Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2263

cannabidiol 100mg/ml oral solution (Epidyolex®)

GW Research Ltd

7 August 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan process

cannabidiol (Epidyolex®) is accepted for use within NHSScotland.

Indication under review: for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome, in conjunction with clobazam, for patients 2 years of age and older.

In two phase III, placebo-controlled studies cannabidiol reduced drop seizure frequency in the clobazam-treated subgroup of children and adults (aged 2 to 55 years) with Lennox-Gastaut syndrome that was inadequately controlled by other anti-epileptic drugs.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome, in conjunction with clobazam, for patients 2 years of age and older.[1]

Dosing Information

The recommended starting dose of cannabidiol is 2.5mg/kg taken twice daily (5mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5mg/kg twice daily (10mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5mg/kg administered twice daily (5mg/kg/day) up to a maximum recommended dose of 10mg/kg twice daily (20mg/kg/day). Any dose increases above 10mg/kg/day, up to the maximum recommended dose of 20mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule. If cannabidiol has to be discontinued, the dose should be decreased gradually. In clinical trials, cannabidiol discontinuation was achieved by reducing the dose by approximately 10% per day for 10 days. A slower or faster down titration may be required, as clinically indicated, at the discretion of the prescriber.

Food may increase cannabidiol levels and therefore it should be taken consistently either with or without food, including the ketogenic diet.

Cannabidiol should be initiated and supervised by physicians with experience in the treatment of epilepsy.[1]

Product availability date

January 2020

Cannabidiol in this indication meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Cannabidiol is an anti-epileptic drug (AED) with a mechanism of action that is in part due to a two-way pharmacokinetic interaction with clobazam, which increases by 3-fold the clobazam active metabolite (N-desmethylclobazam) and increases by 1.5 fold the cannabidiol active metabolite (7-hydroxy-cannabidiol). Cannabidiol may have additional effects, but these are not fully characterised and are not produced via cannabinoid receptors.[1]

Two similar double-blind phase III studies (CARE3 and CARE4) recruited patients aged 2 to 55 years with Lennox-Gastaut syndrome, including a history of at least two types of generalised seizures and slow (<3.0 Hz) spike-and-wave electroencephalogram (EEG). This was inadequately controlled on more than one AED (inclusive of current and previous therapy) and they had at least two drop seizures per week during a 28-day baseline period when they were on stable doses of up to four AED(s). In both studies patients continued on stable doses of AED and randomisation was stratified by age (2 to 5, 6 to 11, 12 to 17 or 18 to 55 years). In CARE4 patients were equally assigned to cannabidiol titrated to 20mg/kg/day divided into two doses or placebo for 14 weeks.

In CARE3 they were assigned in a 2:2:1:1 ratio to cannabidiol titrated to 20mg/kg/day or 10mg/kg/day divided into two doses or matching placebo for 14 weeks. The primary outcome in both studies was change from baseline in 28-day drop seizure frequency during the 14-week treatment period, expressed as a percentage of baseline frequency. These were assessed in the intention-to-treat (ITT) population, which comprised all randomised patients who received study drug and had post-baseline efficacy assessment.[2-4]

The primary outcome in both studies indicated significantly greater reductions in 28-day drop seizure frequency with cannabidiol compared with placebo in the total ITT population and favoured cannabidiol in the clobazam-treated subgroup, which is representative of the licensed indication, as detailed in Table 1. Treatment effects in the ITT population were mainly driven by effects within the clobazam-treated subgroup. The European Medicines Agency (EMA) review noted that the magnitude of treatment effect in patients who were not receiving concomitant clobazam have not been shown to be statistically or clinically relevant.[2-4]

Table 1: CARE3 and CARE4 primary outcome: percent change (reduction) from baseline in 28-day drop seizure frequency.[1,2]

		Total ITT Study Population			Clobazam-Treated Subgroup		
		N	**Change***	**Difference (95%CI)**	**N**	**Change***	**Difference (95%CI)**
CARE4	cannabidiol 20mg/kg/day	86	44%	17% (4.1% to 30%)	42	62%	46% (27% to 60%)
	placebo	85	22%		42	31%	
CARE3	cannabidiol 20mg/kg/day	76	42%	22% (6.7% to 35%)	36	64%	54% (36% to 67%)
	cannabidiol 10mg/kg/day	73	37%	19% (7.7% to 31%)	37	46%	30% (2.4% to 49%)
	placebo	76	17%		37	23%	

CI = confidence interval Difference = compared with placebo; * = difference in 28-day drop seizure frequency during 14-week treatment period compared with 28-day baseline period frequency expressed as a percentage of 28-day baseline frequency.

