AWMSG Secretariat Assessment Report – Limited submission

Eslicarbazepine acetate (Zebinix®) 200 mg and 800 mg tablets, and 50 mg/ml oral suspension

Company: Eisai Ltd

Licensed indication under consideration: As adjunctive therapy in adolescents and children aged above six years, with partial-onset seizures with or without secondary generalisation. Eslicarbazepine acetate (Zebinix®) should be restricted to treatment of highly refractory patients who remain uncontrolled with, or are intolerant to, other anti-epileptic medicine combinations.

Date of licence extension: 8 December 2016

Comparator(s)

The comparators included in the company submission are:

- lacosamide (Vimpat®)
- brivaracetam (Briviact®)
- zonisamide (Zonegran®).

Limited submission details

The limited submission criteria were met based on a minor licence extension

Clinical effectiveness

- Eslicarbazepine acetate (Zebinix®) has previously been recommended by the All Wales Medicines Strategy Group (AWMSG) as an option for restricted use within NHS Wales. Eslicarbazepine acetate should be restricted to treatment of highly refractory patients who remain uncontrolled with, or are intolerant to, other anti-epileptic medicine combinations, within its licensed indication as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation.
- This submission covers the paediatric licence extension for adolescents and children aged above six years, and is restricted to the treatment of highly refractory patients in line with the recommendation for adults.
- Treatment choice in epilepsy is guided by a number of factors including patient co-morbidities, concurrent medications, medicine tolerability and formulation(s) available. AWMSG previously recommended lacosamide and brivaracetam as options for the same indication under consideration. Clinical experts in Wales have confirmed that in general they would expect to use eslicarbazepine acetate as third-line treatment; that is, after failure of monotherapy and first-line adjunctive therapy. Therefore, it is expected that eslicarbazepine acetate would potentially displace lacosamide, zonisamide, oxcarbazepine or brivaracetam. However, in line with the National Institute for Health and Care Excellence (NICE) Clinical Guideline 137, the applicant company highlights that in general oxcarbazepine is used before

lacosamide and zonisamide, and is therefore not a relevant comparator.

- There is no direct head-to-head comparative evidence between eslicarbazepine acetate and the comparators. The company submission includes results from two double blind, randomised and placebo controlled studies: a phase II study (Study 208) in children aged from 6 to 16 years (n = 123) and a phase III study (Study 305) in children aged from 2 to 18 years (n = 304). Target doses were 30 mg/kg/day (Study 208) and 20 mg/kg/day (Study 305) to a maximum of 1,200 mg/day over a maintenance phase of 8 and 12 weeks respectively.
- In Study 208, the least square mean reduction in standardised seizure frequency was significantly higher in children treated with eslicarbazepine acetate compared to placebo ($p < 0.001$; −34.8% and −13.8%, respectively). The percentage of treated patients with a reduction in seizure frequency of at least 50% was 50.6% compared to 25.0% for the placebo group ($p = 0.009$) The European Medicines Agency (EMA) considered these results clinically relevant and comparable to the effects seen in the adult study population.
- In study 305, the relative change in standardised seizure frequency during the maintenance period (−18.1% for eslicarbazepine acetate versus −8.6% for placebo; $p = 0.2490$) and the 50% response rate (30.6% for eslicarbazepine acetate versus 31.0% for placebo; $p = 0.9017$) were similar in patients treated with eslicarbazepine acetate and placebo. The EMA considered the under-dosing of children aged 2–6 years the most likely explanation for the results not being statistically significant. Post-hoc analyses excluding this age group did not demonstrate statistical significance but the EMA concluded that the results showed a trend in favour of eslicarbazepine acetate treatment.
- Eslicarbazepine acetate was generally well-tolerated in the paediatric population; serious adverse events and discontinuations were low, although slightly higher than for adults. No new major safety concerns were identified and the EMA concluded that the safety profile of eslicarbazepine acetate in children older than six years was generally consistent with that in adults.

Budget impact

- The company estimates that 357 children (aged 7 to 17 years) are eligible for eslicarbazepine acetate treatment in NHS Wales in the first year, based on population data for Wales, prevalence and incidence data for the UK, and assumes that 55% of people with epilepsy have partial-onset seizures of which 30% need adjunctive therapy.
- The cost of treatment differs according to the patient's weight. The annual cost per patient for eslicarbazepine acetate and each of the comparators was calculated based on the average dose for each medicine. The company has not provided sensitivity analyses to assess variation in costs due to a patient's body weight.
- Based on the company's market share projections eslicarbazepine acetate is assumed to partly displace all three comparators. An estimated [commercial in confidence figure removed] patients are likely to be prescribed eslicarbazepine acetate in Year 1 based on an anticipated uptake of [commercial in confidence figure removed], increasing to [commercial in confidence figure removed] patients in Year 5 based on an anticipated uptake of [commercial in confidence figure removed]. The company estimates that this will result in net medicine acquisition costs of [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5.
- There are limitations to the company's budget impact calculations; including a likely overestimate of patient numbers, estimates are based on average dose rather than age and weight specific, and estimates vary depending on which comparator is displaced. However, overall these are likely to result in an overestimate of the company's budget impact analysis.

