NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cannabidiol with clobazam for treating seizures associated with Dravet syndrome

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?

Issue date: [August 2019]

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: 16 September 2019

Second appraisal committee meeting: 26 September 2019

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Cannabidiol with clobazam is not recommended, within its anticipated marketing authorisation for treating seizures associated with Dravet syndrome in people aged 2 years and older.

1.2 This recommendation is not intended to affect treatment with cannabidiol that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place before this guidance was published, until they and their NHS clinicians consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person, or the child or young person's parents or carers.

Why the committee made these recommendations

This appraisal looks at whether people with Dravet syndrome taking cannabidiol with clobazam have a better quality of life and live longer than those who don't. It also assesses whether using it reflects a good use of limited NHS resources.

Current treatment for Dravet syndrome includes antiepileptic drugs (often 2 or more). People with Dravet syndrome would use cannabidiol with clobazam if 2 other antiepileptic drugs have not adequately controlled convulsive seizures.

Clinical trial evidence shows that, in people with Dravet syndrome, cannabidiol reduces the number of convulsive and non-convulsive seizures when compared with usual care. There is trial evidence for only 14 weeks, so the longer-term effectiveness of cannabidiol is uncertain.

The cost-effectiveness estimates for cannabidiol with clobazam compared with usual care are very uncertain. This is partly because the company's economic model is unreliable and its results favour cannabidiol, even

when assuming the drug is not effective. Also, the model may not capture all aspects of Dravet syndrome that are important to people with the condition. This means that it is not possible to identify a true estimate of cost effectiveness. Because these issues remain unresolved, cannabidiol cannot, at this time, be recommended for use in the NHS. The company is asked to provide more information and amend its model.

2 Information about cannabidiol

Anticipated marketing authorisation indication	On 26 July 2019 the Committee for Medicinal Products for Human Use adopted a positive opinion and recommended the granting of a marketing authorisation for cannabidiol (Epidyolex, GW Pharma) for use as 'adjunctive therapy for seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in conjunction with clobazam, for patients 2 years of age or older'.
Dosage in the marketing authorisation	It is administered orally as 100 mg/ml cannabidiol solution. The recommended starting dose is 2.5 mg/kg taken twice daily for 1 week. After 1 week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg taken twice daily up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day should take into account individual benefit and risk.
Price	The company has not confirmed the list price with the Department of Health and Social Care. The proposed list price is considered confidential by the company.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by GW Pharma, a review of this submission by the evidence review group (ERG) and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

Disease background

Dravet syndrome severely affects the quality of life of patients, carers and their families

3.1 Dravet syndrome is a severe, lifelong and treatment-resistant genetic form of epilepsy that begins in early childhood, usually in babies aged between 6 and 10 months. It is characterised by frequent seizures of different types. Convulsive seizures are characterised by stiffness and jerking, and can last for extended periods. The patient and carer expert explained that convulsive seizures have the biggest effect on quality of life because they may result in injuries and hospitalisation. The patient and carer expert noted that Dravet syndrome affects the families and carers who may find looking after people with Dravet syndrome to be demanding and prevents them from leading normal lives. People with the disease need round-the-clock care and help with almost all aspects of daily life. Parents and carers of children with Dravet syndrome spend less time with their other children. The anxiety that a child with Dravet syndrome may have status epilepticus or die can significantly affect the mental wellbeing of all family members. The committee concluded that Dravet syndrome severely affects the quality of life of patients, families and carers.

