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HEALTH TECHNOLOGY BRIEFING
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Lacosamide for primary generalised tonic-clonic seizures – adjunctive therapy

NIHRIO ID	27110	**NICE ID**	10219
Developer/Company	UCB Pharma Ltd	**UKPS ID**	652065

Licensing and market availability plans	Currently in phase III clinical trials.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Lacosamide is a medicinal product that is being developed for the treatment of Primary Generalised Tonic-Clonic Seizures (PGTCS). Epilepsy is a neurological disorder that is characterised by an imbalance in the excitation and inhibition of the brain and this imbalance causes a phenomenon known as a seizure. Seizures are brief increases in electrical activity within the brain and there are many types. One such type is PGTCS, which occur when the seizure happens all over the brain and affects both sides of the brain from the start, causing muscles to stiffen and convulsions to occur. They can last for a few seconds or minutes and patients can suffer multiple seizures every day.

Lacosamide is a currently licensed drug for partial onset seizures with or without secondary generalisation. It works by stabilising electrical activity in the brain. One of the ways in which it is thought to work is by preventing sodium from entering the nerve cells when they begin to fire rapid and repetitive electrical signals. An accumulation of sodium in the nerve cells is necessary for the electrical signal to build up and be passed on. Lacosomide is in clinical development to supplement the current anti-epileptic drugs (AEDs) used to treat patients with PGTCS, particularly in patients for whom the current combinations are ineffective.

PROPOSED INDICATION

Primary Generalised Tonic-Clonic Seizures (PGTCS) in combination with other antiepileptic drugs.[a]

TECHNOLOGY

DESCRIPTION

Lacosamide (Vimpat) is an antiepileptic medicinal product. The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid that has been specifically synthesised as a anticonvulsive drug.[1] The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated.[2] It is thought that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation.[1] Turning off or slowing down these sodium channels in the brain may help stop a seizure and allow the brain cells to recover.[3] Furthermore, it was found that the collapsin-response mediator protein 2 (CRMP-2 alias DRP-2) was identified as a binding partner.[1] The CRMP family of proteins are implicated in the development processes of the nervous system and therefore there is tentative evidence that lacosamide may prove disease modifying although available evidence is contradictory.[1,4]

Lacosamide is in clinical development as adjunctive therapy for uncontrolled Primary Generalized Tonic-Clonic Seizures (PGTCS) in subjects with idiopathic generalized epilepsy. In the phase III clinical trial, (NCT02408523), lacosamide is administered as tablets or as an oral solution as follows:[5]

- Tablet (50 mg): starting with 100 mg/day at week 1, then weekly increase in steps of 50 mg or 100 mg/day - maximal dose 400 mg/day for adult subjects and paediatric subjects >= 50 kg;
- Oral solution (10 mg/ml): starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day) - maximal dose 12 mg/kg/day for paediatric subjects < 30 kg and 8 mg/kg/day for paediatric subjects 30 kg to < 50 kg.

INNOVATION AND/OR ADVANTAGES

Lacosamide exerts its anticonvulsant activity predominantly by selectively enhancing slow sodium channel inactivation.[2] This has a potential advantage over some other antiepileptic drugs (AEDs) which act through enhancement of fast inactivation of voltage-gated sodium channels that may aggravate generalised seizures.[6]

Additionally, lacosamide displays amphiphilic properties which means that it is lipophilic enough to be orally bioavailable and penetrate the blood–brain barrier yet it is sparingly but sufficiently soluble in aqueous solution to permit the development of a parenteral formulation without adding a soluble agent.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lacosamide is licensed in the EU/UK as a monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.[7]

[a] Information provided by UCB Pharma Ltd on UK PharmaScan.

Lacosamide is in clinical development for its effects (including in the long term) on epilepsy in children, in neuropathic pain, as an adjunctive therapy in adults and children with partial-onset seizures, in alcohol use disorder, focal epilepsy, glioma, amyotrophic lateral sclerosis and acute kidney injury.[8]

PATIENT GROUP

DISEASE BACKGROUND

Epilepsy is a common condition that affects the brain and causes frequent seizures. A seizure is a sudden burst of electrical activity in the brain that temporarily affects how it works. Some seizures cause the body to jerk and shake (a "fit"), while others cause problems like loss of awareness or unusual sensations. They typically pass in a few seconds or minutes.[9,10] 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 epilepsy and the age of the individual.[11] Epilepsy can be broadly divided into focal and primary generalized types. Focal seizures originate in unilaterally distributed networks, whereas primary generalized seizures arise in bilaterally distributed networks.[6]

