NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cannabidiol for treating seizures caused by tuberous sclerosis complex

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cannabidiol in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using cannabidiol in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 29 November 2022

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 3.

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1 Recommendations

1.1 Cannabidiol is not recommended, within its marketing authorisation, as an add-on treatment option for seizures caused by tuberous sclerosis complex in people 2 years and over.

Why the committee made these recommendations

Usual care for seizures caused by tuberous sclerosis complex includes antiseizure medications. Cannabidiol is licensed as an add-on treatment option for people aged 2 years and over. The company has positioned it for use when seizures are not controlled well enough by 2 or more antiseizure medications or were tried and are not tolerated.

Clinical trials show that cannabidiol plus usual care reduces seizure frequency and increases the number of seizure-free days compared with placebo plus usual care. But its long-term effects are uncertain. It is also uncertain how well cannabidiol works compared with individual antiseizure medications.

There are uncertainties in the economic model, including:

- the dose of cannabidiol that would be used in clinical practice
- how many people would be seizure-free over 7 days
- the quality of life of people with the condition and their carers, especially for carers of people who are seizure-free
- the number of hospital admissions.

When considering these uncertainties, the cost-effectiveness estimates are higher than what NICE considers an acceptable use of NHS resources. So, cannabidiol is not recommended.

2 Information about cannabidiol

Marketing authorisation indication

2.1 Cannabidiol (Epidyolex, GW Research Ltd) is indicated 'for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cannabidiol.

Price

2.3 The list price is £850.29 per 100-ml (100 mg/ml) bottle. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by GW Research Ltd, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Disease background

Tuberous sclerosis complex severely affects the quality of life of patients, carers and their families

3.1 Tuberous sclerosis complex is a rare genetic disorder characterised by growth of noncancerous tumours (known as tubers). Tubers can form in many parts of the body, but most commonly occur in the brain, eyes, kidneys, heart, lungs and skin. Seizures resulting from tubers that have formed in the brain affect up to 85% of people with the condition. Seizures usually start by the age of 2 years as focal onset seizures (which begin in 1 side of the brain) but may progress to generalised seizures involving both sides of the brain. Clinical experts explained that there is high variability in seizure type, severity and frequency depending on where the tubers are located. Any seizure type is possible (with or without the person retaining consciousness). The patient experts explained that

seizures can be traumatic for people with tuberous sclerosis complex and their families. Drop seizures, in which people lose muscle tone or muscles stiffen, are particularly dangerous and are associated with a risk of injury as people crash to the ground. The clinical experts also highlighted that tubers that form in the brain can cause a range of cognitive, behavioural, and psychiatric manifestations (known as tuberous sclerosis complex-associated neurophysiological disorders or TAND) in around half of people with seizures caused by tuberous sclerosis complex. Patient experts highlighted the significant quality-of-life impact from TAND for patients and families. Severe learning difficulties occur in around 30% of people with tuberous sclerosis complex and may impede speech. Impaired movement may also limit all aspects of daily living. Poor behaviour including anger, mood swings, aggression and a lack of perception of risk often makes daily activities impossible and people may need round the clock care. People with the condition also have disrupted sleep, which can impact on the mental health of the entire family. The committee concluded that seizures caused by tuberous sclerosis complex severely affects the quality of life of patients, families and carers.

Current treatments

People with tuberous sclerosis complex and their carers would value a new treatment option

3.2 The clinical experts explained that it is difficult to control seizures associated with tuberous sclerosis complex. They highlighted that the aim of treatment is seizure freedom, but this is rarely achieved in this population. This is because of the complexity and heterogeneity of the underlying disease and variability of tuber locations in the brain. Also because epilepsy is harder to control in people with moderate to severe learning difficulties. The pathway is complex but resective surgery should always be considered in people with structural brain lesions. However, there is a long waiting list for surgery, and a limited number of centres providing it, meaning that combinations of other treatments are often