Current treatments

People with Dravet syndrome and their carers would value a new treatment option

3.2 The clinical, and patient and carer experts agreed that it is often difficult to control seizures associated with Dravet syndrome. Despite a broad range of available antiepileptic drugs, non-pharmacological interventions (such as vagus nerve stimulation and a ketogenic diet) and surgery. They stated that there is an unmet need in Dravet syndrome for an intervention that can effectively reduce seizures without markedly increasing adverse events. The patient and carer expert reported that drugs that initially work can lose efficacy, so they would welcome new treatment options. They

noted that reducing the number of convulsive seizures is the main goal of treatment. They also noted that an increase in the number of convulsive seizure-free days would benefit people with Dravet syndrome. This would be particularly beneficial because it would mean having fewer nights with seizures, when there may be a higher risk of sudden unexpected death in epilepsy. The patient and carer expert considered that reducing the duration of convulsive seizures and the frequency of other seizure types would improve the quality of life of people with Dravet syndrome. The committee concluded that there is an unmet need for treatments that reduce the number and duration of convulsive seizures, and that patients and their carers would value a new treatment option.

Cannabidiol and its positioning in the treatment pathway

The company's positioning of cannabidiol with clobazam in the treatment pathway is appropriate

3.3 The clinical experts explained that the Dravet syndrome treatment pathway is consistent with NICE's clinical guideline on epilepsies: diagnosis and management. This recommends starting treatment with sodium valproate or topiramate and, if seizures are not adequately controlled, adding clobazam or stiripentol. They added that stiripentol is increasingly being used because of evidence that using valproate, clobazam and stiripentol together improves efficacy. They also noted that most people with Dravet syndrome will have tried several antiepileptic drugs by the time they are 2 years and would then be eligible for adjuvant treatment with cannabidiol. The committee was aware that, on 26 July 2019, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion for cannabidiol. It recommended granting a marketing authorisation for cannabidiol for Dravet syndrome, but only as an adjuvant therapy with clobazam. The company proposed that cannabidiol should be considered after 2 other antiepileptic drugs. The clinical experts stated that clobazam is currently used when 2 antiepileptic drugs have not adequately controlled seizures,

and that they would consider adding cannabidiol to clobazam. The committee therefore concluded that the company's positioning of cannabidiol with clobazam in the treatment pathway was appropriate.

Clinical-effectiveness evidence

The committee has not seen data to assess whether the patients in the clinical trials reflect those who would have cannabidiol in the NHS

3.4 Cannabidiol (plus usual care) has been compared with placebo (plus usual care) in 2 randomised controlled trials, GWPCARE1 and GWPCARE2. In GWPCARE2, 2 maintenance doses of cannabidiol (10 mg/kg/day and 20 mg/kg/day) were compared with placebo. In GWPCARE1, the higher maintenance dose of 20 mg/kg/day was compared with placebo. Both trials had a follow up of 14 weeks. The company confirmed that the 10 mg/kg/day maintenance dose of cannabidiol is likely to be the recommended maintenance dose in the marketing authorisation from the European Medicines Agency, with dose increases permitted up to a maximum of 20 mg/kg/day. An open-label extension study, GWPCARE5, in which all patients are having cannabidiol, is ongoing. The company expects to follow patients in this for up to 3 years. The committee was aware that these trials did not include patients aged 18 years or older, who are included in the marketing authorisation and to whom clinicians would offer treatment. The clinical experts stated that, based on their experiences with other antiepileptics, they would expect adults to benefit from cannabidiol. However, they explained that it was uncertain whether the clinical effect would be the same in adults as in children. About two-thirds of the patients in both trials were also taking clobazam, as specified in the expected marketing authorisation (see section 2). Most patients not taking clobazam had previously tried it. The company's submission included the baseline characteristics of the full trial population, but not the baseline characteristics of the subgroup that had cannabidiol with clobazam. Therefore, the committee concluded that it was unable to determine

whether this subgroup reflected patients with Dravet syndrome who would have cannabidiol in the NHS.

