NICE National Institute for Health and Care Excellence

NICE guidance

Fenfluramine for treating seizures associated with Dravet syndrome

Technology appraisal guidance
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Your responsibility

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All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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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 Fenfluramine is recommended as an add-on to other antiseizure medicines for treating seizures associated with Dravet syndrome in people aged 2 years and older, only if:

- seizures have not been controlled after trying 2 or more antiseizure medicines
- the frequency of convulsive seizures is checked every 6 months, and fenfluramine is stopped if it has not fallen by at least 30% compared with the 6 months before starting treatment
- the company provides fenfluramine according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with fenfluramine 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 for them before this guidance was published, until they and their NHS clinician 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 their parents or carers.

Why the committee made these recommendations

Treatment for Dravet syndrome often starts with a single antiseizure drug such as sodium valproate. Other treatments can then be added if seizures are not well controlled. In practice, standard care often involves a combination of 3 antiseizure medicines. Clinicians may offer add-on therapies such as cannabidiol with clobazam, or fenfluramine.

Clinical trial evidence shows that fenfluramine, when added to standard care medicines, reduces the number of convulsive seizures people have. And it may be more effective than cannabidiol plus clobazam in reducing the number of seizures when used with 2 other antiseizure medicines. There is some evidence that adding fenfluramine improves quality of life for people with Dravet syndrome and their carers compared with standard care medicines alone.

The cost-effectiveness estimates are within the range NICE considers an acceptable use

of NHS resources. There is evidence that there are also likely to be benefits from fenfluramine beyond what was in the economic model. These include reducing how long seizures last for, fewer non-convulsive seizures, and quality of life benefits. So fenfluramine is recommended.

2 Information about fenfluramine

Marketing authorisation indication

2.1 Fenfluramine (Fintepla, Zogenix) is licensed for 'the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-seizure medicines for patients 2 years of age and older'.

Dosage in the marketing authorisation

2.2 Fenfluramine is taken orally. It can be used with or without stiripentol. Because of how fenfluramine is metabolised, the recommended maintenance dose after titration is 0.7 mg/kg/day (maximum 26 mg/day) for people not taking stiripentol, and 0.4 mg/kg/day for people taking stiripentol (maximum 17 mg/day). See details of the dosage schedule in the summary of product characteristics for fenfluramine.

Price

2.3 The list price of fenfluramine is £901.44 per 60 ml bottle, £1,802.88 per 120 ml bottle and £5,408.65 per 360 ml bottle (BNF online accessed February 2022). The company has a commercial arrangement. This makes fenfluramine 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 considered evidence submitted by Zogenix, 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

Dravet syndrome severely affects a person's quality of life, and that of their family and carers

3.1 Dravet syndrome is a severe, lifelong and genetic form of epilepsy. It usually presents in the first year of life with recurrent, prolonged convulsive seizures. As well as severe seizures, children have developmental delays and learning disabilities. Comorbidities are common and include autism, attention deficit hyperactivity disorder (ADHD), and difficulties with speech, mobility, eating, behaviour and sleep. A carer expert explained that the high seizure burden and comorbidities have a serious effect on families. They noted that looking after a child with Dravet syndrome is life-changing: 'you can never rest' and are 'on high alert at all times as a carer'. People with the disease often 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, preventing them from leading normal lives. The anxiety that a child with Dravet syndrome may have status epilepticus and the risk of sudden unexpected death in epilepsy (SUDEP) substantially affects the mental wellbeing of all family members. There is also a high unmet need because the condition is resistant to standard care treatments in 90% of people with Dravet syndrome. The committee concluded that Dravet syndrome severely affects the person's quality of life and that of their family and carers.

Managing Dravet syndrome in the NHS and positioning fenfluramine in the treatment pathway

Standard care for Dravet syndrome includes a first-line antiseizure drug then first and second add-on therapies

3.2 NICE's guideline on epilepsies in children, young people and adults recommends the antiseizure drug sodium valproate as the first-line treatment option for Dravet syndrome. A clinical expert noted that first-line sodium valproate is standard care and that topiramate, which was included in the 2012 NICE guideline on epilepsy, is now less used first line. If sodium valproate is not effective or tolerated, clobazam or stiripentol can be added. NICE's technology appraisal guidance on cannabidiol with clobazam for treating seizures associated with Dravet syndrome recommends cannabidiol plus clobazam in people aged 2 and older. The committee noted that cannabidiol plus clobazam is an option as a second add-on, but it does not work for everyone and the combination is not always tolerated. However, it understood that NICE's guidance on cannabidiol concluded that the positioning of cannabidiol plus clobazam after 2 treatments in the treatment pathway was appropriate.