The International League Against Epilepsy has recently updated the precise nomenclature to classify epilepsy, and they have introduced terms such as 'genetic', 'structural-metabolic' and 'unknown', to replace the older terms 'idiopathic', 'symptomatic', and 'cryptogenic', respectively.[12] Correct diagnosis is critical, because the safety and efficacy of AEDs can vary with different epilepsy types, and certain AEDs can actually worsen some primary generalised seizures.[13]

Primary generalized epilepsy is characterised by the variable occurrence of absence, myoclonic or PGTCS, which may occur in combination or separately, associated with generalized, bisynchronous spike-wave discharges on electroencephalogram.[14,15] This type of epilepsy typically emerges in childhood, may resolve in adulthood and is often more responsive to AED treatment than focal epilepsy.[6,16,17]

Tonic-clonic seizures may have a generalised onset, meaning they affect both sides of the brain from the start, and are characterised by the patient losing consciousness, their muscles stiffening (tonic phase) and jerking movements are seen (the clonic phase).[18] Tonic-clonic seizures usually last between 1 and 2 minutes, and postictal confusion lasting longer than 10 minutes frequently occurs – this is characterised by disorientation, poor concentration, poor short-term memory, and decreased verbal and interactive skills.[19,20]

CLINICAL NEED AND BURDEN OF DISEASE

Over 500,000 people in the UK have epilepsy. That is about one in every 100 people. Every day, about 87 people are diagnosed with epilepsy.[21] One in every four people newly diagnosed with epilepsy is over the age of 65 years.[22]

Overall prevalence of epilepsy in England is at 0.8%, but it varies widely throughout the country.[23] This would equate to approximately 444,955 cases with epilepsy in England using the 2017 population estimate.[24] Approximately 60% of people have tonic-clonic seizures,[25] this would equate to 266,973 of epilepsy cases in England in 2017.[26] Some people have epilepsy as a primary condition, in others it can be a consequence of other conditions such as head injury or stroke etc. In adults the prevalence of the condition increases with age.[27]

Over the time period of 2001 to 2014, 9% of deaths related to neurological conditions had a mention of epilepsy deaths.[23] For some, seizures are life-threatening: 1,000 people die in the UK every year because of their epilepsy. Around half of these 1,000 deaths are from sudden unexpected death in epilepsy, in which someone with epilepsy dies and no obvious cause of death can be found. Deaths in people with epilepsy have increased by 70% and people with the condition now die on average eight years earlier than the rest of the population, according to new figures from Public Health England, published in February 2018.[22]

Only 52% of people with epilepsy in the UK are seizure free. It is estimated that with the right treatment, the majority of people with epilepsy (70%) could be seizure free. This 18% treatment gap equates to 108,000 people in England with epilepsy who could be seizure free, but currently are not.[22]

In England in 2017-18 there were 10,490 admissions (of which 792 were day cases), 14,639 finished consultant episodes (FCE) and 31,104 FCE bed days for Generalized idiopathic epilepsy and epileptic syndromes (ICD- 10: G40.3).[28]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Epilepsy's management include the following recommendations:[27]

- Healthcare professionals should adopt a consulting style that enables the child, young person or adult with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare, and take fully into account their race, culture and any specific needs.

- All children, young people and adults with epilepsy should have a comprehensive care plan that is agreed between the person, their family and/or carers as appropriate, and primary and secondary care providers.

- The AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult's lifestyle, and the preferences of the person, their family and/or carers as appropriate.

Treatment can help most people with epilepsy have fewer seizures, or stop having seizures completely and include:[29]

- use of AEDs;
- surgery to remove a small part of the brain that's causing the seizures;
- a procedure to put a small electrical device inside the body that can help control seizures;
- a special diet (ketogenic diet) that can help control seizures.

CURRENT TREATMENT OPTIONS

NICE recommend the following AEDs as adjunctive treatment for GTC:[27]

- Offer clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with GTC seizures if first-line treatments are ineffective or not tolerated.

PLACE OF TECHNOLOGY

If licensed, lacosamide will offer an additional option for patients with PGTCS in combination with other antiepileptic drugs.