In CARE3 the key secondary outcomes were tested in the following hierarchical order: proportion of patients with at least 50% reduction in drop seizures from baseline, percentage change from baseline in total seizures and change from baseline in the subject or caregiver global impression of change (S/CGIC) for cannabidiol 20 mg/kg/day first, then for cannabidiol 10 mg/kg/day. For the submission to the EU licence application only, the key secondary outcomes were also tested in this hierarchical order in CARE4. In both studies all three key secondary outcomes demonstrated a significant improvement with cannabidiol compared with placebo. Available data for secondary outcomes in the clobazam-treated subgroup, representative of the licensed indication, are detailed in Table 2.[1-4] There were no data in this subgroup for S/CGIC. However, in the total population at the end of treatment S/CGIC was improved (slightly improved, much improved, or very much improved) for more patients in the cannabidiol group, compared with placebo, in CARE4: 58% versus 34%; and in CARE3 for more patients in the cannabidiol 20mg and 10mg groups, compared with placebo: 57% and 66% versus 44%. [2]

Table 2: Secondary outcomes of CARE3 and CARE4 in clobazam-treated subgroup.[1,2]

	CARE4		CARE3		
	cannabidiol 20mg/kg/day	Placebo	cannabidiol 20mg/kg/day	cannabidiol 10mg/kg/day	Placebo
N	42	42	36	37	37
≥50% reduction in drop seizure frequency					
Responders	55%	29%	56%	40%	22%
OR (95% CI)	3.1 (1.3; 7.8)		5.1 (1.8; 14)	2.7 (1.0; 7.7)	
Change in total seizure frequency					
Reduction	66%	25%	64%	53%	25%
Difference	55%		51%	37%	

CI = confidence interval; OR = odds ratio

Patients who completed CARE3 and CARE4 (or the phase III studies in Dravet syndrome, CARE1 and CARE2) could receive open-label cannabidiol titrated to 20mg/kg/day in an ongoing safety extension study (CARE5). At an interim analysis, data cut-off 3 November 2016, 67 (18%) of the 366 patients with Lennox-Gastaut syndrome had withdrawn from treatment. Within those remaining on treatment median percent reduction in 28-day drop seizure frequency compared with baseline in CARE3 or CARE4 was similar to that in the double-blind studies: 48%, 56%, 56% and 60% after 1 to 12 weeks (n=364), 13 to 24 weeks (n=334), 25 to 36 weeks (n=314) and 37 to 48 weeks (n=209), respectively, in CARE5.[2,5]

Summary of evidence on comparative safety

Pooled data from the CARE3 and CARE4 studies showed that within adverse events were reported by 88% (207/235) and 71% (114/161) of the ITT population in the cannabidiol and placebo groups respectively (and by 92% (105/114) and 72% (58/80) of the clobazam-treated subgroup). Serious adverse events were reported by 19% and 7.5% of patients (23% and 7.5% in the clobazam subgroup), with adverse events leading to discontinuation by 8.1% and 1.2% of patients (10.5% and 0% in the clobazam subgroup). Common adverse events within the respective cannabidiol and placebo groups in the ITT population included somnolence or sedation, 27% and 8.7% (40% and 11%); decreased appetite, 18% and 5.0% (12% and 5.0%); diarrhoea, 31% and 27% (9.6% and 8.8%); pyrexia, 12% and 12% (15% and 14%); fatigue, 7.7% and 2.5% (10.5% and 0%); and vomiting, 9.8% and 14.3% (7.9% and 16%). The EMA review noted that diarrhoea and decreased appetite were more common in those receiving concomitant sodium valproate. It assessed safety data of CARE3 and CARE4 combined with data from studies CARE1 and CARE2 (in Dravet syndrome), noting that subgroup analyses by disease (Dravet syndrome or Lennox-Gastaut syndrome) did not show any clear difference across the reported adverse events. In these analyses within the cannabidiol and placebo groups rash was reported by 4.2% and 1% of the overall population and pneumonia by 4.8% and 0.7%, respectively. Seizure worsening, occurred in 57.54 versus 53.30 cases per 100 patient-years in the cannabidiol and placebo groups, respectively.[2]

