**Evidence Review for NHS Surrey Area Prescribing Committee**

**Treatment:** Eslicarbazepine acetate (Zebinix®)

**Prepared by:** Jayesh Shah & Linda Honey

**Date:** April 2011 & June 2012

**Introduction:**

The Surrey Area Prescribing Committee considered eslicarbazepine in April 2011 and the following is taken from the minutes:
*An evidence review was presented to the committee to determine the place in therapy for this treatment. The panel members noted the limited, placebo controlled short term studies available. Eslicarbazepine is currently significantly more expensive than the other treatment options available for epilepsy. The committee noted that the SMC do not support the use of eslicarbazepine in Scotland.*
***Recommendation: eslicarbazepine is not routinely supported and considered black on the traffic light system***

In January 2012 NICE issued CG137 on epilepsy and in relation to eslicarbazepine it states:
*If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide*

*Eslicarbazepine is recommended as a treatment option for adjunctive therapy in the following types of epilepsy that may be considered on referral to tertiary centre . It may be tried where first-line, and first-line adjunctive agents have been tried unsuccessfully:*

- ★ *Refractory focal seizures*
- ★ *Benign epilepsy with centrotemporal spikes, Panaycotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) ❁*

*❁Eslicarbazepine is not licenced for this indication or in anyone under 18 years old.*

***NOTE:** First-line, and first line adjunctive, drugs vary with the indication being treated- see NICE CG137 [http://guidance.nice.org.uk/CG137/NICEGuidance/pdf/English](http://guidance.nice.org.uk/CG137/NICEGuidance/pdf/English)*

Following the issue of NICE CG 137 the PCN is asked to review the recommendation made by the Surrey Area Prescribing Committee in April 2011.

**What is Eslicarbazepine (Zebinix®) for?**

Eslicarbazepine is used to treat adults with partial-onset seizures with or without secondary generalisation. This is a type of epilepsy where too much electrical activity in one side of the brain causes symptoms such as sudden, jerky movements of one part of the body, distorted hearing, sense of smell, or vision, numbness or a sudden sense of fear. Secondary generalisation occurs when the overactivity later reaches the whole brain. Eslicarbazepine must only be used as an 'add-on' to other anti-epileptic medicines.

**Dosing Information**

Eslicarbazepine treatment starts at a dose of 400 mg once a day, before increasing it to the standard dose of 800 mg once a day after one or two weeks. The dose may be increased to 1,200 mg once a day depending on how the patient responds to treatment. Eslicarbazepine can be taken with or without food. Eslicarbazepine should be used with caution in patients aged above 65 years because there is not enough information on the medicine's safety in these patients. Eslicarbazepine should also be used with caution in patients with kidney problems and the dose should be adjusted according to how the kidneys are functioning. The medicine is not recommended in patients with severe problems with their kidneys or liver. Eslicarbazepine is also not recommended in children below 18 years of age due to lack of data.

**Pharmacology**

The active substance in Eslicarbazepine, eslicarbazepine acetate, is converted into the anti-epileptic medicine eslicarbazepine in the body. Epilepsy is caused by excessive electrical activity in the brain. For electrical impulses to travel along nerves there needs to be a rapid movement of sodium into the nerve cells. Eslicarbazepine is thought to work by blocking 'voltage-gated sodium channels', which stops sodium entering the nerve cells. This reduces the activity of the nerve cells in the brain, reducing the intensity and the number of seizures.

**Studies**

The effects of Eslicarbazepine were first tested in experimental models before being studied in humans. Three main studies were performed, involving a total of 1,050 adults with partial-onset seizures that were not controlled by other medicines. All three studies compared Eslicarbazepine given at different doses (400 mg, 800 mg or 1200 mg once a day) with placebo. All of the patients also received other anti-epileptic medicines. The main measure of effectiveness for the three studies was the reduction in the number of seizures over 12 weeks. Therefore quite a short term study.

