

# Cannabidiol with clobazam for treating seizures associated with Dravet syndrome

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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# 1 Recommendations

- 1.1 Cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome in people aged 2 years and older, only if:
- the frequency of convulsive seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment
  - the company provides cannabidiol according to the [commercial arrangement](#).
- 1.2 This recommendation is not intended to affect treatment with cannabidiol, with clobazam, 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

Current treatment for Dravet syndrome includes antiepileptic drugs. People with Dravet syndrome would have cannabidiol with clobazam if their convulsive seizures are not controlled well enough after trying 2 or more antiepileptic drugs.

Clinical trials show that cannabidiol reduces the number of convulsive and non-convulsive seizures when compared with usual care.

The cost-effectiveness estimates are uncertain for cannabidiol because of some of the assumptions in the company's model. The cost-effectiveness estimates do not include the benefits of:

- reducing the number of non-convulsive seizures
- reducing the duration of convulsive seizures
- improving the quality of life of the siblings of people with Dravet syndrome.

When taking both the uncertainties and the uncaptured benefits into account, cannabidiol is

considered an appropriate use of NHS resources, and is recommended as an option for treating Dravet syndrome in the NHS.

## 2 Information about cannabidiol

### Marketing authorisation indication

- 2.1 Cannabidiol (Epidyolex, GW Pharma) is licensed 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

- 2.2 It is administered orally as 100 mg/ml cannabidiol solution. The recommended starting dosage is 2.5 mg/kg taken twice daily for 1 week. After 1 week, the dosage should be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dosage can be further increased in weekly increments of 2.5 mg/kg taken twice daily up to a maximum recommended dosage of 10 mg/kg twice daily (20 mg/kg/day). Any dosage increases above 10 mg/kg/day should take into account individual benefit and risk.

### Price

- 2.3 The list price of cannabidiol has been agreed with the Department of Health and Social Care, but is considered confidential by the company until January 2020. The company has a [commercial arrangement](#). This makes cannabidiol available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

## 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 months 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, of the different types of seizure, 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 families and carers. People with the disease need round-the-clock care and help with almost all aspects of daily life. Families and carers may find looking after people with Dravet syndrome demanding, and that it prevents them from leading normal lives, including spending less time with their other children. Also, 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 treatment option that reduces seizure frequency and duration

- 3.2 The clinical, and patient and carer, experts agreed that current treatments often do not control seizures associated with Dravet syndrome. This is 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 effectively

reduces seizures without markedly increasing adverse events. The patient and carer expert reported that drugs which initially work can lose efficacy. The experts would welcome new treatment options, and noted that reducing the number of convulsive seizures is the main goal of treatment. They noted that an increase in the number of convulsive seizure-free days would also benefit people with Dravet syndrome. This is because it would mean having fewer nights with seizures, when there is 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](#). The guideline recommends starting treatment with sodium valproate or topiramate and, if seizures are not adequately controlled, adding clobazam or stiripentol. The clinical experts added that stiripentol is increasingly being used because of evidence that using valproate, clobazam and stiripentol together improves efficacy. They noted that most people with Dravet syndrome will have tried several antiepileptic drugs by the time they are 2 years old and would be eligible for adjuvant treatment with cannabidiol. The committee was aware that the marketing authorisation for cannabidiol is for use 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 concluded that the company's positioning of cannabidiol with clobazam after 2 treatments in the treatment pathway was appropriate.



## Clinical-effectiveness evidence

### The patients in the clinical trials reflect those who would have cannabidiol in the NHS and the subgroup taking clobazam is most relevant to the appraisal

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 dosage of 20 mg/kg/day was compared with placebo. Both trials had a follow up of 14 weeks. The licensed maintenance dosage of cannabidiol is 10 mg/kg/day, with dosage increases permitted up to a maximum of 20 mg/kg/day. An open-label extension study designed for safety, GWPCARE5, in which all patients are having cannabidiol, is ongoing. The company expects to follow patients in this study for up to 5 years. The committee recognised that this study will provide potentially important information on safety. The committee was aware that the 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 antiepileptic treatments, 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. The committee agreed that the baseline characteristics of patients in the subgroup taking clobazam were similar to those with Dravet syndrome who would have cannabidiol in the NHS. It concluded that the subgroup of patients taking clobazam was most relevant to this appraisal, and that it would not consider the overall trial population further.