Additional information

- AWTTC is of the opinion that, if recommended, eslicarbazepine acetate (Zebinix®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

Evidence search

Date of evidence search: 18 February 2019.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Eslicarbazepine acetate (Zebinix®) 200 mg and 800 mg tablets, and 50 mg/ml oral suspension. Reference number: 1214. May 2019.

Appendix: Previous AWMSG secretariat assessment report (published September 2012)

In September 2012, AWMSG appraised eslicarbazepine acetate (Zebinix®) as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation (AWTTC reference number 611). This advice is now incorporated into the Final Appraisal Recommendation (FAR) of eslicarbazepine acetate (Zebinix®) adjunctive therapy in adolescents and children aged above six years, with partial-onset seizures with or without secondary generalisation. Eslicarbazepine acetate (Zebinix®) should be restricted to treatment of highly refractory patients who remain uncontrolled with, or are intolerant to, other anti-epileptic medicine combinations (AWTTC reference number 1214).

The original report for AWTTC reference number 611 is included below for completeness.

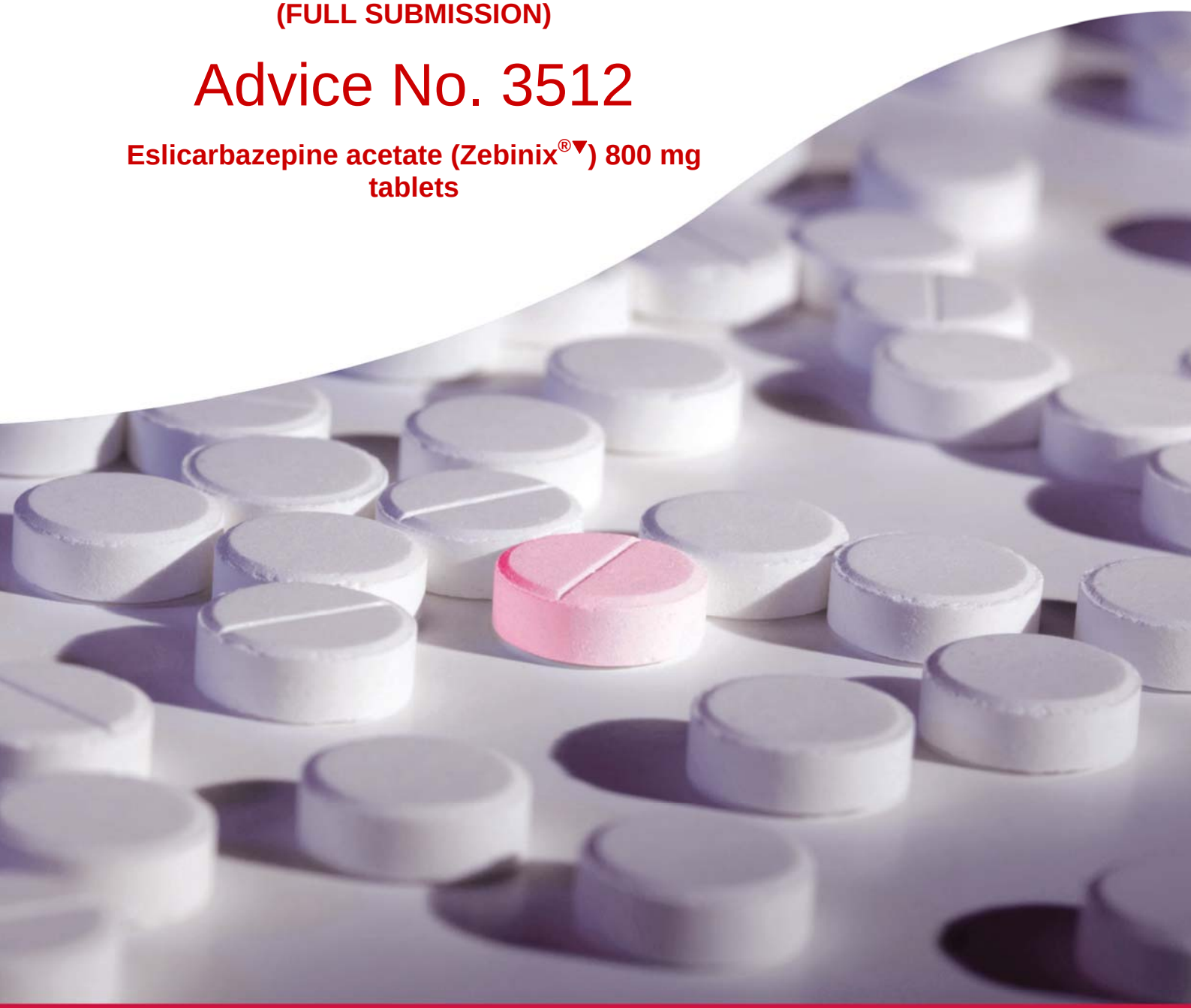
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 3512

Eslicarbazepine acetate (Zebinix®▼) 800 mg tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 3512
Eslicarbazepine acetate (Zebinix®▼) 800 mg tablets

This assessment report is based on evidence submitted by Eisai Ltd on 27 April 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Eslicarbazepine acetate (Zebinix®▼) is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation[2].
Dosing	Eslicarbazepine acetate must be added to existing anticonvulsant therapy. The recommended starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1,200 mg once daily[2].
Marketing authorisation date	21 April 2009[2].