Looking at the results of the three studies taken together, Eslicarbazepine 800 mg and 1200 mg were more effective than placebo at reducing the number of seizures, when used as add-ons to other anti-epileptic medicines. At the start of the study, patients had around 13 seizures per month. Over the 12 weeks of treatment, this fell to 9.8 and 9 seizures per month in patients taking Eslicarbazepine 800 mg and Eslicarbazepine 1200 mg respectively, compared with 11.7 per month than those taking placebo.

**ADR and Side Effects**

Almost a half of the patients treated with Eslicarbazepine experience side effects. The most common side effects with Eslicarbazepine (seen in more than 1 patient in 10) are dizziness and somnolence. Eslicarbazepine should not be used in people who may be hypersensitive (allergic) to eslicarbazepine, carbamazepine or oxcarbazepine. It must not be used in people with second or third degree atrioventricular block.

**Use in Surrey:** from ePACT data for 2011/12 = 22 items £3,119. Secondary care usage is currently unknown

**Cost: (BNF 62 Sept 2011)**

| Drug | Usual dose range | Monthly cost range |
|---|---|---|
| Eslicarbazepine | 0.8 – 1.2g | £154.20 - £231.30 |
| Lacosamide | 200 – 400mg | £86.50 - £144.16 |
| Zonisamide | 300 – 500mg | £94.08 - £156.80 |
| Oxcarbazepine | 0.6 – 2.4g | £24.72 - £98.78 |
| Gabapentin | 0.9 – 3.6g | £10.51 - £35.82 |
| Pregabalin | 300 – 600mg | £64.40 |
| Levetiracetam | 0.5 – 3g | £29.70 - £153.40 |
| Phenobarbital | 60-180mg | £0.71 - £2.13 |
| Phenytoin | 200-500mg | £1.88 - £4.72 |
| Tiagabine | 30 - 45mg | £68.75 - £103.13 |
| Topiramate | 200 – 400mg | £5.23 - £9.94 |
| Vigabatrin | 2 – 3g | £34.54 - £51.81 |

Included in NICE CG137 as other AEDs that may be considered by the tertiary epilepsy specialist

## Additional Information:

### The All Wales Medicines Strategy Group (AWMSG) – March 2012

The All Wales Medicines Strategy Group (AWMSG) issued a Statement of Advice for the use of eslicarbazepine acetate (Zebinix®) for adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation.

The Advice states that in the absence of a submission from the holder of the marketing authorisation, eslicarbazepine acetate (Zebinix®) cannot be endorsed for use within NHS Wales for this indication.

## Eslicarbazepine acetate add-on for drug-resistant partial epilepsy

Reference: **Chang XC, Yuan H,Wang Y, Xu HQ, Zheng RY. Eslicarbazepine acetate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews. 2011, Issue 12. Art. No.: CD008907.** Source: **Cochrane Library**
Date published: **31/12/2011 19:45**

**Background**

The majority of people with epilepsy will have a good prognosis, but up to 30% of patients will continue to have seizures despite several regimens of antiepileptic drugs. In this review we summarized the current evidence regarding eslicarbazepine acetate (ESL) when used as an add-on treatment for drug-resistant partial epilepsy.

**Objectives**

To evaluate the efficacy and tolerability of ESL when used as an add-on treatment for people with drug-resistant partial epilepsy.

**Search methods**

We searched the Cochrane Epilepsy Group Specialized Register (3 November 2011), The Cochrane Central Register of Controlled Trials (CENTRAL issue 4 of 4, The Cochrane Library 2011), and MEDLINE (1948 to October week 4, 2011). There were no language restrictions. We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies. We also contacted the manufacturers of ESL and experts in the field for information about any unpublished or ongoing studies.

**Selection criteria**

Randomized placebo controlled double-blind add-on trials of ESL in people with drug-resistant partial epilepsy.