The EMA review noted that hepatoxicity was the main safety issue. In pooled data from the four phase III studies (CARE1, -2, -3 and -4) within the cannabidiol and placebo groups abnormal liver

adverse events were reported by 15% (68/456) versus 3.1% (9/292), with a higher incidence in the cannabidiol 20mg/kg/day group, compared with the 10mg/kg/day group (18% [54/307] versus 9.4% [13/139]) and a dose-response relationship noted. In the clobazam-treated subgroup these were reported by 20%, 11% and 2.4% of patients in the cannabidiol 20mg/kg/day, 10mg/kg/day and placebo groups, respectively. These were primarily dose-dependent elevations in liver enzymes, primarily transaminases, and the risk was increased in those receiving concomitant sodium valproate and in those with baseline elevated transaminases, with a synergistic increase for patients with both of these risk factors. Concomitant administration of clobazam also increased the risk of elevated transaminases, but to a much lesser extent than sodium valproate. [2]

In the pooled studies irritability was reported by 5.5% and 1.7% of patients in the respective groups and aggression by 3.9% and 1.0%. These were reported mainly within the first two weeks for cannabidiol-treated patients, but it is not clear if these effects were transient. During the studies cognitive tests were performed on a small number of patients and it is not possible to draw any conclusions from this on the effect of cannabidiol on cognitive function or development. Additionally, the long-term impact of cannabidiol on cognitive and endocrine function is unknown.[2]

Cannabidiol oral solution contains alcohol that will lead to an alcohol intake above the upper limit of acceptance for children up to six years of age at the 20mg/kg/day dose. The long-term effect of this is unknown.[2] The summary of product characteristics notes that each millilitre of cannabidiol oral solution contains 79mg of ethanol. Effects of alcohol in children less than 6 years old may include sleepiness, behavioural changes, and impaired ability to concentrate and participate in school activities. The alcohol content should be taken into account in pregnancy and high-risk groups such as patients with liver disease.[1]

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Cannabidiol is one of several medicines licensed for adjunctive treatment of Lennox-Gastaut syndrome, with others including lamotrigine, topiramate and rufinamide.[4,6-8] SMC has issued advice (numbers 416/07, 795/12 and 2146) that rufinamide is accepted for use within NHSScotland for the treatment of Lennox-Gastaut syndrome. Cannabidiol for the treatment of Lennox-Gastaut syndrome has been designated as an orphan medicine in the EU and it meets SMC criteria for an orphan medicine in this indication.

Lennox–Gastaut syndrome usually begins between 3 and 5 years of age and is characterized by multiple seizure types (predominantly tonic, atonic, and atypical absence seizures), slow EEG spike-waves with abnormal background activity when awake, and fast polyspikes during sleep. Other seizure types may occur including generalised tonic-clonic, focal, and myoclonic seizures and all seizures types may progress to status epilepticus. Drop seizures are common and can lead to physical injury. Cognitive impairment is observed in at least three quarters of patients within 5 years of onset and patients often have behavioural and psychiatric comorbidities. Seizures often continue into adulthood. Patients with Lennox-Gastaut syndrome have an increased risk of death,

for example, due to sudden unexpected death in epilepsy (SUDEP). There is no single cause of the disease. However, about two-thirds of patients have an existing neurological condition, for example abnormal development of the brain cortex (cortical dysplasia), congenital infections, stroke, trauma, reduced oxygen supply that occurs before birth (perinatal hypoxia), or infections of the central nervous system such as encephalitis or meningitis.[2]

