Dravet syndrome is a very rare form of epilepsy that begins in childhood. Prolonged seizures begin in the first year of life and the overall development of children with this disease is often severely affected.

Fenfluramine is a new drug given as a tablet for the treatment of Dravet syndrome. Fenfluramine is being studied to see whether it improves the symptoms of Dravet syndrome and that it is safe to use for children with this disease.

If fenfluramine is licensed for use in the UK, it could be a new treatment option for children with Dravet syndrome and may improve the quality of life of children and their families. At the moment, there are no drugs that treat the underlying causes of Dravet syndrome.

NIHR HSRIC ID: 9860
TARGET GROUP

- Dravet syndrome (severe myoclonic epilepsy of infancy); in children aged 2 to 18 years – first line.

TECHNOLOGY

DESCRIPTION

Fenfluramine (ZX008) is a serotonin receptor agonist being developed for the treatment of children with Dravet syndrome, a rare and severe form of myoclonic epilepsy. Dravet syndrome is a clinically diagnosed syndrome; however, 80% of those diagnosed have a mutation in the sodium channel gene, SCN1A. Serotonin-releasing drugs such as fenfluramine may have an effect on epileptic activity in the brain. Fenfluramine is administered orally at 10-30mg per day on an ongoing, continuous basis.

Fenfluramine does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, fenfluramine will offer an additional oral treatment option for children with Dravet syndrome, who currently have few effective therapies available.

DEVELOPER

Brabant Pharma Ltd. (subsidiary of Zogenix Inc).

AVAILABILITY, LAUNCH OR MARKETING

Fenfluramine is a designated orphan drug in the EU and USA and is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is a neurodevelopment disorder beginning in infancy that is characterised by intractable seizures. The development of affected children is typically on track during the first year of life; however, progressive developmental arrest begins to emerge in the second year of life. Patients with Dravet syndrome typically experience their first seizure at 5 to 8 months of age. This is usually a clonic, generalised, or unilateral seizure triggered by fever, sometimes lasting for 15 to 30 minutes, or longer. Within weeks to months, patients experience additional febrile seizures and then begin to exhibit temperature-independent seizures, including tonic, myoclonic, atypical absence, focal, generalised clonic, or generalised tonic–clonic seizures. Complex partial seizures can be triggered by sudden changes in body temperature: usually as a result of getting cold after a shower or bath.

* Patient group personal communication.
Children with Dravet syndrome are often photosensitive⁴; this is seen in approximately 50% of cases⁵.

Patients with Dravet syndrome are at higher risk of febrile seizures, prolonged status epilepticus, and of SUDEP (sudden unexplained death in epilepsy) and have a wide range of associated conditions, which all need to be properly treated and managed². These associated conditions include: behavioural and developmental delays, movement and balance disorders, orthopaedic disorders, delayed language and speech issues, growth and nutrition issues, sleep disturbance, and chronic infections⁶. Dravet syndrome places a heavy emotional burden on families who report that once seizures become more manageable it is the associated co-morbidities that are the most emotionally and physically demanding aspect of the disease⁵.

A major contributor to the cause of Dravet syndrome has been found to be mutation or deletion of the SCN1A gene, found in around 80-85% of patients¹,⁷. SCN1A mutations are also associated with other forms of epilepsy, including intractable childhood epilepsy with generalised tonic-clonic seizures and severe multifocal epilepsy of infancy¹. Mutations in the PCDH19 gene (also seen in female restricted epilepsy with intellectual deficit), are thought to account for about 5% of Dravet syndrome cases in girls⁷. However, expert opinion suggests that some medical professionals dispute that the epilepsy observed in these cases can be attributed to Dravet syndrome⁶.