2.0 DECISION CONTEXT

2.1 Background

Epilepsy is one of the most common chronic neurological disorders, affecting around 50 million people worldwide[3] and approximately 600,000 people in the UK (based on 2010 figures)[4]. Epilepsy can encompass a range of unique characteristics; however, it is usually defined as a tendency for recurring seizures[5]. Partial seizures have been defined by the National Institute for Health and Clinical Excellence (NICE) as "a seizure that originates within networks limited to one hemisphere, discretely localised or more widely distributed"[6]. Based on Welsh Government data and a study by Sander et al., the applicant company estimates that, in Wales, there are 11,725 patients with partial seizures with or without secondary generalisation[1,7–9].

Two-thirds of patients with active epilepsy have their condition controlled with anti-epileptic drugs (AEDs). Where monotherapy with an AED is unsuccessful, adjunctive therapy is often considered[6]; the applicant company estimates that approximately 39% of patients with epilepsy will require adjunctive treatment, and, of these, approximately 36% remain refractory to their first-line adjunctive therapy[1].

Eslicarbazepine acetate is an AED that acts by blocking voltage-gated sodium channels, subsequently leading to a decrease in repetitive neuronal firing[10]. NICE Clinical Guideline (CG) 137 states that, where first-line adjunctive treatment is ineffective or not tolerated, eslicarbazepine acetate may be considered by a tertiary epilepsy specialist in patients with refractory seizures[6]. The company has suggested that eslicarbazepine acetate will be used in highly refractory and heavily pre-treated patients that remain uncontrolled with existing AED combinations[1].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Lacosamide (Vimpat®▼)
- Zonisamide (Zonegran®▼)
- Topiramate
- Oxcarbazepine

The company has suggested lacosamide is the most appropriate comparator (see section 3.2 AWTTC critique)[1].

2.3 Guidance and related advice

- NICE. Clinical Guideline 137. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (2012)[6].
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (2003)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of three phase III trials comparing eslicarbazepine acetate with placebo for the treatment of partial seizures with or without secondary generalisation. In the absence of a direct comparison between eslicarbazepine acetate and other AEDs, the company performed a systematic literature review and subsequent indirect comparison with lacosamide[1].

3.1 Clinical effectiveness of eslicarbazepine acetate versus placebo

The phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies 301, 302 and 303 compared the use of eslicarbazepine acetate with placebo in adult patients ≥ 18 years experiencing simple or complex partial seizures with or without secondary generalisation for at least 12 months before screening. Patients must have had at least four partial seizures during the baseline phase, despite treatment with up to three concomitant AEDs (patients received 1–2 AEDs in study 301 and 302, and 1–3 AEDs in study 303)[1,12–14].

After enrolment, patients entered part one of the trial; this consisted of an eight-week baseline period followed by a two-week titration period, a twelve-week maintenance phase and, in studies 301 and 303 only, a four-week tapering-off period. Patients were randomised to receive 400 mg, 800 mg or 1,200 mg once daily doses of eslicarbazepine acetate or placebo (study 303 did not include a 400 mg treatment group). The primary efficacy endpoint was seizure frequency during the twelve-week maintenance period in the intention to treat (ITT) population, standardised to frequency per four weeks. A statistically significant decrease in seizure frequency was demonstrated for the 800 mg and 1,200 mg eslicarbazepine acetate doses when compared to placebo in all three studies; a statistically significant result was not demonstrated in the 400 mg treatment group. Secondary endpoints supported these findings. See Table 1 for detailed results.

Table 1. Primary and secondary efficacy results for eslicarbazepine acetate (over the 12-week maintenance period).

	Treatment regimen			
	Placebo	Eslicarbazepine acetate		
		400 mg	800 mg	1,200 mg
Study 301[1,10]	n = 99	n = 97	n = 97	n = 94
Primary endpoint				
LS mean seizure frequency per four weeks (95% CI)	7.6 (6.8, 8.6)	6.7 (6.0, 7.7) NS	5.7 (5.0, 6.5) p = 0.0028	5.4 (4.6, 6.1) p = 0.0003
Major secondary endpoints				
Median relative reduction in standardised seizure frequency (%)	-16.4	-25.8	-36.1 p < 0.01	-45.3 p < 0.001
Patients with a ≥ 50% decrease in seizure frequency (%)	19.6	23.2	33.7 p < 0.05	42.9 p < 0.001
Patients with seizure freedom (%)	2.0	2.0	4.1	8.2
Study 302[1,10]	n = 99	n = 95	n = 88	n = 85
Primary endpoint				
LS mean seizure frequency per four weeks (95% CI)	9.8 (8.7, 11.1)	8.7 (7.7, 9.9) NS	7.1 (6.2, 8.2) p < 0.01	7.0 (6.0, 8.1) p < 0.001
Major secondary endpoints				
Median relative reduction in standardised seizure frequency (%)	-5.0	-20.9	-32.6 p < 0.01	-32.9 p < 0.001
Patients with a ≥ 50% decrease in seizure frequency (%)	18.0	19.8	32.0 p < 0.01	35.1 p < 0.001
Patients with seizure freedom (%)	2.0	1.0	3.0	5.2
Study 303[1,10]	n = 79	–	n = 80	n = 69
Primary endpoint				
LS mean seizure frequency per four weeks (95% CI)	7.3 (6.3, 8.5)	–	5.7 (4.9, 6.7) p = 0.048	5.5 (4.6, 6.5) p = 0.021
Major secondary endpoints				
Median relative reduction in standardised seizure frequency (%)	-17.0	–	-37.9 p < 0.05	-41.9 p < 0.05
Patients with a ≥ 50% decrease in seizure frequency (%)	22.6	–	34.5	37.7
Patients with seizure freedom (%)	1.2	–	4.8	3.9
CI: confidence intervals, LS: least square, NS: not significant				