used. First-line treatment is monotherapy with an antiseizure medication. If seizures remain uncontrolled, a range of antiseizure medications are added. A clinical expert explained that a person's condition would be classed as refractory to treatment if their seizures are inadequately controlled on 2 or more antiseizure medications at a therapeutic dose. In these people, further adjunctive antiseizure medications and non-pharmacological treatments (ketogenic diet and vagus nerve stimulation) are used. Everolimus is also commissioned under an NHS clinical commissioning policy for treating refractory focal onset seizures associated with tuberous sclerosis complex in people aged 2 and above, when surgery and vagus nerve stimulation has failed or is not considered appropriate. A clinical expert stressed that there is an unmet need for treatments to control seizures and behavioural problems associated with the condition. This is because the range of current antiseizure medications do not control seizures for long and are often associated with side effects. The committee concluded that people with tuberous sclerosis complex and their carers would value a new treatment option.

The appropriate comparator for cannabidiol is usual care including antiseizure medications, surgery and vagus nerve stimulation

3.3 The scoped positioning for cannabidiol was as an adjunctive therapy in people whose seizures are inadequately controlled by established clinical management. In its submission, the company updated the population to include people in whom usual care is unsuitable or not tolerated. This was based on the International League Against Epilepsy's definition of refractory epilepsy as 'failure of adequate trials of 2 tolerated and appropriately chosen' antiseizure medications to achieve sustained seizure freedom. The committee noted that the company's population was narrower than the marketing authorisation which specified only that cannabidiol should be used adjunctively. The ERG was concerned that usual care may differ in people when antiseizure medications are not tolerated compared with when they are ineffective. This is because antiseizure medications can be continued adjunctively if seizures remain

inadequately controlled, but are stopped if not tolerated. The ERG also highlighted the possibility that everolimus may form usual care in the company's additional population. The clinical experts explained that everolimus has a different indication to cannabidiol because of its mode of action. Everolimus treats the underlying cause of tuberous sclerosis complex. It has also been shown to reduce the size of existing tumours and slow the formation of new tuberous sclerosis complex-related tumours including astrocytomas (tumours arising from the glial cells in the brain), kidney and lung lesions, and skin conditions. The committee noted that everolimus requires close monitoring and can only be used in people with focal seizures after consideration of surgery and vagus nerve stimulation. So, the population who would have everolimus at the same point in the pathway as cannabidiol was likely to be very small. The committee agreed that usual care including antiseizure medications with or without surgery or vagus nerve stimulation was the appropriate comparator.

Clinical-effectiveness evidence

The GWPCARE6 trial is the key trial for cannabidiol and is broadly generalisable to NHS clinical practice

3.4 Cannabidiol (plus usual care) has been compared with placebo (plus usual care) in the randomised controlled trial, GWPCARE6. In this, 2 maintenance doses of cannabidiol (25 mg/kg/day, [n=75]; and 50 mg/kg/day, [n=73]) were compared with placebo (76 people). However, because the marketing authorisation for cannabidiol is granted for a maximum 25 mg/kg/day, the company did not present results from the 50 mg/kg/day dose in its submission. GWPCARE6 had a dose titration period of 4 weeks, followed by 12 weeks at the maintenance dose. It included people aged 1 to 65 years, 7 of whom were from the UK. A clinical expert stated that the baseline characteristics and usual care treatments in GWPCARE6 were similar to those expected in UK clinical practice. However, the committee noted differences between arms in the

amount of people who had vigabatrin and clobazam (2 of the most common antiseizure medications). A clinical expert stated that vigabatrin is unlikely to impact the effectiveness of cannabidiol because it treats infantile spasms as opposed to seizures. However, both patient and clinical experts reported that clobazam increases the effectiveness of cannabidiol when taken adjunctively. So, the GWPCARE6 results may not be generalisable to UK clinical practice if clobazam use differs between the trial and the NHS. The committee noted that cannabidiol's marketing authorisation mandates use with clobazam for Lennox–Gastaut and Dravet syndromes, but not for tuberous sclerosis complex. A clinical expert explained that clobazam is currently used in NHS practice in a similar way to GWPCARE6. Also, its use would not be expected to increase if cannabidiol was recommended. This is because clobazam is associated with side effects so its risks and benefits would be evaluated on an individual basis and dose adjustments of both drugs may be needed. The company also submitted data from the following ongoing studies to support cannabidiol's long-term effect:

- An open-label extension study to GWPCARE6 in which all patients are having cannabidiol at a starting dose of 25 mg/kg/day with an expected follow up of 2 years; 72-week data from an interim analysis is available.
- An expanded access programme in the US in which 34 people are having cannabidiol up to a maximum of 25 to 50 mg/kg/day (depending on study site). Data is available for up to 4.4 years of follow-up.