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

3.5 The primary end point in both GWPCARE1 and GWPCARE2 was the percentage change in convulsive seizure frequency from baseline per 28 days between groups. The company provided results from the trials for the subgroup of patients taking clobazam (see [section 3.4](#)). The reduction in median convulsive seizure frequency per 28 days in GWPCARE2 for patients taking cannabidiol 10 mg/kg/day compared with placebo was 37%, which was

statistically significant at the 95% confidence level ( $p=0.0042$ ). The clinical and patient experts noted that this size of reduction was meaningful for people with the condition. The company did not provide evidence of how many patients taking cannabidiol with clobazam became free of convulsive seizures, but the committee was aware that this reflected only a few patients. There was also a reduction in the secondary end point of total seizure frequency per 28 days of 43% compared with placebo ( $p=0.0003$ ). 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 GWPCARE2 also included a 20 mg/kg/day arm, and that the European Medicines Agency concluded that there was no consistent difference in dose response between 10 mg/kg/day and 20 mg/kg/day. The committee was aware that the summary of product characteristics states that the recommended maintenance dosage of cannabidiol is 10 mg/kg/day (see [section 2](#)). It agreed that GWPCARE2 was most relevant to the decision problem. In response to consultation, the company provided interim analysis for seizure frequency after 3 years of follow up from the open-label extension, GWPCARE5, for the subgroup of patients taking cannabidiol and clobazam. This showed that reduction in seizure frequency with treatment was broadly maintained for up to 3 years. The committee concluded that cannabidiol with clobazam reduces seizure frequency compared with usual care, but that the long-term efficacy after 3 years 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 was concerned that the trial had a short follow up, which may not have captured all

cannabidiol's adverse effects. It was aware that more data on safety would be available from GWPCARE5, which is ongoing (see [section 3.4](#)). The clinical and patient experts explained that patients would be closely monitored, and treatment would be stopped if adverse events were not manageable. 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 every 6 months and stop cannabidiol if it is not effective

3.7 The 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 has not reduced by at least 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 potential 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. At the first committee meeting, the committee had concluded that applying the stopping rule at 3 months, as suggested by clinicians, would be appropriate. This was because the timing aligned with clinical practice and the follow up in the clinical trials. At the second meeting, the company explained that stopping at 3 months would be inappropriate because titrating to a therapeutic dose is likely to take longer than 3 months. The committee was aware that the company had not provided evidence of how long titration takes in clinical practice, but agreed that it may be appropriate to increase the dose slowly for some patients. The company had also included stopping rules in its model at 12 months and 24 months. The committee considered that clinicians would likely evaluate patients more frequently, that is, every 6 months at a minimum. It therefore concluded that a stopping rule as proposed by NHS England is appropriate, and that response to treatment defined by a reduction in convulsive seizures compared with the

6 months before starting cannabidiol should be assessed every 6 months.

## Company's economic model

### The company's exploratory analysis with health states defined by narrower ranges of seizures is appropriate

3.8 The company presented a Markov state-transition cohort model to estimate the cost effectiveness of cannabidiol. In response to committee queries, the company explained that it had considered using other types of models, but did not consider that these would be better than a Markov model. It used efficacy inputs derived from the subgroup of patients in the trial who also took clobazam. The model had a time horizon of 90 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 convulsive seizures (freedom from seizures). The company derived the remaining health states by dividing the overall trial population evenly into 3 health states by the frequency of seizures at the beginning of the trials. The committee was concerned that the ranges of seizures were very wide for some health states (for example, from more than 8 seizures to 25 seizures or less) and were not based on a clinical rationale. In response to consultation, the company provided an exploratory analysis in which the health states were defined by narrower ranges of seizures. The company chose health states to ensure that most patients who had a 50% change in the number of seizures, which the company stated was clinically meaningful, would move to a different health state at the end of each cycle. The committee was aware that the company had defined the health states specifically for the subgroup of patients taking clobazam based on clinical rationale. The committee concluded that the health states with narrower ranges of seizures were appropriate for decision making.