Part two of the phase III trials consisted of a one-year open-label extension to evaluate the safety and tolerability of eslicarbazepine acetate. Results showed that treatment over 52 weeks with eslicarbazepine acetate maintained the reduction in seizure frequency[15–17].

3.1.1 Indirect comparison of eslicarbazepine acetate versus lacosamide

The company identified three randomised, multicentre, double-blind, placebo-controlled studies that compared the use of lacosamide with placebo in patients with partial onset seizures with or without secondary generalisation and were receiving concomitant therapy with 1–3 AEDs: SP754, SP677 and SP755[18–20]. Using these studies and studies 301, 302 and 303 described previously, the company performed a mixed treatment comparison of eslicarbazepine acetate (800 mg/day) versus lacosamide (400 mg/day). The relevant data from the studies were pooled, using the placebo arms of the individual trials as the common comparator. The company stated that a 400 mg once-daily dose of lacosamide was used in the base case as it optimises the best risk–benefit ratio and was the median dose used in the open-label study. The efficacy analysis was based on the 50% response rates, with the statistical interpretation based on a point estimate, which reflects the most likely value. The response rates were estimated to be 37.4% for 800 mg eslicarbazepine acetate and 35.7% for 400 mg lacosamide. The relative risk response rate for 800 mg eslicarbazepine acetate versus 400 mg lacosamide was 1.05 (95% credible limit 0.51–2.12), which corresponds to an odds ratio of 1.08 (95% credible limit 0.34–3.34)[1].

3.1.2 Evidence of comparative safety

In a pooled analysis for studies 301, 302 and 303, the overall incidence of treatment-emergent adverse events (TEAEs) increased with increasing doses of eslicarbazepine acetate (60.7% for 400 mg, 62.7% for 800 mg and 67.5% for 1,200 mg eslicarbazepine acetate, versus 46.4% placebo)[10]. The most common TEAEs encountered were dizziness, headache, nausea and somnolence[12–14]. Serious AEs occurred in 3.7% of patients in the eslicarbazepine acetate group (including all doses) versus 1.4% for placebo. The discontinuation rate due to TEAEs was 8.7% in the 400 mg group, 11.6% in the 800 mg group and 19.3% in the 1,200 mg treatment group versus 4.5% for placebo[10].

In the lacosamide trials, most TEAEs were considered to be mild to moderate. The most commonly reported TEAEs in all three trials were dizziness, nausea and vomiting. The discontinuation rate due to TEAEs in the lacosamide treatment groups were 16.5% in study SP754, 17% in study SP677 and 8.7% in study SP755[18–20].

From the indirect comparison, the company reports that the percentage of patients who discontinued due to TEAEs was found to be similar between eslicarbazepine acetate and lacosamide[1].

3.2 AWTTC critique

- AWTTC requested lacosamide, zonisamide, topiramate and oxcarbazepine as comparators based on clinical expert opinion in Wales. NICE CG137 states that, where first-line adjunctive treatment is ineffective or not tolerated, eslicarbazepine acetate, lacosamide and zonisamide may be considered by a tertiary epilepsy specialist in patients with refractory seizures[6]. The company provided data for an indirect comparison between eslicarbazepine acetate and lacosamide only[1].
- The company reports a numerically greater response rate for eslicarbazepine acetate, but this is not statistically significantly different and the credible interval around the point estimates of response rates are very wide, reflecting the uncertainty in the estimates[1]. Results of the indirect comparison should be

interpreted with caution due to the inherent limitations in the method and the differences in the patient population across the studies; patients in the eslicarbazepine acetate studies tended to have lower seizure frequencies prior to enrolment and had received fewer concomitant AEDs than those in the lacosamide studies. In addition, different AED regimens were used[18–20].

