Retigabine for partial onset epilepsy - refractory

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Retigabine 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
Retigabine (D20443; D23129; GKE841) is a first-in-class potassium channel agonist with selectivity for neuronal cells and a positive modulator of GABAergic neurotransmission; it also increases GABA synthesis with minor effects on sodium and calcium channels. Retigabine is intended to be used in addition to standard treatment and is an oral immediate-release (IR) anticonvulsant, administered at 600, 900 or 1,200 mg per day, in three equally divided doses.

Retigabine is also in a phase IIa clinical trial for postherpetic neuralgia.

Innovation and/or advantages
Retigabine is a first-in-class anticonvulsant and, as an adjunctive treatment, may be more efficacious in controlling seizures than current treatment alone.

Developer
GlaxoSmithKline UK Ltd (and Valeant Pharmaceuticals).

Availability, launch or marketing dates, and licensing plans:
In phase III clinical trials.

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

Relevant guidance
- 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. 2006.
- SIGN. Diagnosis and management of epilepsy in adults. 2003.

Clinical need and burden of disease
Epilepsy is the most common serious neurological condition in the UK 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). An epileptic seizure is a brief disturbance of consciousness, behaviour, emotion, motor function, or sensation that is due to abnormal electrical discharge in the brain. Epilepsy is not usually diagnosed unless the person has had at least two unprovoked seizures.

Partial-onset seizures are classified as simple partial seizures, complex partial seizures, or secondarily 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 in association with focal EEG changes or on recurrent auras leading to a complex partial seizure or a secondarily generalised seizure.

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.

**Existing comparators and treatments**

Current NICE guidelines recommend monotherapy with an antiepileptic drug (AED) where possible:

- 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.
- Lamotrigine, oxcarbazepine and topiramate can be given as monotherapy, or if they do not control seizures, in combination with another drug.
- Gabapentin, levetiracetam, tiagabine and vigabatrin are generally used as combination therapy with another drug.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>RESTORE 2; VRX-RET-E22-302; EUDRACT No. 2005-002182-36; NCT00235755: retigabine vs placebo; phase III.</th>
<th>RESTORE 1; VRX-RET-E22-301; NCT00232596: retigabine vs placebo; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Valeant Pharmaceuticals.</td>
<td>Valeant Pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Completed; abstract.</td>
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<tr>
<td>Location</td>
<td>Europe, Israel, Australia, and South Africa.</td>
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<td>Design</td>
<td>Randomised, double blind, placebo controlled.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=538. Epilepsy; adjunctive therapy; refractory with ≥4 partial-onset seizures over the 8 week baseline phase; receiving up to 3 concomitant AEDs. Randomised to retigabine 600 or 900mg/day or placebo for 4 weeks in addition to current AEDs. Those completing 4 weeks entered a maintenance phase of 12 weeks.</td>
<td>n=301. Epilepsy; adjunctive therapy; refractory with ≥4 partial-onset seizures over the 8 week baseline phase; receiving up to 3 concomitant AEDs. Randomised to retigabine 1,200mg/day or placebo for 4 weeks in addition to current AEDs. Those completing 4 weeks entered a maintenance phase of 12 weeks.</td>
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<tr>
<td>Follow-up</td>
<td>4 weeks; 12 week maintenance phase.</td>
<td>4 week prospective baseline; 12 week maintenance phase.</td>
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<tr>
<td>Primary outcome</td>
<td>Total partial seizure frequency.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Response; Clinical Global Impressions (CGI) and Patient Global Impressions (PGI) assessments.</td>
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<td>Key results</td>
<td>Retigabine was generally well tolerated.</td>
<td>8% on retigabine vs. 2% on placebo were seizure-free during maintenance (p&lt;0.03).</td>
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</table>
Adverse effects

- Most common (>10%) adverse events (placebo, retigabine 600mg, retigabine 900mg): dizziness (6%, 17%, 26%); somnolence (10%, 14%, 26%); headache (14%, 11%, 17%); and fatigue (3%, 17%, 15%). Discontinuations due to adverse events: placebo, 8%; retigabine 600mg, 14%; retigabine 900mg, 26%, occurring mostly during forced titration.

- Most common AEs (retigabine, placebo): dizziness (8%, 2%); confusion (6%, 1%); fatigue (3%, 0%). AEs were generally mild-to-moderate severity. Study discontinuation: retigabine, 27%; placebo, 9%, with most discontinuations occurring during forced titration.

Trial

- Retigabine vs placebo

Sponsor

- Valeant Pharmaceuticals

Status

- Published

Design

- Randomised, double-blind, placebo-controlled

Participants and schedule

- n=399. Epilepsy; adjunctive therapy in refractory with partial-onset seizures. 8 week baseline phase then randomised to 600, 900, or 1200mg/day or placebo for 16-weeks (8 week forced titration and 8 week maintenance).

Follow-up

- 24 weeks

Primary outcome

- Change in monthly seizure frequency

Secondary outcomes

- ≥50% reduction in seizure frequency (responder rate); emergence of new seizure types; CGI; PGI; safety

Key results

- Median percent change in monthly total partial seizure frequency from baseline was –23% for 600mg, –29% for 900mg, and –35% for 1,200mg vs –13% for placebo (p < 0.001 for overall difference across all treatment arms). Responder rates for retigabine were 23% for 600mg, 32% for 900mg (p=0.021), and 33% for 1,200mg (p=0.016), vs 16% for placebo.

Adverse effects

- Most common AEs: somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia, and diplopia.

Estimated cost and cost impact

The cost of retigabine is not yet known. The cost of other drug treatments are:

- Gabapentin 300mg 3 times daily. £30.58
- Levetiracetam 250mg twice daily. £29.70
- Tiagabine 5mg twice daily. £43.37
- Vigabatrin 1g daily (in single or 2 divided doses). £30.84

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
- None identified
Costs

- Increased unit cost compared to alternative
- New costs: Additional therapy
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- Savings:
- Other:

References

9. Brodie M and Mansbach H. Retigabine 600 or 900mg/day as adjunctive therapy in adults with partial onset seizure. Epilepsia 0 Suppl. 0 (Abst. 1.25 ), 2008.