Cannabidiol (Epidiolex) for Dravet syndrome – second and subsequent line

NIHR HSRIC ID: 10063

Lay summary

Cannabidiol is a new drug for the treatment of Dravet syndrome, which is a severe form of epilepsy that begins in infancy. Cannabidiol is taken by mouth and the precise way it works in humans is unknown. Some studies suggest that this drug may offer a new treatment option for children and young adults with Dravet syndrome, a group of patients who currently have few treatment options available.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Dravet syndrome: uncontrolled; children and young adults – second and subsequent line.

TECHNOLOGY

DESCRIPTION

Cannabidiol (Epidiolex; GW42003; GWP42003) is a small-molecule cannabinoid compound extracted from the Cannabis sativa plant being developed for the adjunctive treatment of Dravet syndrome in patients inadequately controlled by current anti-epileptic drugs. The precise mechanism by which cannabidiol exerts its anti-convulsant effects in humans is unknown, although it is thought to act on the mitochondrial VDAC1 protein channels. Altering the action of VDAC1 is expected to have an effect on epileptic activity in the brain, and will therefore reduce or prevent seizures in Dravet syndrome. In the phase III study, cannabidiol was given as an oral solution containing 100mg/mL of the active substance for a 2 week period during which the dose was titrated to 20mg/kg/day in two equal divided doses, followed by 12 week maintenance therapy.

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

Cannabidiol is in phase III development for Lennox-Gastaut Syndrome (LGS) and Tuberous Sclerosis Complex (TSC), and in phase II development for schizophrenia and partial epilepsy.

INNOVATION and/or ADVANTAGES

If licensed, cannabidiol will offer an additional oral treatment option for children and young adults with Dravet syndrome, a group who currently have few effective therapies available.

DEVELOPER

GW Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

Cannabidiol is a designated orphan drug in the EU and USA. Cannabidiol is 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. Children with Dravet syndrome are often photosensitive; this is seen in approximately 50% of cases.

Patients with Dravet syndrome are at higher risk of febrile seizures, prolonged status epilepticus, and of sudden unexplained death in epilepsy (SUDEP), and have a wide range of associated conditions, which all need to be properly treated and managed. 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 infections.

Mutation or deletion of the SCN1A gene has been identified as a major contributor to the cause of Dravet syndrome and is found in around 80-85% of patients. SCN1A mutations are also associated with other forms of epilepsy, including intractable childhood epilepsy with generalised tonic-clonic seizures and severe multifocal epilepsy of infancy. Mutations in the PCDH19 gene (also seen in female restricted epilepsy with intellectual deficit), are thought to account for around 5% of cases of Dravet syndrome in girls.

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

**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 births. The prevalence of Dravet syndrome is estimated to be between 1 in 20,000 to 1 in 40,000 population. If these figures were generalisable to England, there could be between 1,350 and 2,700 patients with Dravet syndrome. Myoclonic seizures appear between the age of 1 and 5 years in 85% of children with Dravet syndrome. Between 15-25% of patients with Dravet syndrome have a family history of febrile convulsions or epilepsy. Dravet syndrome-related mortality is estimated to be 14-20%. The causes of death vary, and include SUDEP, status epilepticus, infection, and drowning.

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

**RELEVANT GUIDANCE**

- **NICE Guidance**

* Assuming the population of England to be approximately 54 million (ONS population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-2014).
• NICE advice. Partial seizures in children and young people with epilepsy: zonisamide as adjunctive therapy (ESNM37). March 2014.

**NHS England Policies and Guidance**

This topic is relevant to:

**Other Guidance**

• No relevant guidance identified.

**CURRENT TREATMENT OPTIONS**

Currently, treatments for Dravet syndrome consist mainly of antiepileptic medications to help control seizures2. These include sodium valproate, levetiracetam, topiramate, clonazepam, clobazam and zonisamide2.5. Stiripentol is also licensed for use in combination with clobazam and valproate as adjunctive therapy for refractory generalised tonic-clonic seizures in children, and occasionally adults, with Dravet syndrome12.

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 epilepsies3,13. In one study, 65% of patients with Dravet syndrome treated with a ketogenic diet experienced a greater than 50% reduction in seizure frequency14.

Many patients with Dravet syndrome experience prolonged seizures (status epilepticus) that require emergency intervention7. In these circumstances rescue medication such as diazepam or midazolam will be administered7.

Children with Dravet syndrome should also receive physical, occupational, speech and social therapies10. Surgery is not indicated in most patients with Dravet syndrome10.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02091375, GWEP1332 Part B; children aged 2-18 years; cannabidiol vs placebo; phase III.</th>
<th>NCT02224703, GWEP1424, 2014-002939-34; children aged 2-18 years; cannabidiol vs placebo; phase III.</th>
<th>NCT02224573, GWEP1415, 2014-001834-27; children aged ≥2 years; cannabidiol; phase III extension.</th>
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<td>Sponsor</td>
<td>GW Research Ltd.</td>
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<tr>
<td>Location</td>
<td>Design</td>
<td>Participants</td>
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<tr>
<td>USA and Europe</td>
<td>Randomised, placebo-controlled.</td>
<td>n=120; aged 2-18 years; Dravet syndrome; no previous cannabinoid based medications.</td>
<td>Randomised to oral cannabidiol solution (100mg/mL), up-titrated to target dose of 20mg/kg/day in two equal divided doses, followed by twice daily dosing for 14 wks; or placebo oral solution, to up-titrated to target dose of 20mg/kg/day in two equal divided doses, followed by twice daily dosing for 14 wks.</td>
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<tr>
<td>USA and Europe</td>
<td>Randomised, placebo-controlled.</td>
<td>n=150 (planned); aged 2-18 years; Dravet syndrome; no previous cannabinoid based medications.</td>
<td>Randomised to cannabidiol solution, up-titrated to target dose of 10mg/kg/day in two equal divided doses, followed by 12 wk maintenance therapy; or cannabidiol solution, up-titrated to target dose of 20mg/kg/day in two equal divided doses, followed by 12 wk maintenance therapy; or placebo oral solution, up-titrated to target dose of 20mg/kg/day in two equal divided doses, followed by 12 wk maintenance therapy.</td>
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<td>USA and Europe</td>
<td>Non-randomised, uncontrolled.</td>
<td>n=540 (planned); aged ≥2 years; must have completed treatment arm in initial study.</td>
<td>Patients receive cannabidiol. Target dose of 20mg/kg/day in two equal divided doses using oral cannabidiol solution (100mg/mL). Titration to target dose over 11 days.</td>
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b Company provided information.
convulsive seizures of 39% compared to 4-week baseline compared with a reduction of 13% in the placebo group (p=0.01).c.

Adverse effects (AEs)

Cannabidiol was generally well tolerated. The most common AEs (>10% of cannabidiol-treated patients) were somnolence, diarrhoea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection and convulsion.c.

Expected reporting date

- Study completion date reported as Jun 2017. Study completion date reported as June 2016.

ESTIMATED COST and IMPACT

COST

The cost of cannabidiol is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

☐ Reduced mortality/increased length of survival ☑ Reduced symptoms or disability
☒ Other: improved quality of life ☐ 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: uncertain unit cost compared to existing treatments ☐ None identified

Other Issues

☐ Clinical uncertainty or other research question identified ☑ None identified
REFERENCES