**Data collection and analysis**

Two review authors independently selected trials for inclusion and extracted data. Outcomes investigated included 50% or greater reduction in seizure frequency; seizure freedom; treatment withdrawal; adverse effects; and drug interactions. Primary analyses were by intention to treat. The dose response relationship was evaluated in regression models.

**Main results**

Four trials (1146 participants) were included; all studies were funded by BIAL. The overall relative risk (RR) with 95% confidence interval (CIs) for 50% or greater reduction in seizure frequency outcome was 1.86 (95% CI 1.46 to 2.36). Dose regression analysis showed evidence that ESL reduced seizure frequency with an increase in efficacy with increasing doses of ESL. ESL was significantly associated with seizure freedom (RR 3.04, 95% CI 1.44 to 6.42). Participants seemed more likely (albeit not significantly) to have ESL withdrawn for adverse effects (RR 2.26, 95% CI 0.98 to 5.21) but not for any reason (RR 1.07, 95% CI 0.73 to 1.57). The following adverse effects were significantly associated with ESL: dizziness (RR 3.09, 99% CI 1.76 to 5.43); nausea (RR 3.06, 99% CI 1.07 to 8.74); and diplopia (RR 3.73, 99% CI 1.19 to 11.64).

**Authors' conclusions**

Elsicarbazepine acetate reduces seizure frequency when used as an add-on treatment for people with drug-resistant partial epilepsy. The trials included in this review were of short-term duration and focused on adults.

**NICE Clinical Guidance 137 Epliepsy January 2012**

If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide

Eslicarbazepine is recommended as a treatment option for adjunctive therapy in the following types of epilepsy that may be considered on referral to tertiary centre . It may be tried where first-line, and first-line adjunctive agents have been tried unsuccessfully:

- ★ Refractory focal seizures
- ★ Benign epilepsy with centrotemporal spikes, Panaycotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) ☸

☸Eslicarbazepine is not licenced for this indication or in anyone under 18 years old.

**NOTE:** First-line, and first line adjunctive, drugs vary with the indication being treated- see NICE CG137 http://guidance.nice.org.uk/CG137/NICEGuidance/pdf/English

## New Medicines Profile: Eslicarbazepine

Publisher: **North West Medicines Information Centre**
Date published: **22/02/2010 16:08**

### Summary

by: **Lindsay Banks**


- Eslicarbazepine acetate is a new antiepileptic drug (AED) which is licensed as add-on therapy in adults with partial-onset seizures with or without secondary generalisation.
- In three 12-week clinical trials eslicarbazepine has been shown to be more effective than placebo at a dose of 800mg or 1,200mg once daily as add-on treatment in patients receiving one or more AEDs in the management of simple and complex partial seizures with or without secondary generalisation. There are no active-comparator trials.
- Data from open-label extension studies of one year duration suggest that the efficacy of eslicarbazepine is maintained.
- Eslicarbazepine has similar adverse effects to oxcarbazepine. The most common adverse effects are dizziness, somnolence, headache, diplopia, nausea and abnormal coordination. These are more frequent in patients treated concurrently with carbamazepine.
- Data on eslicarbazepine are limited. Further trials are needed to ascertain if it offers advantages over other AEDs in terms of efficacy, safety and quality of life. For patients who have not responded well to other treatments it may be an alternative although it is not clear which patients would benefit most.
- Currently there are no published economic analyses however, compared with alternative AEDs eslicarbazepine is expensive.


## Scottish Medicines Committee – Nov 2010

**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.

## Recommendations

**Option 1:** Eslicarbazepine is supported for use in line with NICE CG137 when adjunctive treatment is ineffective or not tolerated following a discussion or referral to a tertiary epilepsy specialist for:

- ★ Refractory focal seizures
- ★ Benign epilepsy with centrotemporal spikes, Panaycotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type)

Eslicarbazepine would be considered as amber* on the traffic light system

**Option 2:** Not routinely recommended for use in NHS Surrey and considered as black on the traffic light system.

**Comments from June 2012**
**Removed for governance purposes**