Cannabidiol with clobazam reduces seizure frequency, but long-term efficacy is uncertain

3.5 The primary endpoint in both GWPCARE1 and GWPCARE2 was the percentage change in convulsive seizure frequency from baseline per 28 days. The company provided results from the trials for the subgroup of patients who were taking clobazam. The company considers these results to be confidential, so they cannot be reported here. There was a statistically significant reduction in median convulsive seizure frequency per 28 days in GWPCARE2 for patients taking cannabidiol 10 mg/kg/day compared with placebo. The clinical and patient experts noted that this reduction was meaningful for people with the condition. The company did not provide evidence of how many people taking cannabidiol with clobazam had no convulsive seizures, but the committee was aware that only a few patients in the trials had no convulsive seizures. There was also a statistically significant reduction compared with placebo in the secondary endpoint of total seizure frequency per 28 days.. In GWPCARE1, with cannabidiol 20 mg/kg/day there was also a reduction in both convulsive and non-convulsive seizure frequency compared with placebo. The committee was aware that the likely recommended maintenance dose of cannabidiol would be 10 mg/kg/day (see section 3.4), and agreed that GWPCARE2 was most relevant to the decision problem. The company stated that the interim results of the open-label extension study (GWPCARE5) showed sustained efficacy with cannabidiol over 48 weeks of follow up. The committee noted that the company had not presented it with detailed methods or results for the open-label extension study in the subgroup of patients taking cannabidiol with clobazam. The committee concluded that cannabidiol with clobazam reduces seizure frequency compared with usual care, but that the long-term efficacy is uncertain.

Adverse events

Cannabidiol is associated with adverse events that are manageable

3.6 The trial results showed that a large proportion of patients having cannabidiol with clobazam had adverse events. The most commonly occurring adverse events in this group were somnolence or sedation, decreased appetite, diarrhoea, fever, fatigue and vomiting. The clinical experts noted that people with Dravet syndrome often experience adverse effects from their medications. They also noted that cannabidiol's adverse effects are mostly, but not always, mild and tolerated. The patient and carer expert stated that the choice of treatment depends on the balance of its safety and tolerability, with adverse events representing an important consideration. The committee concluded that, while cannabidiol's adverse effects are mostly manageable, they are an important consideration when making decisions about whether to start or continue cannabidiol.

Stopping treatment

It is appropriate to assess response to treatment at 3 months and stop cannabidiol if it is not effective

3.7 The anticipated marketing authorisation for cannabidiol does not specify a stopping rule, that is, stopping treatment if or when it does not work. However, NHS England proposed during the technical engagement stage of the appraisal that cannabidiol should be stopped if the frequency of convulsive seizures does not reduce by 30% from baseline. The clinical experts noted that they took account of broadly similar criteria when advising patients, and their families and carers about whether to continue other antiepileptic drugs. The patient and carer expert explained that they would not want to continue a treatment unnecessarily when it does not work well because this would increase the drug burden and, potentially, the adverse effects. The committee was aware that the company implemented the stopping criteria proposed by NHS England in its model after 6 months of treatment with cannabidiol. However, during technical

engagement, clinical experts reported that they review patients every 3 months in the first year then annually. The committee considered that applying the stopping rule at 3 months would be appropriate and aligned with the follow up in the clinical trials. It recalled that there may also be clinical benefits to reducing the duration of convulsive seizures (see section 3.2). The company clarified that the duration of convulsive seizures was challenging to record accurately. The committee concluded that the stopping rule proposed by NHS England is appropriate, but that response to treatment should be assessed after 3 months of treatment.

Company's economic model

The health states in the company's model do not adequately represent Dravet syndrome

3.8 The company presented a Markov state-transition cohort model to estimate the cost effectiveness of cannabidiol. It used efficacy inputs derived from the subgroup of patients in the trial who also took clobazam. The model had a time horizon of 50 years and a cycle length of 3 months. It had 4 health states, based on the number of convulsive seizures a patient had each month, to capture the costs and health effects. One health state corresponded to 0 seizures (freedom from seizures). The company derived the remaining health states by dividing the trial population evenly into 3 health states by the frequency of seizures at the beginning of the trials. The committee was concerned that the health states based on seizure frequency had been arbitrarily derived because they were not based on any clinical rationale and represented wide ranges of seizure frequencies. It would have preferred to see scenario analyses categorising the health states differently. In particular, the committee would have preferred to see narrower seizure frequency ranges to better capture the effect of changes in this parameter on costs and benefits. It also noted the company did not model the benefits associated with reducing non-convulsive seizures because it considered convulsive seizures to be more important to people with Dravet syndrome