Lamotrigine, topiramate, rufinamide and cannabidiol are licensed specifically for the treatment of Lennox-Gastaut syndrome.[1,6-8] However, sodium valproate[9] and clobazam[10] are licensed for use in epilepsy and are widely used. Sodium valproate is often used to prevent the initial recurrence of convulsive seizures, and benzodiazepines (for example, diazepam, midazolam, clonazepam, or clobazam) are frequently co-administered to limit the duration of long-lasting seizures.[2] The National Institute of Health and Care Excellence (NICE) guideline recommends for Lennox–Gastaut syndrome first-line treatment with sodium valproate. Lamotrigine is recommended as adjunctive treatment in children, young people and adults if first-line treatment with sodium valproate is unsuitable, ineffective or not tolerated.[11] Other AEDs that may be considered by epilepsy specialists are rufinamide[8] and topiramate.[7] Felbamate can be also be offered by centres providing tertiary epilepsy specialist care and when treatment with lamotrigine, rufinamide and topiramate has proved ineffective or not tolerated.[11] Polytherapy is common and seizure control is difficult to achieve with current therapies.[2] Clinical experts consulted by SMC note that Lennox-Gastaut syndrome is often refractory to existing AED and there is an unmet need for effective AED to treat this condition.

In the main phase III studies (CARE3 and CARE4) cannabidiol compared with placebo significantly reduced frequency of drop seizures, with a percent change relative to baseline of 17% to 22% over placebo. This was driven mainly by effects in the clobazam-treated subgroup where the difference over placebo was about 30% to 54%. The EMA concluded that the magnitude of effect in patients who were not receiving clobazam has not been convincingly demonstrated as statistically or clinically relevant. Cannabidiol is only licensed for use in conjunction with clobazam. The EMA considers that its therapeutic effects are produced mainly via an interaction that increases clobazam levels about 3-fold.[2-4]

The primary outcome was supported by the key secondary outcome; proportion of patients with at least a 50% reduction in drop seizures, within the clobazam-treated subgroup cannabidiol increased this by about 18% to 34% over placebo. There were also benefits with cannabidiol in total seizure frequency reduction and S/CGIC.[2-4]

One limitation of the evidence base is that relevant data for the licensed indication are from the clobazam-treated subgroup. This comprised 49% (110/225) and 44% (84/191) of patients in CARE3 and CARE4, respectively. Across both studies within this subgroup only 78 and 37 patients received cannabidiol 20mg/kg/day and 10mg/kg/day respectively. Subgroup data may limit the power of efficacy and safety analyses, but are most likely to represent the benefits and adverse events that may be observed in practice.[2]

Also, the change in 28-day drop seizure frequency was expressed as a percentage relative to baseline frequency rather than an absolute difference. Median 28-day drop seizure frequency in the cannabidiol 20mg/kg/day and 10mg/kg/day and placebo groups was 85.5, 86.9 and 80.2 at baseline in the ITT population (69.0, 87.0 and 76.3 in the clobazam-treated subgroup) and 44.9,

50.0 and 72.7, respectively, during the treatment period in CARE3; and in CARE4 within the cannabidiol 20mg/kg/day and placebo groups was 71.4 and 74.7 (59.0 and 83.5) at baseline and 31.4 and 56.3, respectively, during the treatment period.[2]

The uptake of cannabidiol can be increased about 4-fold when it is taken with food, compared to the fasted state. The CARE3 and -4 studies did-not specify whether cannabidiol should be taken with or without food, which may limit interpretation of efficacy and safety data. Also, the dose titration schedule in these studies (2.5mg/kg/day then increments of 2.5mg/kg/day over 2 days) is different to the licensed schedule (5mg/kg/day then increased after one week to 10mg/kg/day). However, population pharmacokinetic modelling indicated little difference in concentrations between the different titration schedules. Seizure data (type and frequency) were collected by the patient or caregivers in a daily diary. During the EMA review there were concerns about the quality of data collection due to the limited training of caregivers and potential unblinding of caregivers, who were aware of other clinical information such as dose adjustments, adverse events and changes in the patient's well-being. However, additional analyses led to a conclusion that the results were robust despite these potential limitations.[2]

