Zonisamide (Zonegran) for newly diagnosed partial seizures in epilepsy

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Zonisamide (Zonegran) for newly diagnosed partial seizures in epilepsy

Target group
- Epilepsy: newly diagnosed partial seizures – first line; monotherapy.

Technology description
Zonisamide (Zonegran, AD 180) is a 1,2-benzisoxazole derivative that exhibits a broad spectrum of antiepileptic activity. The exact mechanism of action is unknown, but it appears to block voltage-sensitive sodium and T-type calcium channels and the propagation of seizure discharges; zonisamide may also protect neurons from free-radical damage. Zonisamide is intended as a first line monotherapy treatment for epileptic patients with newly diagnosed partial seizures. In phase III clinical trials it was administered orally at an initial dose of 100mg/day then increased fortnightly until a final dose of 300mg/day was achieved.

Zonisamide is licensed in the UK for the adjunctive treatment of epilepsy in adult patients with partial seizures, with or without secondary generalisation. Recognised side effects include- anorexia, depression, agitation, irritability, confusional state, ataxia, dizziness, memory impairment, somnolence and diplopia. It is also in phase III clinical trials for the treatment of epilepsy in children.

Innovation and/or advantages
If licensed for this indication, zonisamide will offer an alternative monotherapy regimen for this patient group.

Developer
Eisai Ltd.

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.
- 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\(^6\). The mortality risk in people with epilepsy, particularly those with more severe seizures, is 2-3 times higher than the general population\(^6,10\), due to sudden unexpected death in epilepsy (SUDEP), underlying pathology related to the condition, and accidents\(^8\). About 40% of patients develop epilepsy below the age of 16 years, while about 20% do not develop their condition until age of 65 years or older\(^8\).

It has been estimated that 70% of people with active epilepsy can control recurrent seizures with antiepileptic drugs (AEDs)\(^9\), therefore approximately 42,900-68,640 patients in England and Wales with partial onset seizures are refractory to treatment. In 2009, there were 3,807 hospital admissions due to localisation-related (partial) seizures in England, equating to 17,913 bed days\(^10\).

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\(^8,11\). NICE guidelines recommend monotherapy with an AED where possible\(^8\). Current first line pharmacological treatment options for partial onset seizures include: carbamazepine, lamotrigine, oxcarbazepine, sodium valproate, levetiracetam and gabapentin\(^11\).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00477295, E2090-E044-310; zonisamide vs carbamazepine; phase III.</th>
<th>NCT00848549, E2090-E044-314; zonisamide vs carbamazepine; phase III extension of NCT00477295.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Eisai Ltd.</td>
<td>Eisai Ltd.</td>
</tr>
<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^12), manufacturer.</td>
<td>Trial registry(^13), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK) and other countries.</td>
<td>EU (inc UK) and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=682; adults; epilepsy; untreated newly diagnosed partial seizures. Randomised to zonisamide or carbamazepine. Zonisamide group received initial dose of 100mg daily increased by 100mg fortnightly until a final dose of 300mg daily was achieved in week 6. Carbamazepine group followed the same fortnightly dose escalation regimen starting at 200mg daily and achieving 600mg daily by week 6. Doses maintained unless seizure more than two weeks after dose increase.</td>
<td>n=580 (planned); adults; epilepsy; untreated newly diagnosed partial seizures; completed trial NCT00477295. Participants continued with dose level achieved in previous trial. Doses adjusted depending on seizure-free status or tolerability/adverse events.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment period 26 weeks; follow-up 52 weeks.</td>
<td>Patients attend clinic every 13 weeks; follow-up at months 12, 15, 18 and 24.</td>
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<tr>
<td>Primary outcome</td>
<td>Proportion of patients remaining seizure free at 26 weeks.</td>
<td>Occurrence of seizures.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Proportion of patients remaining seizure free at 52 weeks; safety; AEs; quality of life (QoL) measured by QoL in epilepsy</td>
<td>Safety; AEs; QoL.</td>
</tr>
</tbody>
</table>
inventory (QOLIE-31-P), SF-36 and EQ-5D.

| Expected completion date | - | Sept 2011. |

**Estimated cost and cost impact**

The cost of zonisamide has not yet been determined for this indication. However, zonisamide (Zonegran) for the adjunctive treatment of epilepsy in adult patients with partial seizures costs £109.81 per month (300-500mg daily as maintenance therapy). The cost of other selected monotherapy treatment options for partial seizures in adults are:

<table>
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<tr>
<th>Drug</th>
<th>Dose (maintenance therapy)</th>
<th>Cost per 28 days</th>
</tr>
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<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>
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<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
- Reduction in associated morbidity 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: will require initiation in specialist epilepsy clinics.
- Staff requirements
- Decreased use
- None identified

**Costs**

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- New costs:
- Savings:
- None identified

**Other issues**

- Clinical uncertainty or other research question identified:
  - Expert suggests that further research may be required to monitor behavioural/psychiatric symptoms as potential adverse outcomes.
- None identified

**References**

4 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.