Stiripentol can be used as a first or second add-on treatment

3.3 The clinical experts noted that Dravet syndrome is one of the epilepsy syndromes most resistant to antiseizure drugs. People with the condition often need add-on treatments. A combination of 3 drugs often provides the best seizure control, most commonly sodium valproate, stiripentol and clobazam. The clinical experts noted that stiripentol is an important part of standard care and is usually used at the early stage of disease, particularly for children. They also explained that, although stiripentol is licensed to be used with clobazam, in practice stiripentol is usually used in children newly diagnosed with Dravet syndrome and added to sodium valproate as the first add-on therapy. This is because the combination of sodium valproate and clobazam (another option for first add-on, see section 3.2) often causes drowsiness. Clobazam may or may not then be added as a second add-on after stiripentol. Alternatively, stiripentol may

be used as a second add-on if clobazam is the first add-on to sodium valproate. The committee concluded that stiripentol is part of standard care and could be used either as a first or second add-on therapy to other standard antiseizure drugs for treating seizures in Dravet syndrome.

The treatment sequence for add-on therapies after first-line antiseizure drugs is individualised to the person

3.4 The clinical experts noted that often the new add-on treatment will not immediately replace the previous treatment. The goal is to control seizures with as few medications as possible. Rather, the new treatment is added sequentially to assess its impact, usually over about 3 months to allow sufficient titration and monitoring. When adding cannabidiol, which requires treatment with clobazam, clinicians do not add both drugs at the same time, because it is difficult to identify which drug was associated with adverse effects (or benefits). An existing treatment may be tapered down slowly before removing it if the condition responds to a newly added treatment. The choice of what treatment to add or remove is individualised to the person. The carer expert explained that they would not continue a treatment if it does not work because of the burden of taking medicines and potential adverse effects. The committee concluded that the sequence of adding treatments to antiseizure drugs is individualised in clinical practice.

The company's positioning of fenfluramine as a second add-on treatment is appropriate

3.5 The clinical experts noted that, while fenfluramine can be offered as an add-on drug at any point in the pathway according to its licence and with or without clobazam, it would be offered in NHS clinical practice after stiripentol, clobazam, or both, as a second add-on treatment. They also noted that both stiripentol and clobazam might be stopped if fenfluramine is added and effective. The committee agreed that the company's positioning of fenfluramine as a second add-on treatment in the treatment pathway is appropriate.

Comparators at the second add-on position in the treatment pathway include cannabidiol plus clobazam and other standard care drugs

3.6 The company focused its submission on the comparison between fenfluramine and cannabidiol plus clobazam as a second add-on treatment. It explained that this was because cannabidiol plus clobazam is the only therapy with enough data, and is currently accepted as clinically and cost effective. The clinical experts explained that, as a second add-on, cannabidiol plus clobazam is a relevant comparator to fenfluramine. The committee agreed but noted that there are other options for a second add-on treatment in the pathway (see section 3.3 and section 3.4). For people who cannot tolerate cannabidiol plus clobazam, drugs comprising standard care are the appropriate comparator, which might include stiripentol. The committee concluded that the company's positioning of fenfluramine as a second add-on compared with cannabidiol plus clobazam is appropriate. However, the continued use of other drugs that comprise standard care is also a relevant comparator for people who cannot take cannabidiol or clobazam.

Clinical effectiveness evidence

Fenfluramine is an effective treatment for Dravet syndrome in the short term compared with placebo

3.7 The company submitted evidence from 2 phase 3, double-blind, placebo-controlled randomised controlled trials, Study 1 and Study 1504. In these studies fenfluramine as an add-on to standard care drugs was compared with placebo in children and young people with Dravet syndrome aged between 2 and 18 years. Study 1 (n=119) excluded patients taking stiripentol and assessed the efficacy of fenfluramine at 2 dosages: 0.2 mg/kg/day (this dosage is not licensed and was assessed in the trial for dose–response relationship) and 0.7 mg/kg/day. Study 1504 (n=87) needed patients to be taking stiripentol and assessed the efficacy of fenfluramine 0.4 mg/kg/day. Study 1 and Study 1504 had follow-up periods of 14 weeks and 15 weeks, respectively. The primary

end point of both trials was percentage change in convulsive seizure frequency per 28 days during the treatment period compared with baseline. Evidence showed that, among patients not taking stiripentol in Study 1, fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day were associated with a 62.3% (95% confidence interval [CI] -48 to -73%, p<0.001), and 32.4% (95% CI: -6 to -51%, p=0.02) greater reduction than placebo, respectively. For patients taking stiripentol (Study 1504), fenfluramine 0.4 mg/kg/day was associated with a 54% (95% CI: -67 to -36%, p<0.001) greater reduction than placebo.

3.8 Both trials reported on change in mean convulsive seizure-free days per 28 days from baseline as a secondary end point. Results suggested that fenfluramine is associated with a greater increase in convulsive seizure-free days than placebo across all dosages (this data is confidential and cannot be reported here). Both trials assessed quality of life in patients using the Pediatric Quality of Life Inventory (PedsQL) and reported on changes from baseline in PedsQL scores associated with different dosages. Study 1 (in people not taking stiripentol) showed that, at 14-week follow up, both fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day were associated with a greater improvement from baseline in PedsQL than placebo. Mean scores were (standard deviation): 5.9 (15.1), p=0.02 and 6.8 (11.2), p=0.003 for fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day, respectively; and -1.6 (10.4) for placebo. However, results of Study 1504 (in people taking stiripentol) showed that, at 15-week follow up, changes from baseline in mean total PedsQL score were not statistically different (alpha level = 0.05 [2-sided]) between fenfluramine 0.4 mg/kg/day and placebo (mean [standard deviation]: -0.9 [11.8] compared with -0.3 [12.4], p=0.0618). Results for carers' quality of life appeared to be in the same direction of treatment effect (this data is confidential and cannot be reported here). The committee concluded that fenfluramine is more effective than placebo in reducing convulsive seizure frequencies in people with Dravet syndrome in the short term.