The committee concluded that the main trial data to support cannabidiol's treatment effect comes from GWPCARE6, the patient population for which is broadly generalisable to NHS clinical practice.

Cannabidiol reduces seizure frequency and increases the number of seizure-free days compared with usual care alone, but long-term efficacy is uncertain

3.5 The primary endpoint for GWPCARE6 was the percentage change in tuberous sclerosis complex-associated seizures during the treatment period (4-week titration plus 12-week maintenance periods). For people taking 25 mg/kg/day cannabidiol with usual care, there was a statistically significant reduction in tuberous sclerosis complex-associated seizures with cannabidiol compared with placebo with usual care (30% reduction, 95% confidence interval 14% to 43%, $p<0.001$). There were 5% of people having cannabidiol 25 mg/kg/day who were seizure-free throughout the maintenance period compared with 0% taking placebo. People in the cannabidiol arm also experienced an additional 2.8 seizure-free days compared with placebo. This was supported by data from the open-label extension study, in which 63% of people taking cannabidiol had a reduction in their seizures of 50% or over and 19% were seizure-free at 72 weeks. However, the committee noted that the primary outcome of the open-label study was a safety endpoint and that data on seizure-free days had not been collected during the study. It also acknowledged that, by pooling usual care treatments, cannabidiol had not been compared with individual antiseizure medications. It concluded cannabidiol plus usual care likely reduces seizure frequency and increases the number of seizure-free days compared with usual care alone, but long-term efficacy is uncertain.

Adverse events

Cannabidiol is associated with adverse events that are manageable, but monitoring and adjustment of concurrent medications may be needed

3.6 GWPCARE6 showed that a large proportion of patients having cannabidiol had adverse events. The most common adverse events in this group were diarrhoea, decreased appetite and somnolence (drowsiness). A clinical expert noted that people with tuberous sclerosis complex often experience adverse effects from their medications. They also noted that cannabidiol's adverse effects are mostly, but not always, mild and tolerated. They stated that the choice of treatment depends on the

balance of its safety and tolerability, with adverse events representing an important consideration. The committee also recalled that cannabis-based medicines can increase the exposure of other antiseizure medications, so dose modifications for concomitant medications may be needed in clinical practice. It agreed that, while cannabidiol's adverse effects are mostly manageable, they are an important consideration when making decisions about whether to start or continue treatment. The committee concluded that cannabidiol is associated with adverse events that are manageable but monitoring and adjustment of concurrent antiseizure medications may be needed.

Stopping treatment

It is appropriate to assess response to treatment at 6 months and stop cannabidiol if it is not effective

3.7 Cannabidiol's marketing authorisation does not specify a stopping rule, that is, stopping treatment if or when it does not work. However, the company proposed that cannabidiol should be stopped if the frequency of seizures caused by tuberous sclerosis complex does not reduce by 30% from baseline. Baseline seizure frequency in the model was taken from the 28-day baseline period in GWPCARE6, assumed to represent the 6 months before starting treatment which would be used in clinical practice. The company implemented this stopping rule every 6 months in its model. The committee noted that this aligned with the stopping rule from NICE's technology appraisal guidance on cannabidiol with clobazam for treating seizures associated with Dravet syndrome and cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome. However, the company had implemented an additional stopping rate for cannabidiol in tuberous sclerosis complex. This was based on stopping rates in GWPCARE6 in the short term, the open-label extension study in the medium term and NICE's guidance on cannabidiol for Lennox–Gastaut syndrome in the long term. The committee concluded

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that this was acceptable, and it was appropriate to assess response to treatment at 6 months and stop cannabidiol if it is not effective.