### The company's approach to modelling the number of seizure-free days is acceptable

3.9 The company incorporated into the model the number of days each month that a patient did not have a convulsive seizure. It did this 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 end point 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. In response to a committee concern, the company stated that it designed the substates so that each health state in the model was mutually exclusive to avoid 'double counting' the benefit. The committee recalled that patients value both fewer seizures and more seizure-free days (see [section 3.2](#)) so it was appropriate to capture both in the model. However, the committee considered that other approaches to modelling, such as discrete event simulation, may have been more appropriate to capture the benefits of different numbers of seizure-free days. It concluded that the company's approach was acceptable.

## **The company's approach to capturing the benefit of reducing non-convulsive seizures may not be valid but these benefits should be considered**

3.10 The committee recalled that the clinical trials showed that cannabidiol also reduced non-convulsive seizures (see [section 3.5](#)), but this benefit was not captured in the model. In response to consultation, the company included in its model a mechanism for capturing the benefits associated with reducing non-convulsive seizures. It did this by applying an additional disutility value in each health state derived from a public preference study of epilepsy health states (de Kinderen et al. 2016). The company assumed that patients who have fewer convulsive seizures would also benefit from having fewer non-convulsive seizures. Because cannabidiol (compared with not taking cannabidiol) reduces the frequency of non-convulsive seizures, people who take cannabidiol would avoid disutility from both. The ERG was concerned that the company's approach may have led to double counting the benefits of reducing convulsive seizures. It was also unable to reproduce the utility estimates derived by the company. While the clinical trial data showed that cannabidiol decreased the frequency of non-convulsive seizures, the company had not used these data directly in its model. The committee therefore concluded that the company's approach to capturing non-convulsive seizures in the model may not have been valid. However, it recognised that reducing non-convulsive seizures was important to patients and carers (see [section 3.2](#)), and concluded that it would take this into account in its decision making.

## Assumptions in the economic model

### The model generates more favourable results for patients that stop cannabidiol than would be expected

3.11 The ERG highlighted concerns that, when it tested the model for validity, the model estimated higher quality-adjusted life years (QALYs) for cannabidiol when setting all the clinical inputs in the model equal for both cannabidiol and usual care. The ERG expected that the estimated QALYs would be the same for both treatments, but could not identify problems in the model code. In response to consultation, the company stated that it had done further validity testing and confirmed that the model worked as designed. It explained that the issue highlighted by the ERG resulted from the way the company modelled patients who stop cannabidiol. Most patients who stopped cannabidiol in the model were in the health state with the highest seizure frequency, based on trial evidence. However, in each cycle, the company reassigned this group of patients to health states in the same proportions as patients having usual care in that cycle. Because only around 45% of patients having usual care were in the health state with the highest seizure frequency, some patients in each group who stopped cannabidiol may have been reassigned to a health state with a lower frequency of seizures than they were in before stopping cannabidiol. This resulted in the higher gain in QALYs for cannabidiol seen when setting clinical inputs equal. The company justified its assumption about what happens to people who stop cannabidiol, stating that, because it had no clinical data on outcomes for people who stop cannabidiol, it was reasonable to assume that outcomes would be the same as those who never had it. The committee questioned whether the company's assumptions were valid. It would have preferred that the patients who stopped cannabidiol were split into groups of equal size (quantiles), and that the company redistributed the patients in each quantile to the health states in the corresponding quantile in the usual care arm. This approach would have limited the number of patients redistributed from higher seizure frequency states to lower ones, and vice versa. The committee concluded that assuming patients who stopped cannabidiol had the same outcomes as those on usual care meant that the model generated more favourable results for people who stopped cannabidiol than would be expected, but that the size of this bias was unknown.

### The mean body 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 body weight from the trials for each age group. In its first meeting, the committee recognised that good practice in health economic analyses recommends using mean (not median) weights. Moreover, because median weight in the trials was lower than mean weight, using a median weight would have underestimated the dose and cost of cannabidiol. In the second meeting, the company stated that it had done a scenario analysis using mean weights, but still preferred to use median weights because there were 'significant outliers' (patients who are overweight) in the trial. The committee recalled its previous conclusion that the patients in the trial reflected those seen in the NHS (see [section 3.4](#)). It also agreed that patients who are 'outliers' would be offered treatment in the NHS. The committee did not change its conclusion that the company should have used the mean weight from the clinical trials to reflect the costs of cannabidiol. It concluded that it would take into account results based on mean body weight.

