Eslicarbazepine acetate (Zebinix) for partial onset seizures in epilepsy – monotherapy

May 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Eslicarbazepine acetate (Zebinix) for partial onset seizures in epilepsy – monotherapy

Target group

- Epilepsy: partial onset seizures with or without secondary generalisation – monotherapy.

Technology description

Eslicarbazepine acetate (Zebinix) is an antiepileptic, voltage-gated, sodium channel blocker that has a higher affinity for the inactivated state of the channel compared with the resting state. Eslicarbazepine acetate is intended to be a monotherapeutic option for patients with partial onset seizures in epilepsy with or without secondary generalisation. In phase III clinical trials, eslicarbazepine acetate was administered orally at 400-600mg once daily during the first week of treatment. After one or two weeks, the dose was increased to 800-1,200mg once daily. Depending on the response to the treatment, the dose can be increased to 1,600mg or 2,400mg (maximum dose) once daily.

Eslicarbazepine acetate is licensed for the adjunctive treatment of adults with partial onset seizures in epilepsy in the EU. It is also in phase III trials for post-herpetic neuralgia and the adjunctive treatment of adolescents and children with partial onset seizures in epilepsy, and in phase II trials for bipolar disorder and neuropathic pain.

Common adverse events associated with eslicarbazepine acetate when used for the adjunctive treatment of adults with partial onset seizures in epilepsy are dizziness, somnolence, headache, abnormal coordination, disturbance in attention, diplopia, blurred vision, vertigo, nausea, vomiting, diarrhoea, rash and fatigue.

Innovation and/or advantages

If licensed for this indication, eslicarbazepine acetate will offer an alternative monotherapy regimen for this patient group.

Developer

Bial; Sunovion (Eisai Ltd is the European licence holder).

Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

NHS or Government priority area

This topic is relevant to the National Service Framework for Long-term (Neurological) Conditions (2005).

Relevant guidance

- NICE technology appraisal in development. Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. Expected date of issue to be confirmed.
- NICE clinical guideline update in development. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). Expected date of issue to be confirmed.

• Canadian Agency for Drugs and Technologies in Health. Pharmacological treatments in patients with epilepsy: guidelines. April 2011.

• SIGN. Diagnosis and management of epilepsy in adults. 2003.

Clinical need and burden of disease
Epilepsy affects approximately 260,000 to 416,000 people in England and Wales, 55% of whom have partial onset seizures. The mortality risk in people with epilepsy, particularly those with more severe seizures, is 2-3 times higher than the general population due to sudden unexpected death in epilepsy (SUDEP), underlying pathology related to the condition and accidents. About 40% of patients develop epilepsy below the age of 16 years, while about 20% do not develop their condition until age 65 years or older.

It has been estimated that 70% of people with active epilepsy can control recurrent seizures with antiepileptic drugs (AEDs), therefore approximately 42,900-68,640 patients in England and Wales with partial onset seizures remain refractory to treatment. In 2009, there were 3,807 hospital admissions due to localisation-related (partial) seizures (ICD G40.0-G40.2) in England, equating to 17,913 bed days.

Existing comparators and treatments
The aim of epilepsy treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more AEDs. NICE clinical guideline 20 recommends AED monotherapy where possible. Current first line pharmacological treatment options for partial onset seizures include:

• Carbamazepine
• Lamotrigine
• Oxcarbazepine
• Sodium valproate
• Levetiracetan
• Gabapentin

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01162460, BIA-2093-311; eslicarbazepine acetate vs carbamazepine; phase III.</th>
<th>NCT01091662, 093-046; eslicarbazepine acetate; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Bial-Portella CSA.</td>
<td>Sunovion.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹¹, manufacturer.</td>
<td>Trial registry¹².</td>
</tr>
<tr>
<td>Location</td>
<td>Belgium.</td>
<td>USA, Czech Republic and Ukraine.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised.</td>
</tr>
</tbody>
</table>
| Participants and schedule | n=900 (planned); adults; epilepsy; partial seizures; newly diagnosed. Randomised to eslicarbazepine acetate 400mg daily weeks 1 and 2, and 800mg daily week 3 onwards; or carbamazepine controlled release 200mg daily weeks 1 and 2, and 400mg daily week 3 onwards. | n=202 (planned); adults aged ≥16; epilepsy; partial seizures; uncontrolled but stable treatment with 1-2 AEDs in month prior to study entry. Randomised to eslicarbazepine acetate 1,600mg, (600mg daily week 1, 1,200mg daily week 2, and 1,600mg.
If seizures occur, treatment dose increased to 1,200mg daily for eslicarbazepine acetate, or 800mg daily for carbamazepine. week 3-18); or eslicarbazepine acetate 1,200mg (400mg daily week 1, 800mg daily week 2, and 1,200mg week 3-18). Other AEDs tapered off weeks 3-8.