Company's economic model

The company's model structure is appropriate

3.8 The company presented a cohort-level model to estimate the cost effectiveness of cannabidiol. It had 3 health states: alive having cannabidiol with usual care, alive having usual care alone and dead. The alive health states were further divided by the number of seizures per week (seizure-free, 2 and under, over 2 to 7, and over 7) and number of seizures per day (seizure-free, 1 and under, over 1 to 2, over 2 to 4, and over 4). The model used a lifetime horizon and a cycle length of 1 week. The company did not include vagus nerve stimulation, ketogenic diet or surgery as comparators in its model because it stated these would be used equally between arms. So, the comparator was usual care with antiseizure medications. The committee concluded that the company's general model structure was appropriate.

The company's linear regression model approach for seizure-free days and number of seizures is acceptable for decision making

3.9 The company derived efficacy data for the sub-health states for number of seizures per week and number of seizures per day from GWPCARE6 at week 16. For the long-term effect on seizures, the company applied 2 linear regression models sequentially. The first predicted the number of seizure-free days per 7-day cycle in the model using a binomial regression model based on individual patient data from GWPCARE6 at week 16. The second, a negative binomial model, predicted the total seizure frequency on non-seizure-free days per cycle. The company chose this approach to capture correlation between seizure frequency and seizure-free days. It applied the regression coefficients to each patient's baseline seizure frequency to predict outcomes for each 7-day model cycle. Using this approach, the relative treatment effect was maintained

over the modelled time horizon. Results showed a trend for reduced seizure frequency and increased odds of seizure-free days for cannabidiol plus usual care compared with placebo plus usual care. The committee noted that the relative treatment effect was not statistically significant. The company stated this was because the powers of the analyses were low because of use of weekly model cycles and 2 different regression models. The committee noted that the seizure frequency per day predicted by the company's regression model broadly aligned with data from the open-label extension study, but the study did not collect data on seizure-free days. It acknowledged the uncertainty in the company's approach but noted that the ERG had not suggested an alternative method for modelling seizures. It concluded that the company's linear regression models for seizure-free days and seizure frequency were acceptable for decision making.

The proportion of people who are seizure-free over 7 days in the model is uncertain but a 6.61 day cut-off is most appropriate for decision making

3.10 The ERG was concerned that the company had modelled seizure freedom over a 7-day cycle by using the proportion of people who were seizure-free over 6.5 days. This was because a negative binomial regression model cannot predict discrete outcomes (that is, seizure-free over 0 or 7 days). Using this approach, 0% of the placebo and 11% of the cannabidiol arm were seizure-free at 10 weeks (the latter reduced as people stopped treatment over time). The ERG highlighted that using a cut-off of 6.5 days would overestimate the number of people having cannabidiol who were seizure-free per cycle. This is because the predicted number of seizure-free days using the linear regression model results was 6.62 for cannabidiol compared with 5.89 for placebo. It provided a scenario using a cut-off of 7 days, in which no one was seizure-free over the course of a week in either arm but still gained a benefit for cannabidiol in other seizure frequency categories. The

committee recalled that 5% of people taking cannabidiol and 0% of people taking placebo were seizure-free during the maintenance period of GWPCARE6. So, the ERG's scenario was likely conservative. At technical engagement, the company also provided a scenario using a cut-off of 6.61 days to model the number of people per cycle who were seizure-free. The committee recalled that achieving seizure freedom is challenging in this population (see section 3.2). A clinical expert agreed that it was plausible that a small number of people taking cannabidiol may achieve seizure freedom but that this would be unlikely in people having usual care with no further intervention. This also aligned with testimonies from patients who had taken cannabidiol. The committee recognised that the number of seizure-free days is a useful outcome for determining response to treatment. However, it was concerned that measuring this outcome over the course of a week introduced artificial effects into the model that favoured cannabidiol or usual care depending on which cut-off was chosen. It would have preferred the company to use a longer time-period, as in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with Dravet syndrome which modelled the number of seizure-free days in a month. The committee agreed that the proportion of people who are seizure-free over 7 days in the model was uncertain because the company's methodology was problematic. However, it concluded that the true proportion likely lay between those predicted using cut-offs in the company's base case and ERG's scenario. So, a 6.61-day cut-off was most appropriate for decision making.

