National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cannabidiol for treating seizures caused by tuberous sclerosis complex ID1416

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness *It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?*	GW Pharmaceuticals	Yes	Thank you for your comment.
	Epilepsy Action	The available high-quality clinical evidence, including randomised controlled trial data, has demonstrated the safety and efficacy of cannabidiol as a treatment for seizures caused by tuberous sclerosis complex. There is also a need for additional treatment options for seizures caused by tuberous sclerosis complex, particularly for those who are unable to achieve adequate seizure control with currently available treatments including polytherapy. The technology, cannabidiol, has been appraised previously by NICE and was recommended for use as an add-on treatment for seizures associated with Dravet syndrome (NICE TA 614) and seizures associated with Lennox-Gastuat syndrome (NICE TA 615)	Thank you for your comment. This topic has been scheduled.

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		For the reasons set out above, Epilepsy Action believes it is appropriate and indeed necessary for this topic to be appraised by NICE.	
Wording *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	GW Pharmaceuticals	Yes	Thank you for your comment. No changes to the remit needed.
	Epilepsy Action	Epilepsy Action supports the wording of the remit as set out in the draft scope.	Thank you for your comment. No changes to the remit needed.
Timing Issues *What is the relative urgency of this proposed appraisal to the NHS?*	GW Pharmaceuticals	Urgent. The European Commission approved the marketing authorisation for Epidyolex (cannabidiol) in seizures associated with TSC on 16 April 2021.	Thank you for your comment. This topic has been scheduled.
	Epilepsy Action	Refractory epilepsy associated with TSC presents several risks to those affected. These include a risk of sudden unexpected death in epilepsy (SUDEP) and associated seizures pose a risk of status epilepticus, prolonged seizures that can be fatal. Refractory epilepsy also presents an increased risk of adverse neurodevelopmental impact. This is more acute in early onset refractory epilepsy.	Thank you for your comment. This topic has been scheduled.

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		In light of these risks, Epilepsy Action considers this an urgent topic that should be appraised as soon as possible.	

Comment 2: the draft scope

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Background information	GW Pharmaceuticals	The background information states “Everolimus may also be used to reduce the frequency of seizures…”. This is partially incorrect. Everolimus does *not* have a licence for generalised-onset seizures, one of the main seizure types in TSC-associated epilepsy. It is indicated as adjunctive treatment of patients aged 2 years and older whose *refractory partial onset seizures,* with or without secondary generalisation, are associated with TSC.	Thank you for your comment. The background section has not been updated as it is understood that everolimus may be used to treat seizures associated with tuberous sclerosis complex in some cases.
	Epilepsy Action	Include reference to potential risks associated with TSC related refractory epilepsy including status epilepticus, specifically sudden unexpected death in epilepsy (SUDEP) and adverse neurodevelopmental impacts.	Thank you for your comment. The background section has been updated to describe the risks associated with refractory epilepsy associated with tuberous sclerosis complex, including status epilepticus, sudden unexpected

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			death in epilepsy and adverse impact on neurodevelopment.
The technology/ intervention	GW Pharmaceuticals	The brand name in Europe is Epidyolex® (not Epidiolex). Epidyolex now has marketing authorisation. The European Commission approved the marketing authorisation for Epidyolex (cannabidiol) in seizures associated with TSC on 16 April 2021.	Thank you for your comment. The brand name has been updated. The technology section has been updated to include details of the UK marketing authorisation.
	Epilepsy Action	Epilepsy Action considers the description of the technology to be accurate.	Thank you for your comment.
Population	GW Pharmaceuticals	The Marketing Authorisation specifies that patients should be aged ≥2 years. The population should be defined as: People with tuberous sclerosis complex aged ≥2 years whose seizures are inadequately controlled by established clinical management.	Thank you for your comment. The population in the scope has been kept broader than the anticipated marketing authorisation wording. However, the committee will only be able to make recommendations within the marketing authorisation.

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	Epilepsy Action	Epilepsy Action considers the population to be defined correctly.	Thank you for your comment.
Comparators	GW Pharmaceuticals	"Vagal nerve stimulation" should be replaced with "Vagus nerve stimulation" We request that the wording "(with or without steroids)" is removed, as it is not relevant to this appraisal. Steroids are not used routinely in seizures associated with TSC in patients aged ≥2 years. Steroids may be used very short-term, but only in infantile spasms (a specific type of seizure that often starts in infants <1 year old and usually resolves in early childhood or may be replaced by other seizure types). Guidelines indicate that, for infantile spasms only, if vigabatrin is ineffective, a short-term steroid or steroid alternative (e.g. prednisolone or tetracosactide) rather than an anti-epileptic drug can be offered second line. This corticosteroid therapy is generally short-term (approximately 2 weeks followed by taper).1 1. Epidyolex EPAR, available at https://www.ema.europa.eu/en/documents/variation-report/epidyolex-h-c-4675-ii-0005-epar-assessment-report-variation_en.pdf	Thank you for your comment. 'Vagal nerve stimulation' has been updated to 'vagus nerve stimulation'. The wording 'with or without steroids' has been removed from the scope.
	Epilepsy Action	Suggest also referencing Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above).	Thank you for your comment. The examples of comparators considered as part of established clinical management have been updated to