CLINICAL TRIAL INFORMATION

Trial	NCT02408523, EudraCT:2011-003100-21; **VALOR; children and adults aged 4 and over; lacosamide vs placebo; phase III**
Sponsor	UCB Biosciences, Inc.
Status	Ongoing
Source of Information	Trial registry[5,30]
Location	EU (not UK), USA and others
Design	Randomised, parallel assignment, quadruple masked
Participants	n=242; children and adults aged 4 years and older; subject with a confirmed diagnosis at least 24 weeks prior to visit 1 and a disease onset prior to 30 years of age, consistent with idiopathic generalised epilepsy (IGE) experiencing PGTCS (Type IIE) that are classifiable according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures; subject has >=3 PGTC seizures during the 16-week combined baseline (12-week historical baseline plus 4-week prospective baseline); if a brain magnetic resonance imaging (MRI)/computed tomography (CT) scan has been performed, there must be no evidence of any progressive abnormality or any lesion likely to be associated with partial-onset seizures; subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs with no benzodiazepine AEDs OR 1 benzodiazepine marketed AED with 1 to 2 non benzodiazepine marketed AEDs for at least 28 days prior to visit 1 with or without additional concurrent stable vagus nerve stimulation (VNS); subjects are required to have had an electroencephalogram (EEG) report consistent with idiopathic generalised epilepsy (eg, generalised 3Hz epileptiform discharges and a normal EEG background) confirmed by a central reviewer
Schedule	Experimental arm: • Lacosamide 50 mg tablets: starting with 100 mg/day at week 1. Weekly increase in steps of 50 mg or 100 mg/day are allowed. Maximal dose 400 mg/day for adult subjects and paediatric subjects >= 50 kg. • Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for paediatric subjects < 30 kg.) • Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for paediatric subjects 30 kg to < 50 kg.) Placebo arm: • Placebo 50 mg tablets: starting with 100 mg/day at week 1. Weekly increase in steps of 50 mg or 100 mg/day are allowed. Maximal dose 400mg/day for adult subjects and paediatric subjects >= 50kg. • Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for paediatric subjects < 30kg.)

	• Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for paediatric subjects 30kg to < 50kg.)
Follow-up	Treatment period: 24 weeks Follow up period: up to 36 weeks.
Primary Outcomes	Time to the second PGTCS during the 24-week treatment period from visit 2 (week 0) to visit 10 (week 24) [time frame: 24-week treatment period from visit 2 (week 0) to visit 10 (week 24)]
Secondary Outcomes	1. Seizure freedom for PGTCS during the 24-week treatment period from visit 2 (week 0) to visit 10 (week 24) [time frame: 24-week treatment period from visit 2 (week 0) to visit 10 (week 24)]: Seizure freedom for PGTCS for the 24-week treatment period. 2. Time to the first PGTCS during the treatment period from visit 2 (week 0) to visit 10 (week 24) [time frame: during the treatment period from visit 2 (week 0) to visit 10 (week 24)]: Time to the first PGTCS during the 24-week treatment period. 3. Incidence of treatment emergent adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator [time frame: from visit 1 (week 4) to end of study period (up to week 36)]: An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. A treatment emergent adverse event is any event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. 4. Incidence of serious adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator [time frame: from visit 1 (week - 4) to end of study period (up to week 36)]: A serious adverse event is any untoward medical occurrence that at any dose results in death, is life-threatening, requires in patient hospitalization or prolongation of existing hospitalization, is a congenital anomaly or birth defect, is as infection that requires treatment parenteral antibiotics, other important medical events which based on medical or scientific judgement may jeopardize the patients, or may require medical or surgical intervention to prevent any of the above.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Estimated primary completion date April 2019 and estimated study completion date June 2019.

ESTIMATED COST

The cost of lacosamide tablets (14 x 50 mg) is £10.81 and 10mg/ml syrup (200 ml) is £25.74.[31]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline in development. Epilepsies in adults: diagnosis and management update. Expected publication date: April 2021.
- NICE clinical guideline. Epilepsies: diagnosis and management (CG137). January 2012 (updated April 2018).
- NICE quality standards. Epilepsy in adults (QS26). February 2013.
- NICE interventional procedures guidance in development. Deep brain stimulation for refractory epilepsy. Expected publication date: TBC.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy (all ages). 170036P. March 2018.
- NHS England. Clinical Commissioning Policy: Vagal Nerve Stimulation for Epilepsy. NHSCB/D04/P/d. April 2013.

OTHER GUIDANCE

- American Epilepsy Society Guideline. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. 2016.[32]
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (SIGN 143). May 2015.[33]
- American Academy of Neurology and the American Epilepsy Society. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. 2015.[34]
- American Academy of Neurology. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. 2013.[35]

ADDITIONAL INFORMATION

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