National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: January 2018

Perampanel (Fycompa) for paediatric epilepsy

NIHRIO (HSRIC) ID: 13251 NICE ID: 9149

LAY SUMMARY

Epilepsy is a condition in which the brain is affected by abnormal discharge of electrical activity, causing seizures (fits). There are several different types of epileptic seizures, depending on what part of the brain they start in and which part they affect. Epilepsy can start in any age, but is most common in either childhood or after the age of 60. It is a lifelong condition, however, it may get slowly better over time. Symptoms of epileptic seizures depends on the type of epilepsy (partial or generalised) but may include a complete loss of consciousness or awareness ('blank-out'), unusual movements such as a person's limbs jerking and stiffness in all or parts of the body.

Treatment options usually include single anti-epileptic drugs which adequately control the epilepsy in most people. However, in the cases where people do not improve with one anti-epileptic drug additional ('add on' or 'adjunctive') anti-epileptic therapies may be necessary.

Perampanel is a new class of oral anti-epileptic drug that reduces the abnormal electrical activity in the brain. It is already licensed in the UK as an "add-on" therapy taken by tablets daily for the treatment of epilepsy in people aged over 12 years old. It is currently being developed as an oral suspension for children aged 4-12 years, and will offer an additional 'add-on' treatment option for this patient group.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Paediatric epilepsy (ages 4-12 years; partial-onset seizures with or without secondary generalised seizures or primary generalised tonic clonic seizures) – adjuvant treatment

TECHNOLOGY

DESCRIPTION

Perampanel (Fycompa) is an antagonist of the AMPA receptor (a type of glutamate receptor that participates in excitatory neurotransmission[1]). Glutamate is the main stimulatory neurotransmitter in nerve cells which in the context of epilepsy can trigger and maintain seizures. Perampanel works by inhibiting the excess activity of AMPA receptors thought to be involved in the pathophysiology of epilepsy. Its action reduces the excitatory-inhibitory nerve imbalance occurring in the brains of epilepsy patients, consequently reducing damage to brain cells and preventing seizures.[2]

Perampanel is already indicated for use in adults and adolescents populations (from 12 years of age) and is currently being developed for paediatric populations (age 4 to less than 12 years). In the phase III trial (NCT02849626) perampanel is given as 0.5 mg per ml oral suspension once daily. The treatment phase consists of 3 periods: 1) up to 11-week Titration Period (dose titration on the basis of individual clinical response and tolerability), 2) 12-week Maintenance Period (continuation of perampanel oral suspension once daily at the dose level achieved at the end of the titration Period), and 3) 4-week Follow-up Period (only for those participants not rolling over into the Extension Phase). The Extension Phase of the trial will consist of a 29-week maintenance period and a 4-week follow-up period.[3]

Perampanel is currently licensed in the EU as an adjuvant therapy for the treatment of adults and children from the age of 12 years with partial onset seizures with or without secondary generalisation and in patients from 12 years of age for the treatment of primary generalised tonic-clonic seizures associated with idiopathic generalised epilepsy.[2] Very common side effects of perampanel (occurring in > 1/10) include dizziness and somnolence and common side effect (occurring in >1/100 to <1/10) include decreased or increased appetite, aggression, anger, anxiety, confusional state, ataxia, dysarthria, balance disorder, irritability, diplopia, blurred vision, vertigo, nausea, back pain, gait disturbance, fatigue, increased weight and falls.[4]

In the EU and globally, Perampanel is also under phase II or III development for monotherapy treatment of partial seizures, Lennox-Gastaut syndrome, tonic-clonic seizures and amyotrophic lateral sclerosis.[5]

INNOVATION and/or ADVANTAGES

If licensed, perampanel will offer an additional treatment option for patients aged 4-12 years with partial-onset seizures with or without secondarily generalised seizures or primary generalised tonic clonic seizures.

DEVELOPER

Eisai Ltd

PATIENT GROUP

BACKGROUND

Epilepsy is a common condition that affects the brain and causes frequent seizures. Seizures are bursts of electrical activity in the brain that temporarily affect how it works. Epilepsy can start in any age, but usually either in childhood or in people over 60 years. It is a lifelong condition, however, may slowly improve over time.[6] Epilepsy may be caused by several factors including brain injury due to trauma, infection or oxygen deprivation, scarring of brain tissue, brain tumours, and/or chemical/hormonal imbalances. However, these factors are believed to only explain 30% of epilepsy diagnoses. In cases where the cause is not known, the disease is called idiopathic epilepsy.[7]

In epilepsy there are two main types of seizures occurring: [8]

