NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Cannabidiol for treating seizures caused by tuberous sclerosis complex

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of cannabidiol within its marketing authorisation for treating seizures caused by tuberous sclerosis complex.

Background

Tuberous sclerosis or tuberous sclerosis complex is a rare genetic condition that causes mainly non-cancerous (benign) tumours to develop in different parts of the body. The tumours most often affect the brain, kidneys, heart, lungs, eyes and skin. Two disease causing genes have been identified: TSC1 and TSC2. Tuberous sclerosis is present from birth, although symptoms may not appear immediately. People with tuberous sclerosis complex present at different ages with a variety of clinical manifestations. The effect of tuberous sclerosis complex on the brain can cause epilepsy, a condition that causes seizures. Seizures can progress to become refractory, which is when the seizures no longer respond to anti-epileptic medication (also known as uncontrolled or intractable). In UK clinical practice, this means that 2 different anti-epileptic drugs have failed to control a person's seizures.

The estimated prevalence of tuberous sclerosis complex in the UK is 5.6 per 100,000.[1] Seizures are the most common presenting sign of tuberous sclerosis complex and occur in approximately 84% of people. The proportion of patients with tuberous sclerosis-related refractory epilepsy varies depending on the evidence source between 36% and 63%.[2,3] Based on this, the estimated number of people with tuberous sclerosis-related refractory epilepsy in the UK is 1555.[4]

Although there is no curative treatment for tuberous sclerosis, current treatment can help to manage symptoms. Anti-epileptic drugs such as vigabatrin are administered to control seizures. Everolimus may also be used to reduce the frequency of seizures, which are closely linked to issues with development in infants and children. Early management is important in preventing and reducing the cognitive, neurological and psychiatric consequences for people with tuberous sclerosis complex.

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 treating seizures caused by tuberous sclerosis complex. It has been studied in clinical trials in patients with tuberous sclerosis complex-related seizures which have not been adequately controlled by anti-epileptic drugs.

Intervention(s)	Cannabidiol in addition to current clinical management
Population(s)	People with tuberous sclerosis complex whose seizures are inadequately controlled by established clinical management
Comparators	Established clinical management without cannabidiol, which may include • Anti-epileptic drugs (with or without steroids) • Vagal nerve stimulation • Ketogenic diet • Surgical resection
Outcomes	The outcome measures to be considered include: • change in frequency and severity of seizures • response to treatment • reduction in steroid use • 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:** 'Cannabidiol with clobazam for treating seizures associated with Dravet syndrome' (2019). NICE Technology Appraisal 614. Review date December 2022. 'Cannabidiol with clobazam for treating seizures associated with Lennox-Gastaut syndrome' (2019). NICE Technology Appraisal 615. Review date December 2022. **Related Guidelines:** 'Epilepsies: diagnosis and management' (2012). NICE

	guideline CG137. Currently being reviewed. **Guidelines in development:** 'Epilepsies in adults: diagnosis and management update'. Publication date to be confirmed. 'Epilepsies in children: diagnosis and management'. Publication expected November 2021. **Related Interventional Procedures:** 'Deep brain stimulation for refractory epilepsy in adults' (2020). NICE interventional procedures guidance 678. 'MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy' (2020). NICE interventional procedures guidance 671. **Related Quality Standards:** 'Epilepsy in adults' (2013). NICE quality standard 26. 'Epilepsy in children and young people' (2013). NICE quality standard 27. **Related NICE Pathways:** Epilepsy (2012) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1-3. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Is cannabidiol expected to be used as an add-on in first or second line treatment of tuberous sclerosis complex?

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

Which treatments are considered to be established clinical practice in the NHS for treating seizures caused by tuberous sclerosis complex that are inadequately controlled by established clinical management?

Are the outcomes listed appropriate? Should any other outcomes be included?

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 Hallet L, Foster T, Liu Z et al. (2011) Burden of diseases and unmet needs in tuberous sclerosis complex with neurological manifestations: systematic review. Current Medical Research and Opinion. 27: 1571-1583.

2 Kingswood JC, d'Augeres GB, Belousova E et al. (2017) Tuberous sclerosis registry to increase disease awareness (TOSCA) – baseline data on 2093 patients. Orphanet Journal of Rare Diseases. 12(2): 1-13.

3 Chu-Shore CJ, Major P, Camposano S et al. (2010) The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 51(7): 1236-1241.

4 Office for National Statistics (2020) Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019.