Costs in the model

The ERG's scenario using an average dose of 15 mg/kg/day for cannabidiol is appropriate

3.11 The summary of product characteristics for cannabidiol states that the dose can be increased from a maintenance dose of 10 mg/kg/day to a maximum of 25 mg/kg/day based on response. Yet, the company assumed an average dose of 12 mg/kg/day in its base case. This was

based on clinical expert advice to the company and German dispensing data from 118 people with tuberous sclerosis complex, in which the median cannabidiol dose was 12.2 mg/kg/day in children and 7.8 mg/kg/day in adults. The committee noted that the maintenance dose of cannabidiol mandated by the European regulator for Lennox–Gastaut syndrome and Dravet syndrome was 10 mg/kg/day and there is no evidence that increasing the doses above this results in a different treatment effect. It also noted data from the open-label extension that suggested a maintenance dose above 15 mg/kg/day did not improve response. The ERG was concerned that a maintenance dose of 12 mg/kg/day was not verified by clinical trial data (because people were titrated up to 25 or 50 mg/kg/day in GWPCARE6 regardless of response) and that the proportion of people requiring a higher dose in the open-label extension study was unknown. It presented scenarios varying the average dose of cannabidiol. A clinical expert estimated that the average dose in UK clinical practice was likely to be between 10 and 15 mg/kg/day. This was based on the average dose for treating Lennox–Gastaut and Dravet syndromes in clinical practice, which the expert said was comparable with anticipated use for tuberous sclerosis complex. They explained that although there is potential that doses over 15 mg/kg/day may be more effective, they cause more side effects than lower doses. So, 15 mg/kg/day is likely to be the maximum dose of cannabidiol used in clinical practice as a trade-off between efficacy and side effects. However, many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day. The committee also noted that a 15 mg/kg/day average dose for cannabidiol was accepted in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with Dravet syndrome. The committee agreed that cannabidiol would rarely be used at the maximum licensed dose, but the exact dose in clinical practice was uncertain. It was concerned that the efficacy data in the model came from the 25 mg/kg/day dose used in GWPCARE6 and it had no credible evidence that efficacy at half that dose would be identical. It therefore

considered the ERG's scenario using 15 mg/kg/day to be conservative compared with 12 mg/kg/day. This was because 15 mg/kg/day is the maximum dose expected to be used in clinical practice and is closer to the dose used to inform the efficacy results. It agreed that the dose of cannabidiol that would be used in clinical practice is unknown, but an average dose of 15 mg/kg/day should be used for decision making.

Healthcare resource use is likely overestimated in the company's model

3.12 Annual healthcare resource use based on seizure frequency for people with tuberous sclerosis complex-associated epilepsy was sourced from a two-round Delphi panel of clinical experts. Separate resource use estimates were produced for adults and children. The company validated these estimates using a study by Shepherd et al. (2017). This reported a cost of £44,259 over a period of 3 years for resource use (GP visits, hospitalisation, other drugs and outpatient visits) in UK patients with tuberous sclerosis complex. The committee noted that the costs in the company's model for the same 3-year period for usual care (£55,578) were significantly higher than those in Shepherd et al. and NICE's technology appraisal guidance on cannabidiol for Dravet syndrome and Lennox–Gastaut syndrome. The ERG highlighted that hospitalisation costs and number of hospital days (both in a general ward and intensive care) were also higher in the company's model for tuberous sclerosis complex than in the appraisals for other cannabidiol indications. It conducted a scenario using costs from NICE's technology appraisals of cannabidiol for Dravet and Lennox–Gastaut syndromes. It also provided a scenario that reduced hospitalisation rates by 50% to better align with the other cannabidiol appraisals (the values from the Dravet and Lennox–Gastaut syndrome appraisals could not be used because seizure frequency categories differed across indications). The company explained that the discrepancy in costs was because of inflation rates in NHS reference costs. However, a clinical expert stated that the number of hospital days would likely be lower for tuberous sclerosis complex than for Lennox–Gastaut and Dravet syndromes. The committee noted that the

hospitalisation rates used in the ERG's scenario were not underpinned by evidence, so the true resource use for people with tuberous sclerosis complex was unknown. It concluded that healthcare resource use is likely overestimated in the company's model and considered the ERG's scenario using a lower number of admissions in its decision making.