- It is not possible to determine the effectiveness of eslicarbazepine acetate in highly refractory and highly treatment-experienced patients, the population in which the company suggest it will be used, as no subgroup analyses were undertaken in the studies.
- The Committee for Medicinal Products for Human Use (CHMP) noted that the percentage of patients discontinuing treatment increased noticeably with an increasing dose of eslicarbazepine acetate. Most discontinuations were due to unacceptable AEs[10].
- Eslicarbazepine acetate is administered as a once-daily dose; whereas, some other adjunctive treatments such as lacosamide are administered twice-daily[2,21]. The company suggest that a once-daily dose could improve compliance[1], although no evidence to support this conclusion has been provided.
- Eslicarbazepine acetate involves a one- or two-week titration phase, with a starting dose of 400 mg once-daily to a median effective dose of 800 mg once-daily[1,2]. Alternative AEDs, including lacosamide and zonisamide, require a longer titration period[21,22].
- CHMP commented that in the placebo-controlled eslicarbazepine acetate studies, some TEAEs such as headache, diplopia, nausea and vomiting appear to occur less frequently in comparison to oxcarbazepine, an AED of the same pharmacological class; however, it was acknowledged that conclusive results could only be provided from active comparator studies[10].
- In the eslicarbazepine acetate studies, the main primary and secondary efficacy results were collected over a twelve-week duration. Efficacy was a secondary endpoint in the one-year open-label extension phase[10].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of eslicarbazepine acetate 800 mg once-daily compared to lacosamide 200 mg twice-daily for adjunctive treatment of adults with partial seizures with or without secondary generalisation[1]. The company suggests that eslicarbazepine acetate will be targeted at patients who are highly refractory and highly treatment-experienced.

The analysis is based on a decision analytical model covering four, six-month periods. Patients enter the model starting adjunctive AED (eslicarbazepine acetate or lacosamide), in addition to a common background AED regimen, and experience a response (≥ 50% reduction of seizure frequency from baseline) or no response. In the absence of direct comparative data, an indirect treatment comparison has been conducted to derive relative response rates for eslicarbazepine acetate and lacosamide in this initial period. Patients who experience a response continue to receive the adjunctive AED. Those not experiencing a response enter a six-month 'switch' period, where they gradually down-titrate their adjunctive AED before entering a 'no adjunctive therapy' period, in which they are assumed to receive an unspecified form of treatment for six months or until death. The analysis assumes a two-year time horizon. See Appendix 1 for further details.

4.1.2 Results

Results of the base case analysis are summarised in Table 2. Treatment with eslicarbazepine acetate is estimated to be marginally less costly and marginally more effective than lacosamide. This difference in effectiveness arises from the small, non-statistically significant difference in the point estimates of response rates obtained from the indirect treatment comparison.

Table 2 Company-reported results of a base case cost-utility analysis

Base case	Eslicarbazepine acetate	Lacosamide	Difference
Costs of adjunctive AEDs	£1,629	£1,774	-£145
Total cost	£3,801	£3,956	-£154
Total life-years gained	1.951	1.951	0
Total QALYs	1.701	1.693	0.0078
Incremental cost per QALY gained	Eslicarbazepine acetate strategy dominates*		
*Applies when the results suggest that the drug under appraisal is less costly and more effective than comparator. AED: anti-epileptic drug; QALY: quality-adjusted life-year			

Probabilistic sensitivity analysis conducted for the base case scenario generates probabilities of 62–64% that eslicarbazepine acetate treatment is cost-effective compared to lacosamide at thresholds of £20,000 to £30,000 per QALY gained.

In one-way sensitivity analyses, when the initial six-month response rates for eslicarbazepine acetate and lacosamide were explored within the ranges of their 95% credible limits obtained from the indirect treatment comparison, this reportedly generated positive incremental cost-effectiveness ratios of £4,476 to £12,181 per quality-adjusted life-year (QALY) gained and £5,031 to £11,464 per QALY gained, respectively.

A scenario analysis conducted for a reduced time horizon of six months demonstrated that eslicarbazepine acetate would remain the dominant strategy compared to lacosamide.

4.1.3 AWTTC critique

The base case deterministic analysis should be viewed with caution as the results are driven by small differences observed in the point estimates of response rates obtained from the indirect treatment comparison, which itself has some potential limitations. Sensitivity analyses, based on a wide range of the 95% credible limits around these point estimates, demonstrate a potential for equal or lower QALY gains with eslicarbazepine acetate, and most simulated estimates obtained from the probabilistic sensitivity analyses do not support the dominance of eslicarbazepine acetate. Collectively, the most plausible conclusion would seem to be that eslicarbazepine acetate and lacosamide have comparable efficacy and cost effectiveness.

Strengths of the economic evidence include:

- The company has undertaken a systematic literature review to identify relevant trial data for eslicarbazepine acetate and their proposed comparator to support its economic evidence.
- In the absence of direct comparative data, the company has made attempts to derive indirect estimates of the relative efficacy of eslicarbazepine acetate and the chosen comparator via a Bayesian mixed treatment comparison.