and their families and carers. The company explained that non-convulsive seizures are difficult to count reliably, which the clinical experts agreed with. The committee recalled that reducing non-convulsive seizures is associated with improved quality of life (see section 3.2), and agreed that the model did not capture these benefits. However, it acknowledged that these may be challenging to include in the model. It was also concerned that, in the usual-care arm, after cycle 2, some patients stayed in the highest seizure frequency health state for the rest of the model. It considered this was not clinically plausible. The committee concluded that the modelled health states did not adequately represent Dravet syndrome.

The company's approach to capturing the benefit of seizure-free days increases the complexity of the model

3.9 The company included the number of days in each month without convulsive seizures by dividing each of the 3 convulsive seizure health states into 3 substates based on different numbers of seizure-free days. This was based on an exploratory endpoint in the clinical trials. The company explained that it had chosen this structure because both seizure frequency and days without seizures benefit people with Dravet syndrome. The committee agreed that having more seizure-free days would benefit patients and their carers but was concerned that modelling additional substates increased the complexity of the model structure. The clinical experts explained that the number of seizures and seizure-free days people with Dravet syndrome have each month will fluctuate, and be higher or lower depending on individual circumstances. The committee considered that the company's model was based on discrete health states (frequency of seizures) and substates (seizure-free days) but that the number of seizures would be better represented as a continuous variable. It recognised that modelling seizures as occurring over time at a given rate implies that the number of seizure-free days would follow. The committee considered it unusual to firstly categorise into numbers of seizures, and then subdivide these into number of seizure-free days. It considered that this may have resulted in 'double-counting' the benefits of

reducing the frequency of seizures. It therefore noted that an alternative model structure may have better reflected the condition and captured the benefits of both convulsive seizure-free days and convulsive seizure frequency. One such model structure would be a discrete event simulation model examining the effect of different convulsive seizure rates on individual patients. The committee concluded that it was appropriate to capture the benefits of having more convulsive seizure-free days. However, it was concerned that the company's approach to modelling these increased the complexity of the model.

The usual care arm should be modelled in the same way as the cannabidiol arm

3.10 The committee noted that patients progressed through the company's model differently:

- Patients taking cannabidiol moved between health states for cycles 1 to 9 based on individual patient-level data from GWPCARE2 and GWPCARE5. From cycle 10, patients stayed in the cycle 9 health states until they stopped cannabidiol or died. In cycle 1, patients who stopped cannabidiol moved between health states using transition probabilities derived from the placebo arm of GWPCARE2. From cycle 2 onwards, patients who stopped cannabidiol returned to their (before trial) baseline health state for the rest of the model.
- For usual care, patients moved between health states in cycle 1 based on individual patient-level data for the placebo arms of GWPCARE1 and GWPCARE2. In cycle 2, patients stayed in the same health state before returning to their baseline health state in cycle 3 and stayed in this state for the rest of the model.

The committee was concerned these differences were not clinically justified, introduced unnecessary complexity and had biased the results in favour of cannabidiol. It concluded that it would have preferred the

outcomes in the usual care arm to be based on trial data up to cycle 9, as in the cannabidiol arm.

The results from the company's model are not valid

3.11 The ERG was concerned that the results of the company's model were not valid. The ERG explained that, when it set all the clinical inputs in the model as equal for both cannabidiol and usual care, it expected that the estimated quality-adjusted life years (QALYs) would be the same for both treatments. However, the model produced higher QALYs for cannabidiol. The company stated that the model produced equal QALYs only under certain conditions. The committee did not consider this sufficient. It agreed with the ERG that the model was flawed, and that this test of validity should hold for the base-case settings. The committee recalled that patients receiving each treatment took different paths through the model (see section 3.10) and considered that this may have biased the results in favour of cannabidiol. It was also concerned that there may have been unidentified flaws in the model coding. The committee concluded that the results from the company's model were not valid.