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			include ‘anti-seizure medications’ and ‘everolimus’.
Outcomes	GW Pharmaceuticals	No. We request that the following relevant and clinically meaningful outcome measures are added to the scope: • Change in the number of seizure-free days • Caregiver health-related quality of life. We also request that “reduction in steroid use” is removed. As outlined above, steroids are only used for infantile spasms and for very short periods of time (e.g. 2 weeks followed by taper). Therefore this is not a clinically relevant or meaningful outcome in TSC-associated epilepsy.	Thank you for your comment. The outcomes list is not intended to be fully exhaustive. The outcome ‘change in the number of seizure-free days’ may be considered under the listed outcome ‘response to treatment’. ‘Caregiver health related quality of life’ may be considered under the listed outcome ‘health-related quality of life’. ‘Reduction in steroid use’ has been removed as an outcome.
	Epilepsy Action	Suggest including parent or carer quality of life as an additional outcome measure.	Thank you for your comment. The outcomes list is not intended to be fully exhaustive. The

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			outcome ‘caregiver health related quality of life’ may be considered under the listed outcome ‘health-related quality of life’.
Economic analysis	GW Pharmaceuticals	The educational, societal and out-of-pocket costs of TSC-associated epilepsy are substantial. Therefore, considering only the NHS/PSS perspective is unlikely to reflect the full value of the technology.	Thank you for your comment. The NICE reference case stipulates that the cost-effectiveness of a technology should be considered from an NHS and Personal Social Services perspective. The committee will also be able to consider any additional costs and benefits it feels have not been adequately captured by the cost-effectiveness analysis.
Equality and Diversity	GW Pharmaceuticals	No comments	Thank you.
Other considerations	GW Pharmaceuticals	No comments	Thank you.

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Innovation	GW Pharmaceuticals	We consider Epidyolex to be innovative and that it represents a step-change in the management of seizures associated with TSC. There are currently only a small number of treatments approved for TSC-associated epilepsy, and no drugs that are effective or well-tolerated in the majority of patients. Given the lack of emerging therapeutic options, a variety of other treatments have been tried. However, limited efficacy has been observed and a large proportion of patients remain refractory. Cannabidiol is a novel, innovative therapy for patients with TSC-associated seizures. It offers a unique therapeutic modality and has been shown to be clinically effective with a favourable safety and tolerability profile in patients with TSC who live with the constant threat of seizures and who otherwise have extremely limited treatment options. The QALY calculation is unlikely to include the benefits of: • Improving the quality of life of the wider family, including siblings • Increasing caregiver productivity and the associated societal benefits of the parent(s)/primary caregiver(s) not giving up work to care for a patient with TSC • The long-term impact of improved seizure control on co-morbidities and injuries.	Thank you for your comment. The committee will consider the innovative nature of this technology and any additional benefits of this technology which are not captured by the QALY. No changes to the scope needed.
	Epilepsy Action	Available randomised controlled trial (RCT) evidence of cannabidiol as a treatment for seizures caused by TSC has demonstrated the efficacy of the technology compared to placebo in patients whose epilepsies was previously drug resistant.	Thank you for your comment. The committee will consider the innovative nature of this technology. No changes to the scope needed.

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		This is a substantial health related benefit and offers a much needed additional treatment option that has the potential to improve the way current need is met. As such Epilepsy Action would consider the technology a potential 'step-change' in the management of seizures caused by TSC for patients who are currently unable to achieve adequate seizure control by established clinical management. The impact of drug-resistant epilepsies on patients and support networks, including the potential risks associated with uncontrolled seizures, should be given due consideration in the appraisal process. This includes the risks of seizures, including potential for mortality, and increased prevalence of mental health comorbidities for patients and wider supporter networks.	
Questions for consultation	GW Pharmaceuticals	Is cannabidiol expected to be used as an add-on in first or second line treatment of tuberous sclerosis complex? Add-on. The value of cannabidiol is in the treatment of patients with TSC-associated epilepsy with uncontrolled seizures despite treatment with at least two AEDs. Have all relevant comparators for cannabidiol been included in the scope? Yes.	Thank you for your comment. No changes to the population in the scope have been made. The examples of comparators considered as part of established clinical management have been updated to include 'anti-seizure medications'
	GW Pharmaceuticals	TSC-associated epilepsy is an orphan disease.	Thank you for your comment. The NHS England Clinical

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Additional comments on the draft scope		On 17 January 2018, orphan designation (EU/3/17/1959) was granted by the European Commission for cannabidiol for the treatment of tuberous sclerosis. The NHS England Clinical Commissioning Policy ("Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above) NHS England Reference: 170093P") is also relevant to this appraisal. Everolimus-for-refractory-focal-onset-seizures-associated-with-TSC.pdf (england.nhs.uk)	Commissioning Policy for everolimus has been added to the related national policy section of the scope. The examples of comparators considered as part of established clinical management have also been updated to include 'everolimus'.
	Epilepsy Action	Epilepsy Action welcomes the proposed Health Technology Appraisal of cannabidiol for treating seizures caused by tuberous sclerosis complex. There is a clear need for additional treatment options for people with TSC whose epilepsy is not adequately controlled with available treatment options. The draft scope provides a good basis for appraising this technology and we look forward to engaging with the process going forward.	Thank you for your comment.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

GlaxoSmithKline