The studies do not provide data in children aged less than 2 years or in adults aged more than 55 years. The inclusion criteria specified that patients had epilepsy that was not controlled on current AED.[2] The indication does not specify use in epilepsy inadequately controlled on AED; however, in practice cannabidiol is likely to be used in that patient group.[1] The inclusion criteria specified that patients had at least 2 drop seizures per week over the 4-week baseline period. The studies do not provide evidence in patients who have a seizure frequency lower than this.[2] Moreover, studies were not designed to assess outcomes, such as effects on psychomotor and cognitive development, which would require longer studies. An open-label extension study is ongoing and currently long-term efficacy data are limited.

The size of the safety evidence base may not fully characterise rare adverse events or those that occur after long-term administration.[2] The long-term impact of cannabidiol on cognitive and endocrine function and on development of these during childhood is unknown. The EMA review noted that cannabidiol oral solution contains alcohol that will lead to an alcohol intake above the upper limit of acceptance for children up to six years of age at the 20 mg/kg/day dose. The long-term effect of this is unknown.[2]

Clinical experts consulted by SMC considered that cannabidiol is a therapeutic advancement due to its effects on seizure control in patients with disease that is refractory to other AED. They noted that in practice cannabidiol is likely to be used as an add-on to a patient's existing AED therapy, rather than displace another medicine. However, they noted that if cannabidiol improved seizure control it may be possible to reduce other AEDs. They believe that its introduction to practice would not be associated with any substantial service implications.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of cannabidiol as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Patients with Lennox Gastaut syndrome often have frequent, treatment-resistant, severe and debilitating seizures from a young age. Many patients suffer particularly from drop-seizures, which can lead to injuries. These individuals have severe learning disability, autism and issues with sleep, mobility and feeding. They usually require 24-hour care and are fully dependent all their lives. Patients can sustain seizure-related injuries and have an increased risk of death (approximately 3% to 7%) related to seizures or SUDEP. Overall, Lennox Gastaut syndrome has a devastating and lifelong impact on the patient's quality of life.

- Lennox Gastaut syndrome is an immense strain on the patient's family. Providing and organising 24-hour care is exhausting for parents. For >90% of families, at least one parent stops work or reduces their hours leading to financial difficulties and stress. The unpredictable and severe nature of seizures and increased risk of death causes parents relentless anxiety with some sleeping in the same room as their child and having poor sleep quality. The severity of the illness creates challenges in obtaining help with the patient's care and in participation in social activities. Dealing with the disease puts a significant stain on family relationships and >90% of parents develop mental health issues, with many reporting feelings of social isolation.

- The disease has a substantial impact on the patient's siblings. They may be distressed by witnessing seizures and worry about the health of their sibling and parents. They may take on some care responsibilities, have less attention from their parents and have fewer opportunities to participate in social activities.

- Most patients take a combination of AEDs, which do not adequately control Lennox Gastaut syndrome and are associated with side effects. Clinicians estimate that less than 3% of patients have adequate seizure control with currently available AEDs and there is a significant unmet need for new effective therapies that control seizures with an acceptable side effect profile.

- A reduction in seizures with cannabidiol positively benefits the patient's development, improves their comorbidities and ultimately improves their quality of life allowing them to participate more in family life, school and social activities. There are several reports of patients being more alert with cannabidiol and having improved quality of life through resolution of problematic seizure types. Improved seizure control may reduce risk of seizure-related injury and death and it is hoped that it may reduce the cumulative impact of seizures on developmental problems associated with this neurological disease.

- Improved seizure control lightens the workload of parents caring for a child with Lennox Gastaut syndrome and reduces their anxiety. It gives the family confidence to participate with more in education, work and social activities and, overall, improves the whole family's quality of life.