Limitations of the economic evidence include:

- The company provided a comparison of eslicarbazepine acetate with lacosamide only. AWTTC also requested comparisons against zonisamide, topiramate and oxcarbazepine. These have not been provided by the company, as they argue that lacosamide trial populations are more comparable to those of eslicarbazepine acetate, and, like eslicarbazepine acetate, lacosamide is one of the newer AEDs not currently recommended as first-line adjunctive treatment in NICE guidelines[6].
- The company has acknowledged that in the UK, lacosamide is used in a small minority of the patients who are refractory to their first adjunctive treatment (11.1%). It is unclear as to what treatment options the remaining 88.9% receive, and the cost effectiveness of eslicarbazepine acetate relative to these is unknown.
- The analyses presented by the company are limited to a comparison of eslicarbazepine acetate 800 mg daily against the maximum permitted dose of lacosamide (200 mg twice-daily)[21]. Eslicarbazepine acetate may be titrated up to 1,200 mg daily if required[2]. No exploration of dose titration, and the associated costs, has been presented by the company.
- It is possible that patients enrolled in the lacosamide trials that were included in the indirect comparison have more refractory or more severe epilepsy than those enrolled in the eslicarbazepine acetate trials. There may therefore be an element of bias against lacosamide in the relative response rates to treatment derived from the indirect comparison.
- Reported results from both the probabilistic sensitivity analyses and the one-way deterministic sensitivity analyses mask the fact that, within the ranges of the 95% credible intervals for incremental costs and incremental QALYs gained, eslicarbazepine acetate ranges from being both less costly and less effective than lacosamide through to being both more costly and more effective than lacosamide, reflecting the uncertainty in key parameter values. The base case deterministic analyses should therefore be interpreted with caution.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches identified one abstract published by the company on the cost-effectiveness analysis of eslicarbazepine acetate (800 mg/day) compared to lacosamide (400 mg/day) for adjunctive treatment of adult patients with uncontrolled partial-onset seizures in Scotland[23]. The company reported that mean treatment costs over a two-year time horizon were £3,943 per patient per year for eslicarbazepine acetate and £3,899 per patient per year for lacosamide. The ICER was £16,300 per QALY gained. The probability of eslicarbazepine being cost-effective compared to lacosamide was around 50%, independent of the cost-effectiveness threshold. As only an abstract is available, a full critique of this analysis is not possible. It should be noted that the list price for eslicarbazepine acetate has been reduced since this analysis was conducted.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates there are currently 22,548 people with epilepsy in Wales, of which 11,725 (52%) have focal or partial seizures with or without secondary generalisation. It is anticipated that an additional 626 patients will be diagnosed with partial seizures each year in Wales. Assuming that 39% of patients will be treated with adjunctive therapy, and that 3% of these patients will become seizure-free with the

addition of a second AED, the company estimates that there will be 4,229 (36%) patients eligible for treatment in 2012, rising to 4,247 patients in 2016. Lacosamide is reported by the company to represent 11.1% of this market of refractory and highly pre-treated patients. The company anticipates the use of eslicarbazepine acetate to increase from 15% of the lacosamide market in year 1, to 25% in year 5, equating to 70 patients being treated with eslicarbazepine acetate in year 2012, and 118 patients in 2016.

5.1.2 Company-reported results of budget impact analysis

The company estimates cost savings from the displacement of lacosamide with the use of eslicarbazepine acetate, as summarised in Table 3.

Table 3. Company-reported costs associated with use of eslicarbazepine acetate for adjunctive treatment of adults with partial seizures.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	4,229	4,234	4,238	4,242	4,247
Uptake	15%	17.5%	20%	22.5%	25%
Number of treated patients	70	82	94	106	118
Cost of eslicarbazepine treatment	£116,510	£136,089	£155,677	£175,302	£195,010
Cost of lacosamide treatment	£132,322	£154,558	£176,805	£199,093	£221,475
Overall net costs	-£15,812	-£18,469	-£21,127	-£23,791	-£26,465

No sensitivity analyses to address uncertainty in the budget impact estimates have been reported in the company submission.

5.1.3 AWTTC critique of the budget impact analysis

The budgetary impact analysis assumes that eslicarbazepine acetate will potentially displace lacosamide only. However, according to company estimates, lacosamide is used by only 11.1% of the eligible patient population in the UK. No information is provided about the use of other AEDs for adjunctive treatment of patients with partial seizures, and displacement of other potential comparators (e.g. oxcarbazepine, zonisamide) with eslicarbazepine acetate could result in additional costs rather than cost savings. The company estimates of cost savings are therefore subject to uncertainty.

5.2 Comparative unit costs

A wide range of medicines may be used as adjunctive therapy in patients with partial seizures; Table 4 includes examples. The most recent guidance from NICE (Clinical Guideline 137[6]) and all relevant Summaries of Product Characteristics should be consulted for further details.

Table 4. Examples of acquisition costs of AEDs for adjunctive treatment of adults with partial seizures with or without secondary generalisation.