(1) Generalised seizures: including tonic clonic, absence, myoclonic or atonic seizures and
(2) Focal (or partial) seizures

Generalized seizures affect the whole brain by an abnormal electrical disturbance. In these seizures, the person affected becomes unconscious. Before a seizure, the person might experience unusual symptoms that will alert them to a seizure starting.[9] A generalised tonic clonic seizure is a seizure that starts with a tonic phase, in which the person cries out or groans as air is forced out of the lungs. The person then becomes stiff and unconscious. The clonic phase follows, in which the person's limbs begin to jerk. These seizures usually take around 1-3 minutes.[10]

Focal (partial) seizures occur when the electrical disturbance in the brain is focussed in just one part of the brain. Therefore, the type of seizure will depend on exactly where in the brain it comes from and what functions that area of the brain is responsible for.[11] Temporal lobe epilepsy is the most common form, occurring in the temporal lobe in the brain which is responsible for language, feelings, emotions and memory.[12] Frontal lobe epilepsy is the second most common focal seizure and these seizures usually affect speech and start and end suddenly.[13] Parietal lobe epilepsy is rare and originates in the parietal area usually resulting in strange sensations. They are also known as sensory seizures.[14] Occipital lobe epilepsy is very rare and affects sight. Symptoms may include seeing patterns, flashing lights or colours, or images that appear to repeat before the eyes.[15]

CLINICAL NEED and BURDEN OF DISEASE

Accurate estimates of incidence and prevalence are difficult to achieve because identifying people who may have epilepsy is difficult. However, epilepsy has been estimated to affect between 362,000 and 415,000 people in England. 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). The annual estimated cost of established epilepsies is approximately £2 billion (direct and indirect costs).[16] The proportion of children and young people aged 17 years or younger with a diagnosis of epilepsy and receiving AEDs is 0.30% (300 people in 100,000), which equates to approximately 34,000 in England.[17]

60% 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.[18]

In 2016-17, there were 54,202 finishes consultant episodes (FCE) for epilepsy (ICD 10 code G40), 39,928 hospital admissions and 125,453 FCE bed days. Out of the 54,202 FCE, 3,965 concerned children aged 5-9 years and 2,620 children aged 10-14 years.[19]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Epilepsies: diagnosis and management (CG137). January 2012
- NICE quality standard. Epilepsy in children and young people (QS27). February 2013
- NICE interventional procedures guidance. Deep brain stimulation for refractory epilepsy (IPG416). January 2012
- NICE interventional procedures guidance. Vagus nerve stimulation for refractory epilepsy in children (IPG50). March 2004

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2016 Proposed changes to service specification for Children's Epilepsy Surgery: Consultation outcome report
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy. D03/P/c
- NHS England. 2013 Clinical Commissioning Policy: Vagal Nerve Stimulation for Epilepsy. NHSCB/D04/P/d
- NHS England. Children's Epilepsy Surgery Service (CESS) in England. Children's epilepsy brain surgery referrals – a quick reference guide for paediatricians in England.

OTHER GUIDANCE

- Expert committee on paediatric epilepsy, Indian academy of paediatrics. Guidelines for the diagnosis and management of childhood epilepsy (2007)
- SIGN – Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsies in children and young people – A national clinical guideline (2005)

CURRENT TREATMENT OPTIONS

Treatment of epilepsy in children, young people and adults usually starts with anti-epileptic drugs (AEDs). This should be initiated by a specialist and details of the person's epilepsy syndrome, prognosis and lifestyle taken into account. The AED treatment strategy is individualised according to seizure type, epilepsy syndrome, co-medication and comorbidity and others.[20]

Sodium valproate is recommended as first-line treatment to children, young people and adults with newly diagnosed generalised tonic clonic seizures. Lamotrigine might be used if sodium calproate is unsuitable. Carbamazepine and oxcarbazepine might also be used. Clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate may also be given as adjunctive treatment in generalised tonic clonic seizures when first-line treatment effects are ineffective or not tolerated.[20]

Focal seizures are usually treated with a combination of different AEDs and adjuvant therapies depending on what is best tolerated and what is effective for the patient:

- Anti-epileptic drugs:
  - Carbamazepine or lamotrigine -first-line.
  - Levetiracetam, oxcarbazepine or sodium valproate - used if carbamazepine and lamotrigine are unsuitable or not tolerated.
- Adjunct treatment:
  - Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate can be offered if first-line treatments are ineffective or not tolerated.