Assumptions in the economic model

The mean weight from the clinical trials should be used to model the weight-based dose of cannabidiol

3.12 To model the weight-based dose of cannabidiol (see section 2), the company divided the population into 4 age groups and used the median weight from the trials. The committee was concerned that, because median weight in the trials was lower than mean weight, this would have underestimated the dose and cost of cannabidiol. It concluded that the mean weight from the clinical trials should have been used.

The placebo data from the clinical trials should not be combined in the model

3.13 The company based the efficacy of placebo plus usual care in the model on the combined individual patient-level data from the placebo plus usual-

care arms in GWPCARE1 and GWPCARE2. The committee recalled that it has not seen the baseline characteristics in each trial used in the model (see section 3.4) but was aware that these may have been different. It was also aware that the efficacy of cannabidiol in the model was based on GWPCARE2 alone because this was the only trial that included the expected recommended maintenance dose of 10 mg/kg/day. The committee was concerned that combining the placebo arms of the trials would have

- broken randomisation
- incorrectly modelled the efficacy of cannabidiol compared with placebo
- introduced uncertainty because of potential differences in baseline characteristics.

It concluded that the combined placebo data from the clinical trials should only have been used in a scenario analysis, and that the company should use placebo data from GWPCARE2 in its base case.

The company's approach does not appropriately account for the lack of comparator arm in the open-label extension study

3.14 The committee recalled that the company's model used different assumptions for patients in the treatment arm than for those in the usual-care arm (see section 3.10). Based on the data from the open-label extension study, the company assumed that, after cycle 2, patients in the usual-care arm returned to their baseline health states, while patients taking cannabidiol continued to benefit from cannabidiol. The committee appreciated that the company had essentially treated regression to the mean in the treatment group as the effect of cannabidiol but had stripped the placebo group of the same effect. The committee noted that this meant that the relative treatment benefit of cannabidiol increased after cycle 2 and did not reflect the difference between groups from the trial. The company explained that it had modelled the treatment effect in this way because there are no data for placebo plus usual care after cycle 2

(everyone received cannabidiol in the open-label extension study). The committee considered that this approach had biased the analyses in favour of cannabidiol. It further noted that it had not seen evidence that the subgroup of patients taking cannabidiol with clobazam maintained treatment benefit during the open-label extension study. The committee concluded that it would have preferred the company to have accounted for the lack of a comparator arm in the open-label extension study rather than assuming patients would return to baseline. It suggested that one way of doing this would be to extrapolate the relative treatment effect from GWPCARE2 beyond the controlled part of the trial.

The effectiveness of cannabidiol is likely to diminish over time

3.15 The company assumed in its model that, beyond 9 cycles (27 months), patients on cannabidiol stayed in the same health state defined by seizure frequency (that is, the treatment effect of cannabidiol was maintained until the patient stopped treatment or died). This was because there were no data after 24 months of follow up in the open-label extension. The clinical experts stated that they would expect the effectiveness of cannabidiol to diminish over time because this is seen with other antiepileptic drugs. The company considered that it had captured a reduction in efficacy over time in a scenario analysis in which it increased the annual rate at which patients in the highest seizure-frequency health state stopped cannabidiol, increasing the rate from 5% to 10% a year. It argued that being in this health state implied that patients were no longer deriving benefit from cannabidiol and so would stop taking it. The clinical experts stated that the proportions of patients on cannabidiol at 3 and 5 years in the company's base-case analysis of the full trial population were plausible. However, the committee considered the rates at which people stopped treatment, and a reduction in treatment effect reflected separate issues. This was because a waning treatment effect would have applied to all patients, but not all of them would have moved to the health state with the highest seizure frequency and stopped cannabidiol. The committee recalled that the company had provided no clinical evidence for the effectiveness of

cannabidiol after 27 months of treatment. It also recalled that it had not seen clinical evidence for the population in the anticipated marketing authorisation from the open-label extension study (see section 3.5). The committee concluded that it would have preferred to see scenario analyses in which the efficacy of cannabidiol diminished after 27 months.