Seizures tend to be difficult to control throughout childhood and learning disabilities persist and are usually severe⁴. As the condition progresses most children become unsteady on their feet (ataxic)⁴. Usually by the age of 14-16 years the seizures tend to become less frequent, though moderate to severe cognitive impairment and intractable epilepsy into adulthood is common⁴,⁷.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

The worldwide incidence of Dravet syndrome is estimated to be less than 1 in 40,000 live births; in the UK this is estimated to be 1 in 28,000 live births⁷. Expert opinion suggests it is likely that the incidence of Dravet syndrome is underestimated, particularly in areas of the world where premature mortality is high⁵. The prevalence of Dravet syndrome is estimated to be between 1 in 20,000 to 1 in 40,000 population⁸. If these figures were generalisable to

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⁴ Patient group personal communication.
⁵ Expert personal communication.
England, there could be between 1,350 and 2,700 patients with Dravet syndrome\textsuperscript{d}. Myoclonic seizures appear between the age of 1 and 5 years in 85% of children with Dravet syndrome\textsuperscript{9}. Between 15-25% of patients with Dravet syndrome have a family history of febrile convulsions or epilepsy\textsuperscript{9}. The rate of Dravet syndrome-related mortality is estimated to be 14-20\%\textsuperscript{10}. The causes of death vary and include SUDEP, status epilepticus, infection, and drowning\textsuperscript{10}.

The population likely to be eligible to receive fenfluramine could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**


**CURRENT TREATMENT OPTIONS**

Currently, treatment for Dravet syndrome consists mainly of antiepileptic medications to help control seizures\textsuperscript{1}. These include sodium valproate, levetiracetam, topiramate, clonazepam, clobazam and zonisamide\textsuperscript{1,4,e}. Stiripentol is also licensed for use in combination with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in children, and occasionally adults, with Dravet syndrome\textsuperscript{1,2,12,e}. Expert opinion suggests that there is little published evidence regarding the effectiveness of these drugs in the treatment of Dravet syndrome\textsuperscript{e}. They are used due to theoretical, animal model and anecdotal human data\textsuperscript{e}.

While Dravet syndrome is largely refractory to common antiepileptic drugs, ketogenic diet therapy has recently been used in the management of Dravet syndrome and related severe myoclonic epilepsies\textsuperscript{2,12}. In one study, 65\% of patients with Dravet syndrome treated with a ketogenic diet experienced a greater than 50\% reduction in seizure frequency\textsuperscript{13}. However, expert opinion advises that a ketogenic diet cannot be considered to be more effective than the use of anti-epileptic medications\textsuperscript{e}.

\textsuperscript{d} Assuming the population of England to be approximately 54 million (ONS population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-2014).

\textsuperscript{e} Expert personal communication.
Many patients with Dravet syndrome experience prolonged seizures (status epilepticus) that require emergency intervention\(^6\). In these circumstances rescue medication such as diazepam, midazolam or paraldehyde\(^1\) will be administered\(^6\).

Children with Dravet syndrome should also receive physical, occupational, speech and social therapies\(^9\). Surgery is not indicated in most patients with Dravet syndrome\(^9\). From a patient perspective, difficulties can arise in the diagnosis of the condition, access to specialist care, and qualification for respite and therapy services\(^1\).

**Efficacy and Safety**

Not reported.

**Estimated Cost and Impact**

**Cost**

The cost of fenfluramine is not yet known.

**Impact - Speculative**

**Impact on Patients and Carers**

☐ Reduced mortality/increased length of survival  
☐ Reduced symptoms or disability  
☑ Other: expert opinion suggests that seizure control, even late in life, could improve cognition of patients\(^6\).

☐ No impact identified

**Impact on Health and Social Care Services**

☐ Increased use of existing services  
☐ Decreased use of existing services  
☐ Need for new services: expert opinion suggests that cardiac monitoring may be required, for example by cardiology review, ECG or echocardiography\(^8\).

☐ Re-organisation of existing services  
☐ Other.  
☐ No impact identified

**Impact on Costs and Other Resource Use**

☐ Increased drug treatment costs  
☐ Reduced drug treatment costs: expert opinion suggests that if fenfluramine were effective, it could result in a decline in the use of other anti-epileptic drugs (e.g. stiripentol) which can be very expensive\(^6\).

☐ Other increase in costs.  
☑ Other: unknown drug treatment costs.  
☐ Other reduction in costs.  
☐ None identified

**Other Issues**

\(^1\) Patient group personal communication.
Clinical uncertainty or other research question identified: expert opinion suggests that approximately 85% of children with Dravet syndrome will survive to adulthood. As the indication states that fenfluramine will be for the treatment of Dravet syndrome in children there is uncertainty regarding whether this drug will be available for adults with this disease.

None identified

REFERENCES