AED	Example dose	Annual cost per patient
Eslicarbazepine acetate (Zebinix®▼) 800 mg	800 mg to 1,200 mg once daily	£1,655 to £2,482
Lacosamide (Vimpat®▼) 50 mg, 100 mg, 150 mg and 200 mg	100 mg to 200 mg twice daily	£1,128 to £1,879
Oxcarbazepine (Trileptal®) 150 mg, 300 mg and 600 mg	600 mg to 2,400 mg daily in divided doses	£248 to £993
Zonisamide (Zonegran®▼) 25 mg, 50 mg and 100 mg	300 mg to 500 mg daily in 1–2 divided doses	£1,226 to £2,044
Topiramate (non-proprietary) 25 mg, 50 mg, 100 mg, and 200 mg	200 mg to 400 mg daily in 2 divided doses	£64 to £121
Lamotrigine (non-proprietary) 25 mg, 50 mg, 100 mg, and 200 mg	100 mg to 400 mg daily in 1–2 divided doses	£36 to £86
Levetiracetam (non-proprietary) 250 mg 500 mg 750 mg and 1 g	500 mg to 1,500 mg twice daily	£570 to £1,720
Gabapentin (non-proprietary) 100 mg and 300 mg (caps), 600 mg and 800 mg (tabs)	900 mg to 3,600 mg daily in 3 divided doses	£137 to £467
Pregabalin (Lyrica®) 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg	150 mg to 600 mg daily in 2–3 divided doses	£840 to £1,259
Tiagabine (Gabitril®) 5 mg, 10 mg and 15 mg	15 mg to 45 mg daily in 2–3 divided doses	£570 to £1,710
Vigabatrin (Sabril®) 500 mg	1,000 mg to 3,000 mg daily in one or two divided doses	£225 to £675
Retigabine (Trobalt®▼) 50 mg, 100 mg, 200 mg, 300mg, 400 mg	600 mg to 1,200 mg in 3 divided doses	£1,015 to £1,664
Costs are based on BNF[24] and MIMS[25] list prices for 25 May 2012. This table does not imply therapeutic equivalence of drugs or the stated doses. See all relevant SPCs for full indications and dosing details[2,21,22,26–35].		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, eslicarbazepine acetate (Zebinix®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Dates of evidence search: 17 May 2012 and 21 May 2012
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional health economic information
Table 1A. Health economic model details

	Base case model	Appropriate?
Comparator(s)	Eslicarbazepine acetate (Zebinix®▼) 800 mg/day is compared against lacosamide (Vimpat®▼) 400 mg/day. The background antiepileptic therapy is assumed to be the same for both comparator regimens.	AWTTC requested lacosamide, zonisamide, topiramate and oxcarbazepine as comparators; the company provided a comparison of eslicarbazepine acetate 800 mg daily with lacosamide 200 mg twice-daily only. According to the company submission, lacosamide is used by 11.1% of the patients who are refractory to their first adjunctive treatment. It is unclear as to what treatment regimens the remaining patients receive, and which treatment strategies are most commonly used in Wales. The company's assumption that the background antiepileptic therapy would be the same for both comparators is a pragmatic approach.
Population	The company states that the modelled population reflects adults with epilepsy who experience partial seizures refractory to 1–3 AED treatments, as per the clinical trials. However, it further suggests that the primary decision problem is the cost-effectiveness of eslicarbazepine acetate as adjunctive treatment of partial epilepsy for patients who are highly refractory and heavily pre-treated and who remain uncontrolled with existing AED combinations.	The licensed indication for eslicarbazepine acetate is as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. The company suggests its primary use will be in highly refractory and heavily pre-treated patients; however, it is not clear that patients enrolled in the eslicarbazepine acetate clinical trials were highly refractory and highly treatment experienced.
Model type and description	A CUA has been conducted based on a decision analytical model consisting of four, six-month periods. Patients enter the model starting adjunctive therapy with either eslicarbazepine acetate or lacosamide. During each six-month period, patients are classified into two health states: 'response' (defined as ≥ 50% reduction in seizure frequency) and 'no response'. Patients who experience a response continue to receive the adjunctive medication. If patients have no response, they enter the 'switch' period, where they gradually down-titrate their adjunctive AED over a six-month period before entering the 'no adjunctive therapy' period, in which they are assumed to receive an unspecified form of treatment until death or the end of the fourth six-month period.	CUA is the preferred type of analysis. The model is simplistic and it appears that patients failing on adjunctive treatment with either eslicarbazepine acetate 800 mg daily or lacosamide 400 mg daily are assumed to receive no further adjunctive treatment, presumably because the company is targeting the use of eslicarbazepine acetate to those who are considered to be highly refractory to treatment and would have experience of failed treatment with several other adjuvant AEDs previously (however, it is not clear that patients enrolled in the eslicarbazepine acetate clinical trials were highly refractory and highly treatment experienced). The SPC for lacosamide suggests initial target therapeutic dose of 100 mg twice daily, with a maximum dose of 200 mg twice daily[21]. The SPC for eslicarbazepine acetate suggests a target dose of 800 mg daily, increased to 1,200 mg daily if required[2]. The company has limited its analyses to a comparison of lacosamide 400 mg daily (maximum dose) and eslicarbazepine acetate 800 mg daily. Dose titration appears not to be considered for patients not responding to treatment.
Perspective	NHS Wales and Personal Social Services.	The analysis considers direct medical costs from the perspective of NHS Wales. Personal Social Services costs are not included in the model.

Table 1A. Continued.

