Perampanel for adjuvant treatment of primary generalised tonic-clonic seizures

SUMMARY

Perampanel is intended as adjuvant treatment for primary generalised tonic-clonic seizures. If licensed, perampanel, a first-in-class, non-competitive, AMPA-type glutamate receptor antagonist, will offer an additional treatment option for this patient group. AMPA receptors are ligand-gated ion channels that bind glutamate, leading to sodium influx and neuronal depolarisation. Nerve cell damage can lead to increased levels of glutamate, resulting in pathological activation of AMPA receptors. Perampanel is licensed in the EU as adjunctive treatment for partial-onset seizures, with or without secondary generalised seizures, in patients with epilepsy aged 12 years and older.

Epilepsy affects more than 500,000 people in the UK, and is defined as a neurological condition characterised by recurrent epileptic seizures unprovoked by any immediately identifiable cause. Accurate estimates of incidence and prevalence are difficult to achieve because identifying people who may have epilepsy is difficult. Epilepsy has been estimated to affect between 362,000 and 415,000 people in England. Sixty per cent of people with epilepsy have convulsive seizures, of which two thirds have focal epilepsies with secondary generalised seizures, and the other third will have tonic-clonic seizures. In 2012-13, there were 1,257 admissions for other generalised epilepsy and epileptic syndromes in England, resulting in 4,656 bed days and 1,405 finished consultant episodes.

Perampanel is currently in one phase III clinical trial comparing its effect on change in primary generalised tonic-clonic seizure frequency against treatment with placebo. This trial is expected to complete in June 2014.
TARGET GROUP


TECHNOLOGY

DESCRIPTION

Perampanel (Fycompa; E 2007; ER-155055-90) is a first-in-class, non-competitive, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)-type glutamate receptor antagonist. AMPA receptors are ligand-gated ion channels that bind glutamate, leading to sodium influx and neuronal depolarisation. Nerve cell damage can lead to increased levels of glutamate, resulting in pathological activation of AMPA receptors. Perampanel is intended as adjuvant treatment for primary generalised tonic-clonic seizures. It is administered orally up to 8 mg once daily on a continuing basis.

Perampanel is licensed in the EU as adjunctive treatment for partial-onset seizures, with or without secondary generalised seizures, in patients with epilepsy aged 12 years and older. The most commonly reported adverse reactions associated with perampanel treatment are dizziness, somnolence, ataxia, dysarthria, back pain, nausea, vertigo, diplopia, blurred vision, aggression, anxiety, and decreased/increased appetite, anger, confusional state, balance disorder, irritability, gait disturbance, fatigue, weight increase and fall.

INNOVATION and/or ADVANTAGES

If licensed, perampanel, a first-in-class, non-competitive, AMPA-type glutamate receptor antagonist, will offer an additional treatment option for this patient group.

DEVELOPER

Eisai Limited.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Epilepsy affects more than 500,000 people in the UK, and is defined as a neurological condition characterised by recurrent epileptic seizures unprovoked by any immediately identifiable cause. An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. The clinical presentation of epilepsy depends on a number of factors, primarily the parts of the brain affected, the pattern of spread of epileptic discharges through the brain, the cause of the epilepsy and the age of the individual. Seizures can affect sensory, motor, and autonomic function; consciousness; emotional state; memory; cognition; or behaviour. Not all seizures affect all of these factors, but all influence at least one.
Seizures are divided into two main types: partial seizures (also called focal seizures) and generalised seizures. Partial epileptic seizures originate within networks limited to one hemisphere. They may be localised or more widely distributed and for each seizure type, initial onset is consistent from one seizure to another. There are two types of partial seizures: simple partial and complex partial seizures. Generalised epileptic seizures originate in, and rapidly engage, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures but do not necessarily include the entire cortex. Although individual seizure onsets can appear localised, the location and lateralisation are not consistent from one seizure to another. There are six main types of generalised seizures: absence seizures, myoclonic jerks, clonic seizure, atonic seizure, tonic seizure and tonic-clonic seizure. Tonic-clonic seizures are characterised by initial generalised muscle stiffening (tonic phase), followed by rhythmic jerking of the limbs (clonic phase), usually lasting a few minutes. The person may bite their tongue and may be incontinent. They may feel confused or sleepy afterwards, and take a while to recover fully.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:
- The National Service frameworks for long-term conditions (including long-term neurological conditions) (2005).

CLINICAL NEED and BURDEN OF DISEASE

Worldwide, about 65 million people have epilepsy, making it the most common neurological disorder after stroke, and a major burden for public health systems. Accurate estimates of incidence and prevalence are difficult to achieve because identifying people who may have epilepsy is difficult. Epilepsy has been estimated to affect between 362,000 and 415,000 people in England. In addition, there will be further individuals, estimated to be 5–30% of diagnosed cases (amounting to up to another 124,500 people), who have been diagnosed with epilepsy, but in whom the diagnosis is incorrect. Incidence is estimated to be 50 per 100,000 per year and the prevalence of active epilepsy in the UK is estimated to be 5–10 cases per 1,000. Two-thirds of people with active epilepsy have their epilepsy controlled satisfactorily with anti-epileptic drugs (AEDs). Sixty per cent of people with epilepsy have convulsive seizures, of which two thirds have focal epilepsies with secondary generalised seizures, and the other third will have tonic-clonic seizures. About one third of patients have less than one seizure a year, one-third have between one and 12 seizures per year and the remainder have more than one seizure per month.