## The company's assumption that patients on usual care remain in the same health state is appropriate

3.13 In its original base case, to model beyond the data from the randomised controlled trial, the company used data from the open-label extension study for cannabidiol. However, for usual care, it assumed that the patients returned to the health state they started in. The committee did not consider this an appropriate way to account for the lack of comparator data in the open-label extension. In response to consultation, the company changed its base-case analysis so that patients on usual care remained in the same health states from the end of cycle 2 (6 months) until the end of the model or death. It argued that this assumption disadvantaged cannabidiol because it overestimated the clinical effectiveness of usual care. It also stated that any contribution to efficacy from the psychological effects of being in a trial is likely to have been higher in the blinded clinical trial than in the open-label extension study. This would have underestimated the relative efficacy of cannabidiol compared with usual care. The company therefore included a scenario in which patients in the usual care arm returned to their baseline health states after cycle 9. The committee agreed that the company's new base-case assumption was in line with its preferences, and a suitable approach to account for the lack of a comparator arm in the

extension study.

## The effectiveness of cannabidiol is likely to diminish over time and the model should account for this

3.14 In its model, the company assumed that patients on cannabidiol stayed in the same health state (defined by seizure frequency) beyond 9 cycles (27 months). That is, the treatment effect of cannabidiol was maintained until the patient stopped treatment or died. Because data from the open-label extension showed that the effect of cannabidiol had persisted for 36 months, the company assumed that the effect lasted as long as the patient took cannabidiol. The clinical experts stated that they would expect the effectiveness of cannabidiol to diminish over time, as with other antiepileptic drugs. The company considered that it had captured reduced effectiveness over time in a scenario analysis in which it increased the annual rate at which patients in all health states (except the seizure-free health state) stopped cannabidiol. Specifically, it increased the stopping rate from 5% to 10% of patients per year. The company argued that patients, their carers or clinicians would ensure the drug was stopped if it was ineffective (see [section 3.7](#)). It also noted that, while there was no evidence that the efficacy of cannabidiol would be maintained after 36 months, equally, there was no evidence that it would diminish. The committee agreed that the company had made a reasonable attempt to account for treatment waning. However, it would have preferred that the company's analysis had also accounted for a reduction in effect over time in patients before they stop cannabidiol. The committee concluded that the effectiveness of cannabidiol was likely to diminish over time. It also concluded that the company's scenario analysis captured some, but not all, of the effects on quality of life or efficacy diminishing over time.

## There is insufficient evidence to prove that cannabidiol prolongs life

3.15 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 than those who do not take cannabidiol. In its model, the company assumed that people without convulsive seizures were less likely to die from epilepsy-related causes, and people taking cannabidiol were more likely to be free from convulsive seizures. The company used an



observational study of people with epilepsy (Trinka et al. 2013) to model a 58% reduction in risk of death associated with being free from seizures. The clinical experts commented that the model overestimated the reduction in risk of death for people without convulsive seizures. In response, the company halved the reduction in risk of death associated with being seizure free in its model to 29%. It also provided a scenario analysis in which it removed the assumption that cannabidiol extends life. The committee was aware that the company had not observed a reduction in mortality associated with cannabidiol in its clinical trials either because no effect exists, or because the trial was not long enough. The committee agreed that it was plausible that people who are free of convulsive seizures may be at a lower risk of death. However, it appreciated that people who were free of seizures may be otherwise healthier than people with frequent seizures. This, at least in part, could have accounted for some of the size of the association between seizure frequency and death. The clinical experts agreed with this concern. In summary, the committee was concerned that the company's base-case assumption was not supported by trial evidence, and that the observational evidence was likely confounded. It concluded that there was insufficient evidence to prove that cannabidiol prolongs life. It preferred the company's scenario analysis that removed the assumption that cannabidiol extends life.