The model may underestimate the mortality of people who are free from convulsive seizures

3.16 The committee was aware that the trials did not show that treatment with cannabidiol prolonged life, but that the company had proposed that people taking cannabidiol live longer. This is because, in its model, the company assumed that people without convulsive seizures are less likely to die from epilepsy-related causes, and people taking cannabidiol are more likely to be free from convulsive seizures. Specifically, the company modelled a 58% reduction in risk of death based on observational evidence for people with Dravet syndrome who were completely free from seizures. The clinical experts explained that they were unaware of any evidence showing that other treatments reduce mortality in Dravet syndrome. The committee recalled that convulsive seizures, particularly those at night time, could lead to sudden unexpected death in epilepsy (see section 3.2), and was aware that status epilepticus may be associated with high mortality. The committee considered it reasonable that a treatment that reduced convulsive seizures would prolong life, and that this association may also apply to health states other than being free from seizures. The committee appreciated that people who are free of seizures may be otherwise healthier than people with frequent seizures, and that this could partially account for the size of the association between seizure frequency and death. The clinical experts stated that the company had likely overestimated cannabidiol's potential to prolong life. The committee was aware that relatively few patients in the model were free from seizures, so changing this assumption would likely have had a small effect on the cost-effectiveness results. It concluded that the model may have underestimated the mortality of patients free from convulsive

seizures. It would have preferred to see scenario analyses in which the reduction in risk of death was smaller.

Costs in the economic model

The company should model the costs of increasing the dose of cannabidiol

3.17 The draft summary of product characteristics for cannabidiol states that the dose can be increased from a maintenance dose of 10 mg/kg/day to 20 mg/kg/day (see section 2). The company assumed in its base case that all patients would have a maintenance dose of 10 mg/kg/day for the entire treatment duration with cannabidiol. However, it explained that it expected some people would be offered higher doses if they had seen a large drop in their frequency of seizures to try to free them of seizures. To attempt to capture the cost of the dose increases, the company did a scenario analysis using a higher average dose for all patients. It calculated this by assuming that the proportion of people who would have a 20 mg/kg/day dose was the same as the proportion in the clinical trials with a greater than 75% reduction in convulsive seizures. The clinical experts agreed that the population the company identified as candidates for a dose increase was appropriate. They stated that they would not increase the dose of cannabidiol in people whose condition was not responding. However, they would expect the condition to respond well in about 20% of people, who would potentially be seizure free with a higher dose of cannabidiol. This was a smaller proportion than that chosen by the company. The committee recognised that the current model may have overestimated the costs of cannabidiol. It concluded that the company should have included and justified the costs of increasing the dose of cannabidiol for some people in its base-case analysis. It noted that it would have preferred to see scenario analyses exploring how sensitive the cost-effectiveness results were to the proportion of people on higher doses.

Modelling adverse events

The company should include the effect of adverse events on quality of life in the model

3.18 The committee recalled that cannabidiol was associated with adverse events (see section 3.6). The company included the cost of adverse events in the model, based on pooled safety results from the clinical trials for Dravet syndrome and Lennox-Gastaut syndrome. However, it did not model their effect on quality of life. It justified this by stating that adverse events were not severe so the loss in quality of life would be very small. The committee agreed that there may be some differences between the safety profile in Dravet syndrome and Lennox-Gastaut syndrome. It also recalled that the patient expert stated that minimising adverse events was an important consideration in choice of treatment because of their effect on quality of life. The committee concluded that the company should have included the effect of adverse events on quality of life in its model. It also concluded that the incidence of adverse events should have been based on data from the subgroup using cannabidiol with clobazam in the Dravet syndrome trials.