If these approaches do not result in improvement, a tertiary epilepsy specialist may be consulted, which can offer a range of additional options including; eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide if adjunctive treatment is ineffective or not tolerated.[20]

Other lifestyle and surgical interventions are available in addition to AEDs might help patients. These include ketogenic diet in children and young people, psychological interventions, vagus nerve stimulation or deep brain stimulation.[20]

EFFICACY and SAFETY

Trial	NCT02849626, EudraCT-2014-002167-16; adjunctive therapy in children (ages 4 to < 12 years); phase III
Sponsor	Eisai Inc
Status	Ongoing, recruiting
Source of Information	Trial registry[21], Global Data[22]
Location	7 EU countries (excl UK), USA, Japan, Republic of Korea
Design	Non-randomised, single group assignment, open label
Participants	N= 160 (planned); 4 to <12 years; diagnosis of epilepsy with partial-onset seizures (POS) with or without secondarily generalized seizures or primary generalized tonic-clonic (PGTC) seizures according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures (1981);
Schedule	All subjects 0.5 mg/ml oral suspension of perampanel. The study will consist of a Core Study and Extension Phase. 1. Core Study (consists of 2 phases): a) Pre-treatment phase: 4-week Screening/Baseline Period b) Treatment Phase: - 11-week Titration Period (dose titration on the basis of individual clinical response and tolerability) - 12-week Maintenance Period (continuation of perampanel oral suspension once daily at the dose level achieved at the end of the Titration Period) - 4-week Follow-up Period (only for those participants not rolling over into the Extension Phase).

	2. Extension study: All participants who complete all scheduled visits up to and including Visit 9 in the Treatment Phase will be eligible to participate in the Extension Phase of the study. Consists of 2 periods: a) 29-week Maintenance Period: all participants will continue with their optimal perampanel dose (i.e., dose level that they completed on during the Core Study). b) 4-week Follow-up Period
Follow-up	Participants took part in the core study were followed up for 31 weeks. Participants who took part in the extension study were followed up for 64 weeks. Participants who do not continue in the Extension Phase or those who prematurely discontinue from the study will enter a 4-week Follow-up Period.
Primary Outcomes	Number of participants with any treatment-emergent adverse event (TEAE) and any serious adverse event (SAE) -up to approximately 60 weeks
Secondary Outcomes	• Change in average seizure frequency over 28 days • Responder probability - up to 27 weeks in the Treatment Period; up to 33 weeks in the Extension Phase • Number of participants who are seizure-free in the Maintenance Period of the Core Study - 12 weeks • Change from Baseline in A-B neuropsychological assessment schedule (ABNAS) scores at Weeks 23 and 52 • Change from Baseline in Child Behaviour Checklist (CBCL) scores at Weeks 23 and 52 • Change from Baseline in Lafayette Grooved Pegboard Test (LGPT) scores at Weeks 23 and 52 • Change from Baseline in height at Weeks 23 and 52 • Change from Baseline in weight at Weeks 23 and 52 • Change from Baseline in thyroid values at Weeks 23 and 52 • Change from Baseline in insulin-like growth factor-1 (IGF-1) values at Weeks 23 and 52 • Change from Baseline in electroencephalogram (EEG) values during awake and sleep states at Weeks 23 and 52 • Change from Baseline in the frequency of EEG abnormalities during awake and sleep states at Weeks 23 and 52 • Percentage of participants with any treatment-emergent reports of suicidal ideation and behaviour assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) - up to 27 weeks in the Treatment Period; up to 33 weeks in the Extension Phase

	• Percentage of participants with the indicated intensity of suicidal ideation and behaviours assessed using C-SSRS scores - up to 27 weeks in the Treatment Period; up to 33 weeks in the Extension Phase • Median percent change in seizure frequency per 28 days during the Treatment Phase (Titration Period and Maintenance Period) of the Core Study, and during the long-term treatment (up to 52 weeks) relative to the Pre-treatment Phase Week 4 of Pre-treatment Phase, up to Week 27, up to Week 52 • Percentage of responders (25%, 50%, and 75% responders) during the Maintenance Period of the Core Study and during long-term treatment - Time Frame: Week 12 and up to Week 52 • Percentage of participants who are seizure free during the Maintenance Period of the Core Study and during long-term treatment - Week 12 and up to Week 52 • Change from Baseline in Clinical Global Impression scores - Baseline; Weeks 23 and 52
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date February 2018. Estimated study completion date October 2018.

ESTIMATED COST and IMPACT

COST

Perampanel is currently marketed for other indications and the NHS cost of all dosages of perampanel (2, 4, 6, 8 and 12 mg) is £140 for 28 tablets (excluding VAT). Based on this, the cost per patient per year is estimated to be £1820. Costs may vary in different settings because of negotiated procurement discounts.[23]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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