- Clinicians noted that clinics have been established to monitor liver function and to assess outcomes. They now have experience in adjusting the doses of AED to manage side effects such as raised liver enzymes. They also note the importance of agreeing with the patient's carers realistic treatment aims, criteria for monitoring outcomes and an exit strategy. Clinicians also advised that they would aim to discontinue other AED when commencing cannabidiol, especially in the situation where the patient has seizures not adequately controlled by these

Additional Patient and Carer Involvement

We received patient group submissions from Epilepsy Action, Epilepsy Connections and Epilepsy Scotland. All three organisations are registered charities. Epilepsy Action has received less than 1% pharmaceutical company funding in the past two years, with none from the submitting company. Epilepsy Connections has not received any pharmaceutical company funding in the past two years. Epilepsy Scotland has received less than 1% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis assessing cannabidiol for the treatment of Lennox-Gastaut Syndrome, according to the licensed indication. This compared cannabidiol plus clobazam alongside usual care against usual care alone. Usual care was assumed to align with the distribution of treatments observed within the CARE3 and 4 clinical trials, with the most frequent treatments represented as clobazam, levetiracetam, rufinamide, lamotrigine and valproic acid. SMC clinical experts indicated that multiple different anti-epileptic drugs are used in practice within Scotland, but highlighted that cannabidiol is likely to be used in addition to, rather than displacing, these therapies.

A *de novo* cost-utility analysis was provided in the form of a Markov state-transition cohort model, covering a total of 10 health states. These represented both the number of drop seizures per month ('seizure-free', ≤ 45 seizures, > 45 - ≤ 110 and >110), as well as being subdivided into the number of days without drop seizures per month (≤3, > 3 - ≤ 15 days, > 15 days). Patients could transition to an absorbing health state of death at any time. A 3-month cycle length was used and a lifetime (90 year) time horizon applied. A perspective of NHSScotland and social work was adopted for costs, while outcomes for both patients and two caregivers taken for the original base case. A revised base case, reflecting a 'patient-only' perspective, was provided for consistency with SMC processes but the analysis incorporating carer effects was also considered as a sensitivity analysis.

Clinical effectiveness data were obtained from the randomised CARE3 and CARE4 studies, which informed baseline health state distribution and transitions within the first cycle for both the cannabidiol and usual care cohorts. Patients in the cannabidiol cohort were then modelled to transition between health states up to cycle 9 (27 months), according to data observed in the open-label extension study CARE-5. No further data were available beyond cycle 1 for the usual care cohort. Following cycle 1 (usual care) and cycle 9 (cannabidiol cohort), patients were assumed to remain in the same health state until death. The only exceptions to this were patients who discontinued cannabidiol treatment, at which point they assumed the health state distribution of the usual care cohort at cycle 1. Discontinuation was based on a proposed stopping rule, where patients who do not achieve a reduction in drop seizure frequency from baseline of 30% or greater stop treatment at 6 months, 1 year or 2 years. Longer-term treatment discontinuation was based on an assumption of 10% per annum, although real-world data from an early access program (5% per annum) were tested in a scenario analysis. Mortality was assumed to remain constant regardless of seizure frequency.

Utility estimates were estimated using a direct elicitation exercise, where 11 patients with epilepsy and 19 caregivers of patients with epilepsy were asked to value a series of vignettes through the perspective of a patient with Lennox-Gastaut Syndrome using a Visual Analogue Scale (VAS). Although not derived using a 'choice-based' approach, the company utilised mean estimates from this exercise in the base case (utilities ranged from 0.75 ['seizure-free'] to 0.235 [≤ 3 seizure-free days with more than 110 seizures]). Caregivers participating in the exercise were asked to value an additional three health states representing a carer of a patient with varying frequencies of epilepsy, resulting in disutility ranging from -0.045 (seizure free) to -0.447 (>110 seizures per month). Alternative estimates of utilities, where visual analogue scale was mapped to standard gamble, were provided in sensitivity analysis.[12]

Medicines acquisition costs were included in the evaluation, as well as costs of adverse event management and subsequent treatment of 'drop-outs'. The dose of cannabidiol was assumed to be constant with the 'usual' maintenance dose of 10mg/kg/day in the licensed indication, although the indication allows for patients to receive treatment up to 20mg/kg/day. Scenarios were provided based on assumptions of an average of 11mg/kg/day and 12mg/kg/day, although a conservative analysis utilising the 20mg/kg/day dose (which more closely aligns with the CARE-5 average dose) was provided upon request. Healthcare resource use was estimated by clinical experts consulted by the company as no data were available; these assumed a general increase in resource requirements such as hospitalisation and paediatric consultations correlating with an increase in seizure frequency.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a confidential discount was offered on the list price.