In adults and children with epilepsy, most (70%) will enter remission (seizure free for five years on or off treatment), but 30% develop chronic epilepsy. The number of seizures in the
6 months after first presentation is an important predictive factor for both early and long-term remission of seizures. The UK National General Practice Study of Epilepsy found that the majority (60%) of people with newly diagnosed or suspected epileptic seizures had epilepsy with no identifiable aetiology. Vascular disease was the aetiology in 15% and tumour in 6%. Among older subjects the proportion with identifiable causes was much higher: 49% were due to vascular disease and 11% to tumours.

In 2012-13, there were 1,257 admissions for other generalized epilepsy and epileptic syndromes (ICD-10 G40.4) in England, resulting in 4,656 bed days and 1,405 finished consultant episodes.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

Other Guidance
- International League Against Epilepsy. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. 2011.

CURRENT TREATMENT OPTIONS

The mainstay of treatment for epilepsy is anti-epileptic drugs (AEDs) taken daily to prevent the recurrence of epileptic seizures. Factors determining a patient’s suitability for AEDs include: type of seizure and/or epilepsy syndrome, childbearing potential, the presence of co-morbidity, individual and/or carer preferences, the presence of contraindications to the drug, potential interactions with other drugs, and potential adverse effects. Optimal management of epileptic seizures improves health outcomes and can also help to minimise other, often significant detrimental, impacts on social, educational and employment activity.

Guidelines recommend that children, young people and adults are treated with a single AED wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Combination therapy should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination
therapy do not bring about worthwhile benefits, treatment should revert to the regimen that has proved most acceptable to the patient, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects. If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose, and the first drug should be tapered off slowly. If the second drug is unhelpful, either the first or second drug may be tapered, depending on relative efficacy, side effects and how well the drugs are tolerated before starting another drug.4,6

Current first-line AEDs for primary generalised tonic-clonic epileptic seizures include:16:

- Carbamazepine – sodium channel blockade.
- Lamotrigine – sodium channel blockade.
- Oxcarbazepine – sodium channel blockade.
- Sodium valproate – multiple mechanisms including GABA potentiation, NMDA (glutamate) inhibition, sodium channel and T-type calcium channel blockade.

Adjunctive AEDs include:

- Clobazam – GABA potentiation.
- Lamotrigine.
- Levetiracetam – synaptic vesicle glycoprotein 2A (SV2A) modulation.
- Sodium valproate.
- Topiramate – multiple mechanisms including GABA potentiation, glutamate (AMPA) inhibition, sodium and calcium channel blockade.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01393743, E2007-G000-332; perampanel vs placebo; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Eisai Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry17.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=165 (planned); aged 12 years and older; primary generalised tonic-clonic seizures; experienced ≥3 seizures during the 8-week period prior to randomisation; on a fixed dose of one to a maximum of three concomitant AEDs.a</td>
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<tr>
<td>Schedule</td>
<td>Randomised to perampanel, up to 8mg oral, once daily; or placebo oral once daily for 17 weeks.</td>
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<td>Follow-up</td>
<td>Active treatment period 17 weeks, then participants have the option of entering an extension phase of 52 weeks. In countries where perampanel is not yet available, subjects will have the option of either entering an expanded access program until product is launched or the open-label extension will continue for a total of 104 weeks (in countries where expanded access programmes are not allowed).</td>
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<tr>
<td>Primary outcome/s</td>
<td>Change in primary generalised tonic-clonic seizure frequency per 28 days.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Responder rate.</td>
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<td>Expected reporting date</td>
<td>Primary study completion date reported as June 2014.</td>
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a Minimum of 30 days prior to baseline; only one induced AED (i.e. carbamazepine, oxcarbazepine, or phenytoin) out of a maximum of two AEDs allowed.
ESTIMATED COST and IMPACT

COST

The cost of perampanel for the treatment of tonic-clonic seizures is not yet known. Perampanel (Fycompa) is already marketed in the UK for the treatment of partial-onset seizures, with or without secondary generalised seizures, in patients with epilepsy aged 12 years and older; a pack of 7 x 2mg tablets cost £35.00, and a pack of 28 x 4mg, 6mg, 8mg, 10mg, or 12mg tablets all cost £140.00.18

IMPACT - SPECULATIVE

Impact on Patients and Carers
☐ Reduced mortality/increased length of survival
☒ Other: potential to minimise other, often significant detrimental, impacts on social, educational and employment activity.

☐ Reduced symptoms or disability
☐ No impact identified

Impact on Health and Social Care Services
☐ Increased use of existing services
☐ Re-organisation of existing services
☐ Other:

☑ Decreased use of existing services
☐ Need for new services
☑ None identified

Impact on Costs and Other Resource Use
☒ Increased drug treatment costs: adjuvant therapy.
☐ Other increase in costs:
☒ Other: uncertain unit cost compared to other adjuvant therapies.

☐ Reduced drug treatment costs
☒ Other reduction in costs: if successful in reducing seizure frequency.
☑ None identified

Other Issues
☒ Clinical uncertainty or other research question identified: expert opinion indicates that further research is needed to evaluate the efficacy and tolerability profiles of perampanel for patients with cognitive and psychiatric co-morbidities.b

☐ None identified

REFERENCES


b Expert personal communication.