## Costs in the economic model

### The company's scenario analysis using an average dosage of 12 mg/kg/day is appropriate to capture the costs of increasing the dosage of cannabidiol

- 3.16 The summary of product characteristics for cannabidiol states that the dosage can be increased from a maintenance dosage of 10 mg/kg/day to 20 mg/kg/day (see [section 2](#)). Yet, the company assumed in its base case that all patients would have a maintenance dosage of 10 mg/kg/day for the entire treatment duration with cannabidiol. The company 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. At the committee's second meeting, the company explained that it expected the dosage was unlikely to be increased beyond 15 mg/kg/day in clinical practice. To capture the cost of dosing increases, the company did scenario analyses using an average dosage higher than 10 mg/kg/day for all patients. In 1 scenario it assumed that 20% of patients would increase

their dose. This was based on opinion from clinical experts at the first committee meeting. It also assumed that these people would have the maximum recommended dosage of 20 mg/kg/day; this resulted in an average dosage of 12 mg/kg/day. The company stated that it expected that some people would not have the full recommended maintenance dosage of 10 mg/kg/day in clinical practice. So, it presented a scenario using an average dosage of 9 mg/kg/day. The committee noted that the company had not presented evidence that the doses used in clinical practice would be lower than those recommended in the summary of product characteristics. It concluded that it preferred the company's scenario analysis using an average dosage of 12 mg/kg/day.

## Utility values in the economic model

### The utility values from the company's vignette study are the most suitable for the company's model structure

3.17 The company collected data from responses to the Quality of Life in Childhood Epilepsy questionnaire in its clinical trials, but did not use the data in its model. It stated that there was a low response rate to the questionnaire, and that there is no algorithm to map 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). So, 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', that is, 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 was justified given the lack of data in the literature; however, it also 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 because someone living with, or caring for, someone with the disease may get used to the symptoms, and may have a lower expectation of attaining good health than the general public. The lowest value patients and carers could give each health state was 0, whereas the EQ-5D scale allows for health states below 0 (that is, a

quality of life worse than death). The committee considered that Dravet syndrome had features in common with other disease associated with quality-of-life values below 0. The clinical experts stated that the value the company 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, people may still have non-convulsive seizures, adverse effects and epilepsy-associated comorbidities such as cognitive impairment. The committee was also 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). Although not directly comparable, these values appeared broadly similar to the company's utility values from the vignette study. The committee was aware that, because of the structure of the company's model, if it was to use the values from the literature, the model could not realise the benefits of having more days free of convulsive seizures. This was because it had to use the same values for each substate. The committee highlighted that the methods the company used to obtain the utility values had significant problems. However, it concluded that the utility values from the company's vignette study were appropriate for modelling the health-related quality of life of people with Dravet syndrome.

## **It is appropriate to model the effect on carers' quality of life, and the values from the company's vignette study are the best available source**

3.18 The committee recalled that caring for someone with Dravet syndrome 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 carers of people in the 2 health states reflecting the highest frequency of seizures. The utility decrements were based on the company's vignette study. The committee recalled that the vignette study had limitations (see [section 3.17](#)). It was concerned that the company had captured the effect on the quality of life of carers only for the 2 health states reflecting the highest frequency of seizures. It considered that caring for people with fewer convulsive seizures, comorbidities, or other types of seizures would affect carers' quality of life. The committee would have preferred the company to have used values from a public preference study rather than a vignette study, but accepted that these were not available. In response to consultation, the company and patient groups stated that family members not directly involved in caring, particularly siblings, may also benefit

from their relatives' seizures being better controlled. The committee concluded that it was appropriate to include carers' quality of life in the model and that, although limited, the company's vignette study was the best available source for utility values.