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment period 26 weeks; patients continue treatment if seizure free.</th>
<th>Active treatment period 18 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Percentage of patients remaining seizure free for 26 weeks.</td>
<td>Percentage of patients meeting at least 1 of 5 exit criteria at 16 weeks (exit criteria not reported).</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Percentage of patients remaining seizure free after 1 year; time to first seizure; 31-item quality of life in epilepsy questionnaire (QOLIE-31); adverse events.</td>
<td>Percentage of patients remaining seizure free; completion rate; responder rate; QOLIE-31.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00866775, 093-045; eslicarbazepine acetate; phase III.</th>
<th>NCT00910247, 093-050; eslicarbazepine acetate; phase III extension.</th>
</tr>
</thead>
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<tr>
<td>Sponsor</td>
<td>Sunovion.</td>
<td>Sunovion.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Location</td>
<td>USA and Canada.</td>
<td>USA, Canada and Czech Republic.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, uncontrolled.</td>
<td>Open-label.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=200 (planned); adults aged ≥16; epilepsy; partial seizures; uncontrolled but stable treatment with 1-2 AEDs in month prior to study entry. Randomised to eslicarbazepine acetate 1,600mg, (600mg daily week 1, 1,200mg daily week 2, and 1,600mg week 3-18); or eslicarbazepine acetate 1,200mg (400mg daily week 1, 800mg daily week 2, and 1,200mg week 3-18). Other AEDs tapered off weeks 3-8.</td>
<td>n=348 (planned); adults aged ≥16; epilepsy; partial seizures; completed trial NCT01091662 or NCT00866775. Patients continue on existing dose.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 18 weeks.</td>
<td>Active treatment period 1 year.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Percentage of patients meeting at least 1 of 5 exit criteria at 16 weeks (exit criteria not reported).</td>
<td>AEs.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Percentage of patients remaining seizure free; completion rate; responder rate; QOLIE-31.</td>
<td>Time on eslicarbazepine acetate monotherapy; change in seizure frequency; completion rate; responder rate; QOLIE-31.</td>
</tr>
</tbody>
</table>

**Estimated cost and cost impact**

The cost of eslicarbazepine acetate has not yet been determined for this indication. However, eslicarbazepine acetate (Zebinix) for the adjunctive treatment of epilepsy in adult patients with partial onset seizures costs £154.20 for 28 days at 800mg daily \(^{12}\). The
cost of other selected monotherapy treatment options for partial onset seizures in adults are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (maintenance therapy)</th>
<th>Cost per 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>400mg twice daily</td>
<td>£13.18</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>100mg twice daily</td>
<td>£4.53</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>600mg twice daily</td>
<td>£44.72</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>500mg twice daily</td>
<td>£10</td>
</tr>
<tr>
<td>Levetiracetan (Keppra)</td>
<td>500mg twice daily</td>
<td>£52.30</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>600mg three times daily</td>
<td>£24.85</td>
</tr>
</tbody>
</table>

Claimed or potential impact – speculative

Patients

- ☒ Reduced mortality or increased length of survival
- ☐ Reducing or improved quality of life for patients and/or carers
- ☒ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ None identified

Services

- ☒ Increased use
  - ☐ Service organisation: implementation in specialist epilepsy clinics.
  - ☐ Staff requirements
- ☐ Decreased use
  - ☐ Other:
  - ☒ None identified

Costs

- ☒ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☐ Other:

Other issues

- ☒ Clinical uncertainty or other research question identified:
  - Expert reports there may be a need to monitor behavioural/psychiatric symptoms as secondary outcomes in future trials and clinical practice.
- ☐ None identified

References

1 National Institute for Health and Clinical Excellence. Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. Technology appraisal in development. Expected date of publication to be confirmed.


3 National Institute for Health and Clinical Excellence. The diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). Expected date of publication to be confirmed.


11 Clinicaltrials.gov. Efficacy and safety of eslicarbazepine acetate as monotherapy for patients with newly diagnosed partial-onset seizures.