Utilities in the economic model

The company's health state utilities are uncertain and differ from utilities in other cannabidiol appraisals

3.13 The committee recalled that the company had collected data from responses to the Quality of Life in Childhood Epilepsy and Quality of Life in Epilepsy (QOLIE)-31-P questionnaire in GWPCARE6, but did not use the data in its model. This was because, during the trial, the company considered that the questions were inappropriate for assessing people with severe learning difficulties. The company also noted that data on quality of life in the literature does not consider health states and substates used in the company's model (that is, number of seizures and seizure-free days). So, the company instead asked members of the general public to estimate the quality-of-life associated with each health state and substate in the model. Respondents were asked to consider 'vignettes', that is, descriptions of each health state and, using a time trade-off method, give each a value. Values ranged between less than 0 (worse than death), 0 (death) and 1 (perfect health). The company considered the quality-of-life values it used in its model to be confidential. The committee understood why the company had chosen to use a vignette study given the lack of literature utility values. However, it noted a discrepancy in the health state utilities used for tuberous sclerosis complex compared with those for Lennox–Gastaut and Dravet syndromes. This was especially so for the values published in Lo et al. (2021) which used vignettes from the general public (collected after the guidance publication to align with the committee's preferred assumptions). The company explained that, in part, this might be because of the

difference in seizure severity categories and types of seizures in the other appraisals. The vignettes were considered by the general public who may find it hard to quantify the difference between the worst health state for Lennox–Gastaut syndrome (more than 110 drop seizures per month) compared with that for tuberous sclerosis complex (more than 4 seizures per day). A clinical expert stated that, although the epilepsy aspect of the 3 conditions may be similar, it is difficult to compare the severity of the indications. This is because tuberous sclerosis complex is a multi-organ disease associated with complications such as those in the skin, eyes and lungs that affect quality of life and are not present in the other conditions. So, correcting seizures will only partly correct the quality-of-life decrement associated with severe tuberous sclerosis complex. The committee was concerned that this was not captured in the company's model because the utility values for the seizure-free health state for both people with the condition and their carers was relatively high. It also noted that the health state utility values used in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with Dravet syndrome encompassed a much narrower range than those used in the company's modelling of cannabidiol for tuberous sclerosis complex. In the fenfluramine appraisal, values were derived using empirical measurements collected in clinical trials, which had been mapped to EQ-5D values in a way that matches the NICE reference case. The committee noted that it had not been presented with scenarios that used alternative health state utilities for cannabidiol, so could not determine the impact on the cost-effectiveness estimates. Given the lack of utility values in the literature, it would have liked to see data supporting the plausibility of the vignette values, especially for the seizure-free and most severe health states. However, acknowledging the high level of uncertainty, the committee considered the analyses using the company's utility values in its decision making. It concluded that the company's health state utilities are uncertain and differ from utilities in other cannabidiol appraisals.

The effect on carers' quality of life should be modelled and the ERG's assumption using 1.8 carers is most appropriate

3.14 The committee recalled that caring for someone with tuberous sclerosis complex affects carers' quality of life (see section 3.1), and that capturing this in the model is appropriate. The company included utility decrements in its model for seizure frequency health states (number of seizures per day) based on the vignette study. This was because carer quality of life had not been measured using a preference-based approach in GWPCARE6 so utilities could not be derived directly from the trial. In its base case, the company assumed that people with tuberous sclerosis complex would have a cumulative 2 carers (1 primary caregiver plus others such as partners, friends and family). This was based on a paper by Lagae et al. (2019), which found that people with Dravet syndrome had an average 2.06 carers. The clinical experts explained that there are no significant differences between the burden of care for seizures between cannabidiol indications. However, the total burden of care for people with tuberous sclerosis complex may be higher because of the combined effect of the epilepsy, associated learning disabilities and other comorbidities that occur with the condition. The ERG was concerned that the carer disutilities were applied additively in the company's model. It used 1.8 carers in its base case which aligned with committee's preferred assumptions in NICE's technology appraisal guidance for Dravet syndrome and Lennox–Gastaut syndrome. The committee agreed that the company's approach implied that the caring burden increases linearly the more carers a patient has. However, for a patient with multiple carers, it expected there to be less effect on the quality of life of each carer because they would 'share' some of the burden. So, while the total burden for 2 carers may be greater than the burden for a sole carer, it would likely not be 2 times greater. The committee recalled that people with tuberous sclerosis complex may need help with every aspect of daily life (see section 3.1). However, given the multifactorial nature of the disease and associated care needs of people living with it, reducing seizure frequency