## The company's scenario analysis using 1.8 carers is preferable

3.19 The company assumed that people with Dravet syndrome have 2 carers based on clinical expert opinion. It did not present details on how it solicited clinical expert opinion. The company also provided a scenario analysis using a value of 1.8 carers based on evidence from the literature (Lagae et al. 2017). It noted that other family members of people with Dravet syndrome may have responsibilities for care, which would lower their quality of life (see [section 3.1](#)). The company included a scenario analysis increasing the number of carers in the model to 3 to account for this. For the analysis using 2 carers, the company doubled the decrements from the vignette study (see [section 3.18](#)) and subtracted this from the value reflecting the patient's utility. The committee was concerned 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 company stated that its vignette study accounted for 'sharing' care because it asked everyone taking part to rate their own quality of life, and most people in the study had a partner. The committee recalled that there were several limitations with the company's vignette study (see [sections 3.17 and 3.18](#)), so it was unclear whether the disutility values appropriately captured 'sharing' of care. The committee considered that the company's method of linearly multiplying the disutility values was inappropriate and could have led to perverse results, particularly if the company had modelled a high number of carers. However, in this case, using the value of 1.8 carers limited this effect. The committee acknowledged the substantial detrimental effect that caring can have on quality of life. It recognised that it would be difficult to estimate how much each additional carer reduced the burden of the other carers. The committee concluded that it preferred to use the value of 1.8 carers, which also helped to limit the effect of the inappropriate methodology used by the company to incorporate carer disutility into the model.

## Cost-effectiveness results

### Addressing the remaining uncertainties in the model would likely increase the incremental cost-effectiveness ratios

3.20 The company's updated cost-effectiveness analyses included most of the committee's preferred assumptions:

- using narrower seizure frequency ranges for the health states (see [section 3.8](#))
- removing the effect of non-convulsive seizures as calculated (see [section 3.10](#))
- using the mean weight instead of the median (see [section 3.12](#))
- accounting for waning of cannabidiol's effects (see [section 3.14](#))
- not assuming that cannabidiol lengthens life (see [section 3.15](#))
- using an average dosage of 12 mg/kg/day (see [section 3.16](#))
- including health-related quality-of-life effects for 1.8 carers, which acknowledges shared burden (see [section 3.19](#)).

This resulted in an incremental cost-effectiveness ratio (ICER) of £32,471 per QALY gained. These analyses did not take into account the committee's preference for stopping rules to be applied at 18 months rather than 24 months. However, the committee agreed this was unlikely to have had a substantial effect on the ICER (see [section 3.7](#)). It also recalled that there was additional uncertainty in the cost-effectiveness results because of:

- the company's assumptions around people who stop treatment with cannabidiol (see [section 3.11](#))
- the way the company modelled a waning of treatment effect, which did not capture all the effects that diminishing efficacy over time would have on quality of life (see [section 3.14](#)).

The committee concluded that the cumulative effect of addressing these uncertainties was likely to have increased the ICER.

## Other factors

### There are benefits of cannabidiol that are not captured in the company's model

3.21 The committee recalled that the company had not modelled the effect of reducing the duration of convulsive seizures, nor the effect on the quality of life of the siblings of children or young people with Dravet syndrome (see [section 3.18](#)). It also recalled that the company's approach to modelling fewer non-convulsive seizures was not appropriate (see [section 3.8](#)). The committee considered these factors important for improving quality of life (see [section 3.1](#)). It concluded that it would take these benefits into account in its decision making.

### Cannabidiol does not meet the criteria for an innovative treatment

3.22 The clinical experts stated that they would welcome an additional treatment option for Dravet syndrome. However, they considered that cannabidiol represents only a modest change when managing Dravet syndrome because few people became seizure free (see [section 3.5](#)). The committee concluded that cannabidiol did not meet the criteria for an innovative treatment.

### Cannabidiol is recommended for use with clobazam to treat people with Dravet syndrome

3.23 The committee recalled that it had concluded that it was appropriate to consider other benefits not captured in the company's model (see [section 3.21](#)). It recognised that some of the remaining uncertainties would be addressed in time with ongoing data collection. The committee concluded that, despite these uncertainties (see [section 3.20](#)), when it considered the uncaptured benefits, cannabidiol represents an effective treatment and a good use of NHS resources. It therefore recommended cannabidiol with clobazam to treat Dravet syndrome. It also concluded that seizure frequency should be checked every 6 months and that, if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment, cannabidiol should be stopped (see [section 3.7](#)).

## 4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Dravet syndrome and the doctor responsible for their care thinks that cannabidiol is the right treatment, it should be available for use, in line with NICE's recommendations.

## 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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## Accreditation

