Eslicarbazepine acetate for partial onset epilepsy - refractory

May 2009

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Eslicarbazepine acetate for partial onset epilepsy - refractory

Target group
- Epilepsy: adjunctive treatment of partial-onset seizures in adult patients who are refractory to current treatment.

Technology description
Eslicarbazepine acetate (Zebinix) is an oral prodrug of S-licarbazepine and acts on the voltage-gated sodium channel in its inactivated state. Eslicarbazepine acetate is a third generation drug belonging to the same drug class as carbamazepine and oxcarbazepine.

The recommended initial dose of eslicarbazepine is 400mg once daily. After one or two weeks, the dose is increased to 800mg once daily. Depending on the response to the treatment, the dose can be increased to 1,200mg once daily.

Innovation and/or advantages
Eslicarbazepine acetate offers another treatment option for this patient group with once daily administration.

Developer
Bial (Eisai is the licence holder in Europe).

Availability, launch or marketing dates, and licensing plans:
An application for a Marketing Authorisation with the EMEA was made in March 2008 and approval granted in April 2009.

NHS or Government priority area:
This topic is relevant to The Long-term (Neurological) Conditions National Service Framework (2005).

Relevant guidance
- NICE technology appraisal. The clinical effectiveness and cost effectiveness of newer drugs for epilepsy in adults. March 2004¹.
- HTA. A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery. 2006³.
- SIGN. Diagnosis and management of epilepsy in adults. 2003⁴.

Clinical need and burden of disease
Epilepsy is the most common serious neurological condition in the UK⁵ and is characterised by recurrent, unprovoked seizures (i.e. not an isolated event or due to an underlying acute reversible medical problem such as meningitis or alcohol withdrawal)⁶. An epileptic seizure is a brief disturbance of consciousness, behaviour, emotion, motor function, or sensation that is due to abnormal electrical discharge in the brain⁶. Epilepsy is not usually diagnosed unless the person has had at least two unprovoked seizures¹.

Partial-onset seizures are classified as simple partial seizures and complex partial seizures, either of which may lead to secondary generalised tonic-clonic seizures. The
defining element of simple partial seizures is a seizure with preserved consciousness and this group includes sensory, motor, autonomic, and psychic types. Many patients with complex partial seizures have an aura warning them of their seizure. Diagnosis is based on the repeated, stereotypic occurrence of the same experience supported in some cases by focal changes on an EEG.

About 1 in 200 of the population receives treatment for epilepsy and lifetime prevalence is estimated between 2% and 5%. One study found that the reported prevalence rate increased with age, from 3.9 per 1,000 population at the age of 7 years, to 4.9 per 1,000 population at 16 years\(^2\). Approximately 404,000 people in England and Wales have epilepsy (based on 2003 population census estimate)\(^7\).

Existing comparators and treatments

Current NICE guidelines recommend monotherapy with an antiepileptic drug (AED) where possible\(^1\).