would only go some way towards relieving carer burden. It also recalled that carer health state utility values could not be derived directly from the clinical trial and that the values from the company's vignette were uncertain (see section 3.13). Given this uncertainty, it agreed that the model should use 1.8 carers to align with assumptions used in previous appraisals of cannabidiol.

The seizure-free health state utility for carers may be overestimated

3.15 The vignette calculated the impact of worsening seizure frequencies on carers as an incremental decrease from the carer utility for the seizure-free health state. After technical engagement, the company updated its base case to use a utility value for the seizure-free health state for carers equal to that of an average 43-year-old. This was because in the vignettes, members of the general public were asked to adopt the perspective of the primary caregiver of a 13-year-old child and the average parent of a child this age was 43 years (Office for National Statistics data). The ERG was concerned that the company had not adjusted for carers aging and that other symptoms of tuberous sclerosis complex requiring care may not be captured in the company's estimate. It provided scenarios with lower utility values for the seizure-free health state for carers. The committee considered these in its decision making. It concluded that the seizure-free health state utility for carers may be overestimated.

It is appropriate to include a reduction in carer utility associated with institutionalisation and the ERG's approach is preferable

3.16 Based on the consensus in the Delphi panel, the company assumed that 31% of people with tuberous sclerosis complex-associated epilepsy were institutionalised at an average age of 27 years. However, in its base case it did not model any impact on carer utility during this period. The company stated that carers for people who were institutionalised would still have:

- concerns about the risk of injury from seizures or worsening of seizures in a new environment
- everyday life centred around visiting patients and accompanying them to healthcare visits

The ERG assumed a 50% reduction in carer disutility for 31% of adults in its base-case model. The company also provided scenarios that increased caregiver utility by 50% for the same proportion of people. A clinical expert stated that institutionalisation was expected to be associated with an increase in quality of life for carers. The patient expert agreed that although carers had more free time if a person with tuberous sclerosis complex was institutionalised, concerns and guilt would remain, especially about exposure to abuse. The committee recalled that tuberous sclerosis complex significantly impacts sleep for the whole family, which would improve when a patient was institutionalised (see section 3.1). It noted that the ERG's method was conservative in that it resulted in lower utility values for the less severe health states. However, the committee considered that the increase in carer quality of life in the company and ERG's analyses were not supported by data and other scenarios would be equally plausible. The committee concluded that it is appropriate to include a reduction in carer disutility associated with institutionalisation. Given the lack of evidence to support the size of this reduction, it considered the ERG's approach preferable.

Accounting for TAND aspects in the model

It is appropriate to model cannabidiol's effect on TAND aspects using conservative assumptions to account for uncertainty

3.17 The company included a cost in the model associated with the management of TAND aspects. It also assumed a benefit on TAND aspects for people whose condition responds to cannabidiol, which it modelled as a utility benefit and a reduced cost. The utility benefit for

delaying TAND was estimated by weighting utility increments for common TAND aspects from various literature sources by their prevalence using data from the TOSCA registry (de Vries et al. 2015). 'Responders' to cannabidiol were defined as the proportion of people with a reduction in tuberous sclerosis complex-associated seizures of 50% or more from baseline over 6 months. Based on the Delphi panel consensus that treatment with cannabidiol is likely to be most beneficial at an early age, only people aged 2 to 6 years accrued costs and benefits associated with TAND aspects. The ERG had the following concerns about the company's assumption for TAND:

- Prevalence rates, costs and utility benefits were not based on data collected in the clinical trials.
- The Delphi panel did not reach a full consensus on the level of response to cannabidiol required for delaying TAND aspects.
- The proportion of responders was based on the full trial population but applied only to 2- to 6-year-olds.