Utility values in the economic model

The utility values from the company's vignette study do not accurately reflect the health-related quality of life of people with Dravet syndrome

3.19 The company collected Quality of Life in Childhood Epilepsy data in its clinical trials but did not use the data in the model. It stated that there was a low response rate to the questionnaire. It also stated that there is no mapping algorithm to convert the results to EQ-5D utilities, NICE's preferred measure of health-related quality of life. The company also noted that data on quality of life in the literature are based on percentage reduction in seizures rather than the health states and substates it used in its model (that is, number of seizures and seizure-free days). The company instead asked people with Dravet syndrome and their carers to

estimate the quality of life associated with each health state and substate in the model. Respondents were asked to consider 'vignettes' or descriptions of each health state and, using a visual analogue scale, give each a value between 0 (death) and 1 (perfect health). The company considered the quality-of-life values it used in its model to be confidential. The committee agreed that the vignette approach may have been justified given the lack of data in the literature. However, it noted several limitations. It highlighted that the vignette study relied on patients and carers to value the health states rather than the general public, who may estimate quality of life differently. Using values from the general public is NICE's preferred method. This is because someone living with, or caring for someone with the disease may get used to the symptoms, and have a lower expectation of good health than the general public. It also noted that the lowest value people could give each health state was 0, whereas the EQ-5D scale allows for health states below 0 (that is, worse than death). The clinical experts stated that the value used for the health state reflecting freedom from convulsive seizures lacked face validity. They expected the values to be lower because despite being free from convulsive seizures, patients may still have non-convulsive seizures, adverse effects and epilepsy associated comorbidities such as cognitive impairment. The committee noted that, among people with more than 24 convulsive seizure-free days per month, the utility values were similar whether they had, in total, more than 25 seizures per month or between 8 and 25 seizures per month. The committee considered this implausible because it had heard that convulsive seizures worsen quality of life (see section 3.2). It was aware that the company had done a scenario analysis using values from a general population preference study in Lennox-Gastaut syndrome (Verdian et al. 2018). The committee noted that, although not directly comparable, these values appeared lower than those in the company's vignette study. It concluded that the utility values used by the company did not accurately reflect the health-related quality of life of people with Dravet syndrome.

It is appropriate to include the effect on carers' quality of life in the model, but the company's utility values may not accurately reflect this

3.20 The committee recalled that caring for someone with Dravet syndrome is likely to substantially affect carers' quality of life (see section 3.1), and that capturing this in the model was appropriate. The company did this by including utility decrements in its model for carers of people in the 2 highest seizure frequency health states. The utility decrements were based on the company's vignette study. The committee recalled that the vignette study had several limitations (see section 3.19). It was concerned that the company had captured the effect on the quality of life of carers only for the 2 highest seizure-frequency health states. It considered that people with few convulsive seizures may still have comorbidities and other types of seizures that would affect carers' quality of life. To validate the values from its vignette study, the company presented utility values for carers of people with Dravet syndrome from the literature (Campbell et al. 2018). The committee was aware that the company had incorrectly calculated the utility decrement from Campbell. However, it also agreed that the correctly estimated decrement of around -0.045 was likely to have been too low, and to have underestimated the effect on carers' quality of life. The committee concluded that it was appropriate to include carers' quality of life in the model. However, it thought that the values from the company's vignette study may not have accurately reflected the effect of caring for someone in each of the health states in the model.