	Base case model	Appropriate?
Time horizon	The base case analysis assumes a two-year time horizon. Sensitivity analysis has been conducted for a six-month time horizon.	The model provided by the company appears able to explore up to a 15-year time horizon, but the company suggests it has adopted a two-year time horizon to limit the assumptions required for extrapolation of the available short-term data. Due to the chronic nature of epilepsy, a lifetime horizon would be appropriate to capture all relevant costs and benefits. Longer time horizons (more than two years) were not explored in the model. The short time horizon of analysis is likely to introduce bias, which may (or may not) affect both treatments equally.
Discount rate	A 3.5% annual discount rate is applied to both costs and outcomes. Scenario analyses include discount rates of 0% and 6%.	Appropriate.
Efficacy	Due to a lack of direct comparison studies of eslicarbazepine acetate versus lacosamide, efficacy estimates were derived from a Bayesian indirect comparison of three trials of eslicarbazepine acetate versus placebo and two trials of lacosamide versus placebo. There was no statistically significant difference observed in the proportion of patients achieving a response to treatment, defined as ≥ 50% reduction of seizure frequency, (eslicarbazepine acetate 37.4% [95% CrI 18.1% to 62.1%]; lacosamide 34.4% [95% CrI 13.3% to 64.6%]; RR=1.09 [95%CrI 0.22 to 5.74]). These estimates provide the efficacy data for the initial six-month period that is modelled. Probabilities of transition from responder to non-responder in subsequent six-month periods are independent of treatment received and are reported to be based on five-year observational data used in a published HTA of new AEDs from 2005.	In the absence of direct comparative data, an indirect treatment comparison would seem appropriate. The company reports a numerically greater response rate for eslicarbazepine acetate, but this is not statistically significantly different, and the credible interval around the point estimates of response rates are very wide, reflecting the uncertainty in the estimates. The company acknowledges this and suggests that eslicarbazepine acetate 800 mg daily and lacosamide 400 mg daily are equally efficacious. However, the comparability of the trials included in the analysis is open to question. The number of concomitant AEDs being taken at baseline, and the proportion of patients experiencing secondary generalisation of their primary partial seizures are somewhat lower in the eslicarbazepine acetate trials compared with the lacosamide trials. It would therefore seem possible that patients enrolled in the lacosamide trials had more severe/more refractory epilepsy than those in the eslicarbazepine acetate trials. It is not apparent that this has been considered in the company submission and analyses. The relative efficacy estimates may therefore be biased. The analyses and comparisons presented by the company are limited to lacosamide 400 mg daily (maximum dose) against eslicarbazepine acetate 800 mg daily.
Adverse effects	Adverse events were not considered in the base case analysis, since the company assumed (based on the indirect comparison) the same adverse event rates for eslicarbazepine acetate and lacosamide.	The limited information available regarding the indirect comparison of adverse events would seem to suggest little difference in the adverse event rates considered. As adverse events are effectively excluded from the analysis, withdrawals due to adverse events are also excluded.

Table 1A. Continued.

	Base case model	Appropriate?
Utility values	Utility values for health states 'response', 'no response' and 'no adjunctive therapy' were reportedly taken from published studies of adjunctive therapies in patients with epilepsy.	The utility values assumed in the model are of similar values to those adopted in previous published cost-effectiveness analyses of other AEDs. No sensitivity analyses have been reported by the company around the assumed values.
Resource use and costs	Drug acquisition costs used in the model included the cost of adjunctive treatment (eslicarbazepine acetate 800 mg/day and lacosamide 400 mg/day). Other costs included were: GP and neurologist visits; EEG; A&E admissions and hospitalisation costs, derived from rates of use assumed in previous published studies of other AEDs. Published unit costs are applied. The cost of background AED therapies was not included in the analysis, as these are assumed to be identical for each treatment arm.	Resource use estimates are based largely on Scottish expert opinion used in a previously published cost effectiveness analysis of adjunctive therapy in patients with refractory partial epilepsy. The use of A&E and hospitalisation is reportedly based on outdated cohort study from 1993. The base case analysis estimates total costs to be lower for eslicarbazepine acetate than for lacosamide, driven largely by the small differences in acquisition costs between the drugs at their assumed doses.
Uncertainty	One-way sensitivity analyses were conducted for: initial phase efficacy of eslicarbazepine acetate; initial phase efficacy of lacosamide; differential annual discount rates for costs and benefits (0% and 6%). A scenario analysis was conducted using a six-month time horizon. Probabilistic sensitivity analyses were conducted for the base case and for the scenario using a six-month time horizon.	Few sensitivity analyses have been reported. 95% credible limits for the initial response to lacosamide and to eslicarbazepine acetate are reported to generate positive ICERs of £11,464 to £5,031 and £12,181 to £4,476 per QALY gained. PSA have been reported and suggest that around 64% of simulations fall below a threshold for cost effectiveness of £20,000 to £30,000 per QALY gained. Based on visual inspection of the cost-effectiveness plane, most simulations do not indicate eslicarbazepine acetate to be dominant over lacosamide, and a similar number of simulations suggest eslicarbazepine acetate generates fewer QALYs than lacosamide. The results of the base case deterministic analyses, that report eslicarbazepine acetate to be dominant over lacosamide, therefore should be interpreted with caution.
Model Provided?	Yes	Yes.

A&E: accident and emergency; AEDs: anti-epileptic drugs; AWTTC: All Wales Therapeutics and Toxicology Centre; CUA: cost utility analysis; EEG: electroencephalogram; HTA: health technology appraisal; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year; SPC: Summary of Product Characteristics