al. Long-Term Treatment of Partial Epilepsy with Eslicarbazepine Acetate (ESL): Results of a One-Year Open-Label Extension to Study BIA-2093-303. 2008b. Poster presented at the American Epilepsy Society (AES) Congress, 5-9 December 2008, Seattle, WA, USA.

European Medicines Agency. CHMP assessment report for Zebinix. London, 19 February 2009. Doc.ref.: EMEA/304525/2009

This assessment is based on data submitted by the applicant company up to and including 04 October 2010**.**

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**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/*

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.