The company's approach to modelling carers' quality of life may overestimate the effect of caring for someone with Dravet syndrome

3.21 The company assumed that people with Dravet syndrome have 1.8 carers based on evidence from the literature (Lagae et al. 2017). The committee recalled that people with Dravet syndrome need one-to-one, around-the-clock care (see section 3.1), and the clinical, and patient and carer experts agreed that the company's assumption was appropriate. The committee was also aware that siblings of people with Dravet syndrome may have responsibilities for care, and that their quality of life may be

affected (see section 3.1). The company incorporated the effect on quality of life for carers into the model by multiplying the decrements from the vignette study (see section 3.20) by 1.8 carers and subtracting this from the value reflecting the patient's utility. The committee was concerned that the company's approach meant that the caring burden increased linearly the more carers a patient had. 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' the burden. So, while the total burden for 1.8 carers may be greater than the burden for a sole care, it would likely not be 1.8 times greater. The committee acknowledged the substantial effect that caring can have on quality of life. However, it concluded that the company's approach to incorporating carers' quality of life in the model may have overestimated the effect.

Cost-effectiveness results

Neither the company's base-case analysis nor the ERG's scenarios give an accurate reflection of the cost effectiveness of cannabidiol

3.22 The committee recalled that it had not seen evidence that the population taking cannabidiol with clobazam in the clinical trials was generalisable to NHS practice (see section 3.4). It also agreed that the company's modelling approach did not adequately characterise Dravet syndrome (see sections 3.8 to 3.10). The committee was concerned that the model outputs were not valid (see section 3.11) and that several assumptions in the model may have introduced a bias in favour of cannabidiol. It further noted that the ERG had been unable to adapt aspects of the company's model or rectify these issues. The committee concluded that neither the company's base-case analysis nor the ERG's scenarios gave an accurate reflection of the cost effectiveness of cannabidiol.

The committee would like to see a model that incorporates its preferred assumptions

3.23 The committee recognised that there is an unmet need for new treatments for people with Dravet syndrome, and that their families and carers would also welcome this (see section 3.2). It also recognised that cannabidiol is effective in reducing the seizure burden of people with Dravet syndrome (see section 3.5). The committee agreed that it would like to see a revised model that more adequately reflects Dravet syndrome and captures the costs and benefits of treatment with cannabidiol. The committee's preferred approach is for a model that:

- has a structure that adequately reflects Dravet syndrome and captures the benefits of reducing both the number of convulsive seizures and the number of days free of convulsive seizures
- explores scenarios around defining the health states defined by different seizure frequencies
- models the usual care arm in the same way as the cannabidiol arm
- passes all tests of validity and bias (see section 3.11)
- maintains the relative treatment benefit of cannabidiol compared with usual care for the duration of the open-label extension study
- explores a diminishing treatment benefit of cannabidiol after 27 months, including a scenario in which the treatment effect is removed
- appropriately incorporates the effect on the quality of life of carers
- explores the uncertainty in the utility values for patient and carers
- uses mean, rather than median, body weight from the trials to calculate dosages and costs
- includes the costs of increasing the dose of cannabidiol in some patients
- includes disutilities for the most commonly observed cannabidiol-related adverse events
- explores a smaller reduction in the risk of epilepsy-related death in the seizure-free health state accounting for confounding.

Other factors

Cannabidiol does not meet the criteria for an innovative treatment but there are benefits that are not captured in the model

3.24 The clinical experts stated that they would welcome an additional treatment option for Dravet syndrome but considered that cannabidiol only represents an incremental change in its management. This is because, although the trials showed that the drug reduced the number of seizures, few people became seizure free (see section 3.5). However, the committee recalled that the company had not modelled the effect of reducing the number of non-convulsive seizures (see section 3.8), nor the effect on the quality of life of siblings of children or young people with Dravet syndrome (see section 3.21). It also recalled that these factors were important and improving them could improve quality of life (see section 3.1). The committee concluded that cannabidiol did not meet the criteria for an innovative treatment. However, it noted there were additional gains in health-related quality of life that were not included in the QALY calculations.

4 Proposed date for review of guidance

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

Amanda Adler

Chair, Appraisal Committee

August 2019

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), a technical adviser and a project manager.

Alan Lamb
Technical lead

Ross Dent
Technical adviser

Jeremy Powell
Project manager

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