- If the older drugs (such as sodium valproate and carbamazepine) do not stop seizures, or if there are side effects, one of the newer drugs can be tried, as long as it is suitable for that type of epilepsy.
- Gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate can be given as monotherapy, or if they do not control seizures, in combination with another drug.
- Clobazam, lacosamide, pregabalin, tiagabine, vigabatrin and zonisamide are used as combination therapy (adjunctive or add-on therapy) with another drug.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>BIA-2093-301: eslicarbazepine acetate adjunct vs. placebo; phase III</th>
<th>BIA-2093-302: eslicarbazepine acetate adjunct vs. placebo; phase III</th>
<th>BIA-2093-303: eslicarbazepine acetate adjunct vs. placebo; phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Published(^8).</td>
<td>Abstract(^7,10,11).</td>
<td>Abstract(^12,13,14).</td>
</tr>
<tr>
<td>Location</td>
<td>EU, Croatia, Russia, Ukraine.</td>
<td>EU, Argentina, Australia, Brazil, South Africa.</td>
<td>Mexico, Spain, Portugal.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=402; adults; ≥4 partial-onset seizures per 4 weeks despite treatment with 1-2 AEDs. All participants received 8 weeks single blind placebo, then randomised to: Eslicarbazepine 400, 800, 1,200mg or placebo once daily for 18 weeks (2 weeks titration, 12 weeks maintenance and 4 weeks tapering off).</td>
<td>n=393; adults; ≥4 partial-onset seizures per 4 weeks despite treatment with 1-3 AEDs. Randomised to eslicarbazepine 400mg, 800mg, 1,200mg or placebo once daily for 14 weeks. Titration in 1,200mg group. Open label extension to 52 weeks optional. Participants continued with current anti-epilepsy drugs.</td>
<td>n=252; adults; ≥4 partial-onset seizures per 4 weeks despite treatment with 1-2 AEDs. Randomised to eslicarbazepine 800mg, 1,200mg or placebo once daily after an 8-week baseline. Half the maintenance dose given during 2 weeks before entering a 12 week maintenance period. Open label extension to 52 weeks optional. Participants continued with current anti-epilepsy drugs.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-</td>
<td>14 and 52 weeks.</td>
<td>14 and 52 weeks.</td>
</tr>
</tbody>
</table>
Primary outcomes | Seizure frequency. | Seizure frequency. | Seizure frequency.
--- | --- | --- | ---
Secondary outcomes | Responders, relative reduction or exacerbation of seizure frequency, proportion seizure-free. | Responders. | Responders.
Key results | Seizure frequency adjusted per 4 weeks over the maintenance period was significantly lower than placebo in eslicarbazepine 1,200mg (p=0.0003) and 800mg (p=0.0028). Median relative reduction in seizure frequency was 16% (placebo), 26% (400mg), 36% (800mg) and 45% (1,200mg). | At week 14, difference vs. placebo was significant for eslicarbazepine 800mg and 1,200mg (p≤0.001). Median relative reduction in seizure frequency 5% (placebo), 21% (400 mg), 33% (800mg) and 33% (1,200mg). | At week 14, difference vs. placebo was significant for eslicarbazepine 800mg and 1,200mg (p<0.05). Median relative reduction in seizure frequency 17% (placebo), 38% (800mg), and 42% (1,200mg). Similar efficacy results in patients administered eslicarbazepine with or without carbamazepine.
Adverse effects (AEs) | Most common AEs were mild or moderate, and included dizziness, headache and diplopia. | Most common AEs were mild or moderate, and included dizziness, somnolence and headache. Discontinuation due to treatment-emergent AEs were 3.0% (placebo), 12.5% (400mg), 18.8% (800mg), 26.5% (1,200mg). | Most common AEs were mild or moderate, and included dizziness, somnolence and headache. Discontinuation due to treatment-emergent AEs were 6.9% (placebo), 8.2% (800mg) and 11.3% (1,200mg).

Trial Study 304: refractory partial onset seizures; adjunct eslicarbazepine acetate vs. placebo; phase III.
Sponsor Bial.
Status Ongoing.
Location Europe, Argentina, Brazil.
Design Randomised, double-blind, placebo-controlled.
Participants and schedule n=360; aged 16 years or more, currently receiving AEDs, at least 4 partial onset seizures in 4 weeks during 8-week baseline period. Randomised to eslicarbazepine 800, 1,200mg or placebo once daily for 2-week titration period and a 12-week maintenance period.
Follow-up 14 weeks.
Primary outcomes Seizure frequency.
Secondary outcomes Safety and tolerability, health-related quality-of-life, depressive symptoms.

Estimated cost and cost impact
The cost of eslicarbazepine is not yet known. The cost of some other drug treatments are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>28 days dose range costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>300-1,200mg 3 times daily.</td>
<td>£7.53-7.76</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>250-1,500mg twice daily.</td>
<td>£27.72-83.16</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>100-200mg daily in 1-2 divided doses.</td>
<td>£4.13-5.45</td>
</tr>
</tbody>
</table>
Oxcarbazepine 600-2,400mg daily in divided doses. £22.32-88.44
Topiramate (Topamax) 100-400mg daily in 2 divided doses. £31.40-109.22

Potential or intended impact – speculative

Patients
☐ Reduced morbidity ☐ Reduced mortality or increased length of survival ☐ Improved quality of life for patients and/or carers
☐ Quicker, earlier or more accurate diagnosis or identification of disease ☐ Other: ☐ None identified

Services
☐ Increased use ☐ Service reorganisation required ☐ Staff or training required
☐ Decreased use ☐ Other: ☐ None identified

Costs
☐ Increased unit cost compared to alternative ☐ Increased costs: more patients coming for treatment ☐ Increased costs: capital investment needed
☐ New costs: Adjunctive therapy ☐ Savings: ☐ Other: Unclear until relative cost known

References