The committee noted that the vignettes used to elicit health state utilities may already have captured some of the aspects of TAND, so there was potential for double counting. However, the company explained that it had updated its base case at technical engagement to use conservative estimates (using the lowest utility benefit from the literature and applying TAND aspects to ages 2 to 6 only). A clinical expert explained that evidence supports an improvement in long-term TAND aspects with a reduction in seizure frequency at an early age. However, it is unclear whether this is the case for adults. The committee acknowledged the uncertainty around the company's modelling but recalled that TAND has a significant effect on the quality of life of people with tuberous sclerosis complex and their carers (see section 3.1). It agreed that costs and utility benefits for TAND should be included in the modelling using the company's conservative estimates provided at technical engagement.

Cost-effectiveness estimates

The most plausible ICER is above the range considered a cost-effective use of resources in the NHS

3.18 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life-year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of confidential commercial arrangements for cannabidiol and comparators, none of the cost-effectiveness results are reported here. The committee noted the differences between the ERG's and company's base case in that the ERG excluded TAND aspects, used 1.8 carers and adjusted for institutionalisation. However, both the company and ERG base cases were under £20,000 per QALY gained compared with usual care when considering confidential discounts. The committee agreed that its preferred assumptions to compare cannabidiol with usual care included:

- using a 6.61-day cut-off for the proportion of people who are seizure-free over 7 days (see section 3.10)
- using an average dose of 15 mg/kg/day (see section 3.11)
- considering a lower number of hospital admissions, that is, reduced by 50% (see section 3.12)
- using the health state utilities from the company's vignette while acknowledging the high uncertainty surrounding the estimates (see section 3.13)
- assuming a cumulative 1.8 carers (see section 3.14)
- considering different values for the seizure-free health state utility value for carers (see section 3.15)

- adjusting for institutionalisation using the ERG's approach (see section 3.16)
- including cost and benefits for TAND aspects for people aged 2 to 6 years, using the utility benefit from the company's base case (see section 3.17).

Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Scenarios varying the seizure-free utility value for carers had minimal impact on the ICER. However, changing the average dose of cannabidiol significantly increased the cost-effectiveness estimates. The committee also recalled that healthcare resource use was likely overestimated in the company's model. It noted that when including a 50% reduction in hospitalisation rates, the ICER was significantly over the range considered a cost-effective use of resources in the NHS. So, the most plausible ICER likely lay outside of the acceptable range.

Further evidence could reduce uncertainties in the modelling

3.19 The committee recalled the high level of uncertainty surrounding some of the company's assumptions. It noted that the company should submit the following information in its response to consultation:

- Data to support assumptions about healthcare resource use for tuberous sclerosis complex and sensitivity analyses including the committee's preferred assumptions with varying hospitalisation rates as appropriate.
- Data to support the plausibility of the vignette utility values, especially for the seizure-free and most severe health states.
- Data to support the seizure-free health state utility value for carers.

Other factors

Cannabidiol does not meet the criteria for an innovative treatment

3.20 The clinical experts stated that they would welcome an additional treatment option for tuberous sclerosis complex. However, they considered that cannabidiol represents only a modest change when managing tuberous sclerosis complex syndrome because few people became seizure-free (see section 3.10). The committee concluded that cannabidiol did not meet the criteria for an innovative treatment.

Equalities

3.21 The committee noted that the population for which cannabidiol is indicated includes children and young people. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted the principles that guide the development of NICE guidance and standards. This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The committee also noted that half of people with tuberous sclerosis complex have associated learning difficulties, which is a protected characteristic under the Equality Act 2010. The committee acknowledged and considered the nature of the population as part of its decision making.

Conclusion

Cannabidiol is not recommended for treating tuberous sclerosis complex

3.22 The committee agreed that the most plausible ICER for cannabidiol compared with usual care is likely to be above what NICE considers an acceptable use of NHS resources. It therefore concluded that it could not recommend cannabidiol as an option for treating seizures caused by tuberous sclerosis complex in people aged 2 years and over.

4 Proposed date for review of guidance

Issue date: November 2022

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
September 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), and a project manager.

Emma Douch
Technical lead

Issue date: November 2022

Daniel Davies

Project manager

ISBN: [to be added at publication]