NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome

Draft scope (pre-referral)

Draft 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 or Lennox-Gastaut 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, typically lateralised, febrile seizures. Subsequently infants develop multiple seizure types including myoclonic, absence, focal and generalised tonic–clonic seizures, with developmental plateau 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 80% of deaths in this condition[4].

Lennox-Gastaut syndrome is a severely debilitating form of generalised paediatric epilepsy that begins in early childhood between the ages of 2 and 7 years. It is characterised by tonic seizures, atypical absence seizures, drop seizures and slow mental development. The condition is also associated with behavioural disorders[5]. The incidence of Lennox-Gastaut syndrome is estimated at 2 per 100,000 children[5]. Lennox-Gastaut syndrome related mortality is estimated at around 5%, however the seizures are often resistant to treatment[6].

Dravet syndrome and Lennox-Gastaut syndrome are primarily manged with anti-epileptic drugs, and may be supported by a ketogenic diet or vagus nerve stimulation. For Dravet syndrome 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[7]. For Lennox-Gastaut syndrome NICE clinical guideline 137 recommends sodium valproate as a first-line treatment option, and if seizures are inadequately controlled, lamotrigine as an adjunctive treatment. Further anti-epileptic drugs, including rufinamide, topiramate and felbamate may be considered by tertiary epilepsy specialists.

The technology

Cannabidiol (Epidiolex, GW Pharmaceuticals) 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 mitochondrial VDAC1 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 or Lennox-Gastaut syndrome. It has been studied in placebo controlled trials as an adjuvant treatment for inadequately controlled Dravet syndrome and Lennox-Gastaut syndrome in people taking one or more anti-epileptic drugs.

Intervention(s)	Cannabidiol in addition to current anti-epileptic drugs
Population(s)	• People with Dravet syndrome that is inadequately controlled by anti-epileptic drugs • People with Lennox-Gastaut syndrome that is inadequately controlled by anti-epileptic drugs
Comparators	Established clinical management without cannabidiol
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • proportion of people seizure-free (overall and by seizure type) • seizure severity • 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) None 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.

Questions for consultation

Are the populations defined appropriately?

- Would cannabidiol be used only in people with Dravet or Lennox-Gastaut syndrome that is inadequately controlled by current anti-epileptic drugs?
- How are inadequately controlled Dravet and Lennox-Gastaut syndromes defined in clinical practice?

Have all relevant comparators for cannabidiol been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for Dravet syndrome and Lennox-Gastaut syndrome?

- What combinations of anti-epileptic drugs are considered to be established clinical practice in the NHS for Dravet syndrome and Lennox-Gastaut syndrome?
- Is a ketogenic diet or vagus nerve stimulation established clinical practice in the NHS for Dravet syndrome and Lennox-Gastaut syndrome?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom cannabidiol is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider cannabidiol will fit into the existing NICE pathway, Epilepsy?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cannabidiol will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider cannabidiol to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of cannabidiol can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 European Medicines Agency (2014) Public summary of opinion on orphan designation Fenfluramine hydrochloride for the treatment of Dravet syndrome. Accessed September 2017

2 Dravet Syndrome UK (2016) What is Dravet syndrome. Accessed September 2017

3 Dravet Syndrome UK (2016) Facts about Dravet Syndrome. Accessed September 2017

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

5 Orphanet (undated) Lennox-Gastaut syndrome. Accessed 15 November 17)

6 Abu Saleh, T., & Stephen, L. (2008). Lennox gastaut syndrome, review of the literature and a case report. Head & Face Medicine, 4, 9.

7 Epilepsy Action (2016) Dravet syndrome. Accessed September 2017

Appendix B