The revised ('patient-only' perspective) base case results are shown in Table 3.

Table 3: Revised base case (patient utility only perspective on health benefits)

Technologies	ICER (£/QALY)
Usual-care + placebo	£60,733
Usual-care + CBD	
QALY- quality adjusted life year ICER- incremental cost effectiveness ratio	

Disaggregated analyses highlight that the costs of treatment acquisition are the predominant incremental costs, while management costs per patient represent the largest cost offset. Similarly, the majority of QALY gains are achieved by increased number of cannabidiol patients entering the 'seizure free' health state.

Key scenario analyses, including the original base case incorporating the carer perspective, are shown below. These highlight particular upwards sensitivity to more conservative approaches to estimating utility for caregivers and the number of carers modelled, the use of mapped standard gamble estimates of patient utilities, and factors which increase the average episode-of-care cost of cannabidiol (mean dose, absence of stopping rule and lower discontinuation rates).

Table 4: Key scenario analyses

Scenario number	Parameter	Revised base case	Scenario analyses	ICER
	'Patient only' base case	**N/A**	**N/A**	**£60,733**
1.	CBD dosage	All patients receiving 10 mg/kg/day	Average dose: 12 mg/kg/ day	£75,192
2.			Average dose: 20 mg/kg/day	£127,748
3.		Calculated based on median weight from trials	Calculated based on mean weight	£65,879
4.	Utilities	VAS estimates provided by patients/caregivers	Mapping algorithms to Standard Gamble (highest and lowest estimates)	£58,536 to £86,999
5.	Ratio ICU/General ward	5% in ICU and 95% in general ward	50% in ICU and 50% in general ward	£58,372
6.	Stopping rules	First timepoint at 6 months	No stopping rules	£62,467

7.	Discontinuation rates	Assume 10% per annum after cycle 1	Real-world data (5% per annum) after cycle 1	£70,749
8.	Caregiver disutility	Patient utilities only	Consideration of disutility for primary caregiver	£35,002
9.			Equal disutilities for two caregivers (company base case)	£24,586
10.	Combined scenario (utility of 1 caregiver)	See base case	Scenarios 1, 4, 7, 8	£50,031
11.	Combined scenario (utility of 1.5 caregivers)		Scenarios 1, 4, 7 and 1.5 times carer disutility	£41,738
ICER: incremental cost per QALY; CBD: cannabidiol; VAS: visual analogue scale; ICU: intensive care unit				

Following the New Drugs Committee (NDC) consideration of the submission, the company conducted a further study to assess health related quality of life. This aimed to address some of the concerns raised by NDC about the methods used. For the revised utility study, patient vignettes were iteratively reviewed by two LGS and DS expert clinicians and the carer vignettes were constructed from the perspective of someone who is one of two primary caregivers/parents of a 10-year old child. The vignettes were then valued using the time-trade off methodology in members of the general public in the UK (n=150) and Sweden (n=50).

Key results using this revised approach are presented in table 5. These figures were considered relevant for decision-making by SMC as the approach to estimating utilities was considered an improvement on the base case approach by employing preference-based methods and resolving some concerns regarding multiplicative estimation of carer burden.

Table 5: Key results using revised utility study

Analysis	**ICER with PAS**
Base case using patient only perspective on benefits	£34,128
Base case using patient and carer perspective on health benefits (company base case)	£13,420
Combined scenario (as per scenario 10, table 4)	£26,921

The following limitations are noted regarding the economic evaluation:

- The approach to valuing caregiver disutility as originally presented in the submission was associated with uncertainty. The valuation study required participants to consider the impact

on a single carer, without discussing involvement of a partner or second carer. Despite this, a simple multiplication of utility for two carers was applied, which may overestimate the extent of disutility. An estimate of caregiver disutility for 1 carer was obtained and falls between the original and revised base case (Table 4, scenarios 8 and 9). The revised analysis presented in table 5 helped to address the concerns in the originally submitted analysis. This revised analysis also used preference-based measures and thus addressed the concerns of NDC that the original approach to patient utilities did not use a choice-based method.

