NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cannabidiol within its marketing authorisation for adjuvant treatment of seizures associated with Dravet syndrome.

Background

Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI), is a severe form of epilepsy that affects children and adults. It is caused by defects in genes required for the proper function of brain cells.[1] Seizures in Dravet syndrome begin within the first year of life, and are characterised by initial prolonged seizures accompanying a fever (febrile seizures), which are typically associated with one side of the brain (lateralisation). Subsequently infants develop multiple seizure types (including myoclonic, absence, focal and generalised tonic–clonic seizures) and are affected by developmental delay or regression. People with Dravet syndrome are particularly prone to status epilepticus, a state of continuous seizure requiring emergency medical care.[2]

In the UK, the incidence of Dravet syndrome has been estimated between 1 in 19,000 to 1 in 40,000 live births.[3] Dravet syndrome-related mortality is estimated to be around 20%, with most deaths occurring before 10 years of age. Sudden unexpected death in epilepsy (SUDEP) and status epilepticus cause around half and a third of deaths in this condition respectively.[4]

Dravet syndrome is primarily manged with anti-epileptic drugs, and may be supported by a ketogenic diet or vagus nerve stimulation. NICE clinical guideline 137 recommends sodium valproate or topiramate as first-line treatment options, and if seizures are inadequately controlled, clobazam or stiripentol are recommended as adjunctive treatment. Many children with Dravet syndrome seem to respond best to a specific combination of sodium valproate, stiripentol and clobazam.[5]

The technology

Cannabidiol (Epidiolex, GW Pharma) is a small-molecule cannabinoid compound extracted from the *Cannabis sativa* plant. The precise mechanism of action of cannabidiol is unknown, although it is thought to act on the GPR55 and TRPV1 protein channels, which is expected to have an effect on epileptic activity in the brain. It is administered orally.

Cannabidiol does not currently have a marketing authorisation in the UK for Dravet syndrome. It has been studied in placebo controlled trials as an adjuvant treatment for inadequately controlled Dravet syndrome in people taking one or more anti-epileptic drugs.

Intervention(s)	Cannabidiol in addition to current clinical management
Population(s)	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.
Comparators	Established clinical management without cannabidiol, which may include combinations of: • sodium valproate • topiramate • clobazam • stiripentol • levetiracetam • ketogenic diet • vagus nerve stimulation
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • response rate (overall and by seizure type) • seizure severity • incidence of status epilepticus • mortality • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: None Appraisals in development (including suspended appraisals) Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome (ID1308) Fenfluramine for treating Dravet syndrome (ID1109) Related Guidelines: Epilepsies: diagnosis and management (2016) NICE clinical guideline 137. Review date 2018. Related Quality Standards: Quality standard for the epilepsies in adults (2013) NICE quality standard 26. Quality standard for the epilepsies in children and young people (2013) NICE Quality Standard 27 Related NICE Pathways: Epilepsy (2016) NICE pathway
Related National Policy	NHS England. Manual for prescribed specialised services 2016/17. Chapter 78. Neuropsychiatry services (adults and children) Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4 and 5.

References

1. European Medicines Agency (2014) Public summary of opinion on orphan designation Fenfluramine hydrochloride for the treatment of Dravet syndrome. Accessed May 2018

2. Dravet Syndrome UK (2016) What is Dravet syndrome. Accessed May 2018

3. Dravet Syndrome UK (2016) Facts about Dravet Syndrome. Accessed May 2018

4. Shmuely S (2016) Mortality in Dravet syndrome: A review Epilepsy and Behaviour. Epilepsy & Behavior 64, 69–74

5. Epilepsy Action (2016) Dravet syndrome. Accessed May 2018