- The expected average dose of cannabidiol is unknown, as the licensed indication allows dose escalation to 20mg/kg/day whereas the randomized trial data did not. The submitting company assumed an average of up to 12mg/kg/day will be used in practice, based on a recent observational study only published in abstract form.[13] However, an Expanded Access Programme[14] for cannabidiol reported an average dose higher than the maximum licensed dose, therefore the average dose could plausibly increase further towards 20mg/kg/day. Increases in dose above 10mg/kg/day result in a significant upwards effect on the ICER (Table 4, scenario 1 and 2).
- Median weight was used to estimate total cannabidiol dose, rather than mean. Use of mean weights is more appropriate and results in a moderate increase in the ICER (Table 4, scenario 3).
- No long-term data are available beyond 27 months, yet the treatment benefit is assumed to be maintained for the remainder of 90 years. The submitting company was unable to provide alternative estimates where treatment waning was assumed, although provided a separate scenario where patients were assumed to remain on treatment for three months following loss of efficacy. This had limited effect on the ICER (not shown), although the ICER effect of patients receiving lower long-term benefit whilst remaining on treatment remains unknown.
- A range of combined scenarios were obtained, which test some of the key uncertainties (Table 4, scenarios 10 and 11, table 5, combined scenario). It should be noted that the ICER could plausibly increase beyond this point, as amendments influencing the cost of cannabidiol acquisition (such as the use of mean rather than median dose) have not been included. However, the submitting company did also use some conservative approaches, for example the impact of sudden unexpected death due to epilepsy was not included in the analysis, which could have a positive impact on the cost-effectiveness of cannabidiol. The submitting company also asserted that there were a range of other benefits that were not easily captured in the economic model; wider quality of life impacts on wider members such as siblings; reducing the number of non-drop seizures and reductions in the duration and severity of seizures; potential reductions in concomitant medications; and potential longer term impacts of improved seizure control on cognitive function, behaviour and injury.

The Committee considered the benefits of cannabidiol in the context of SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as cannabidiol is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process and after application of the appropriate SMC modifiers, the Committee accepted cannabidiol for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The National Institute of Health and Clinical Excellence (NICE) published in January 2012 and last updated in October 2019 clinical guideline 137, epilepsies: diagnosis and management. This recommends discussion with or referral to a tertiary paediatric epilepsy specialist when a child presents with suspected Lennox–Gastaut syndrome. Offer sodium valproate as first-line treatment to children with Lennox–Gastaut syndrome. Follow the MHRA safety advice on sodium valproate. It also recommends offering lamotrigine as adjunctive treatment to children, young people and adults with Lennox–Gastaut syndrome if first-line treatment with sodium valproate is unsuitable, ineffective or not tolerated. Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. Only offer felbamate in centres providing tertiary epilepsy specialist care and when treatment with lamotrigine, rufinamide and topiramate has proved ineffective or not *tolerated*.[11]

The Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 148: diagnosis and management of epilepsy in adults in May 2015 and it was updated in 2018. This makes no specific recommendations on the treatment of Lennox-Gastaut syndrome, but notes that drop attacks in patients with Lennox-Gastaut syndrome may respond to rufinamide.[15]

Additional information: comparators

It is expected that cannabidiol will be used in addition to existing AED.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Cannabidiol	**5mg to 10mg/kg/day orally twice daily**	**3,714 to 37,141**

Costs from SMC New Product Assessment Form (NPAF) based on a body weight ranging from 12kg to 60kg. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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15. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 143: Diagnosis and management of epilepsy in adults, May 2015 revised 2018.

This assessment is based on data submitted by the applicant company up to and including 10 March 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.