Fenfluramine may be more effective than cannabidiol plus clobazam in reducing convulsive seizure frequencies

3.9 No trials directly compared fenfluramine with cannabidiol plus clobazam. So the company did a network meta-analysis to assess the effectiveness

of different dosages of fenfluramine (Study 1: 0.2 mg/kg/day and 0.7 mg/kg/day; Study 1504: 0.4 mg/kg/day) and cannabidiol plus clobazam (10 mg/kg/day and 20 mg/kg/day plus clobazam) relative to placebo. The network meta-analysis was done for both the primary and secondary outcomes of Study 1 and Study 1504. The ERG noted there were differences in the use of standard care drugs including clobazam across trials. The network meta-analysis assessed percentage change from baseline in convulsive seizure frequency in 28 days compared with placebo, which was the primary end point of Study 1 and Study 1504 and informed the economic model. The ERG noted that, while the results showed that all doses of fenfluramine and cannabidiol plus clobazam were more effective than placebo in reducing convulsive seizure frequency per 28 days, there was no difference between fenfluramine and cannabidiol plus clobazam in this analysis. During the first meeting, the committee noted that this analysis did not show a difference between fenfluramine and cannabidiol plus clobazam. It also noted that it would prefer to see the absolute changes from baseline associated with different dosages of fenfluramine and cannabidiol plus clobazam. During the consultation, the company explained that data for absolute changes from baseline for cannabidiol plus clobazam is not publicly available, so it was not able to do this analysis. The company instead presented an indirect treatment comparison between fenfluramine, cannabidiol, and placebo on the outcome of percentage change from baseline in convulsive seizure frequency over 28 days using the Bucher method. This additional analysis included data publicly available from 4 trials of cannabidiol plus clobazam (results of the analysis are confidential and cannot be reported here). The committee noted that the comparisons between fenfluramine and different dosages of cannabidiol plus clobazam were mixed but largely favoured fenfluramine. Carer and clinical experts explained during the second meeting that Dravet syndrome is a heterogeneous condition, reflected in the range of seizure frequency and intensity. They said that the differences in results reflected the natural variation in the condition and are expected. The committee noted that the mixed results may be partly because of the small sample sizes in the trials as well as heterogeneity. It questioned why the company did not pool the 2 cannabidiol plus clobazam trials with the same dosing in this additional analysis on the primary end point. The company explained that it was because the committee had requested

analysis of the absolute change in convulsive seizure frequency for cannabidiol plus clobazam from baseline compared with fenfluramine during its first meeting, given the uncertainties in the network meta-analysis of the primary end point. However, the company had no access to such data for cannabidiol plus clobazam. So the company did not combine the cannabidiol plus clobazam trials with the same or different dosages, so that the differences in treatment effect on the primary end point between specific dosages of fenfluramine and specific dosages of cannabidiol plus clobazam can be seen. The company also explained that the 2 cannabidiol plus clobazam trials with the maximum recommended dosing for cannabidiol plus clobazam (20 mg/kg/day) reported different treatment effects for the primary end point. The ERG noted that the heterogeneity across trials may be another reason not to pool trials for analysis. The committee acknowledged that, overall, the evidence suggested superiority of fenfluramine compared with cannabidiol plus clobazam but noted that there was high uncertainty given the heterogeneity across trials.

Stopping treatment

The stopping rule of 30% seizure reduction at 6 months is the most clinically appropriate response criteria

3.10 The marketing authorisation for fenfluramine does not specify a stopping rule. At the first committee meeting, the company proposed that fenfluramine should be stopped after 6 months if the frequency of convulsive seizures had not reduced by at least 30% from baseline. This is in line with the first assessment time set out in the stopping rule in NICE's technology appraisal guidance on cannabidiol with clobazam. The clinical experts said that because seizures can cluster in people with Dravet syndrome, at least 6 months would be needed to assess response to treatment. People with Dravet syndrome are seen every 6 months in clinical practice. In the first meeting, the committee concluded that stopping rules at 6 months and every 6 months thereafter was appropriate. During the second meeting, the committee questioned whether this stopping rule would fully capture any waning of the treatment effect, for example, if there is a slight deterioration in

treatment effect but still some benefit in seizure control compared with baseline. The clinical experts explained that, if some deterioration in response is seen in practice, treatment is not immediately stopped. They said that clinicians would usually consider all the medicines someone is taking and taper one off when another is added. The clinical experts also explained that clinicians would continue if fenfluramine seizure frequency reduced by 30% compared with baseline. A 30% reduction is the minimum to continue although a 50% reduction would be a clearer indicator of benefit. The patient and carer experts noted that parents would not keep their child on treatment if it is not working. They added that duration and severity of seizures is also important and could be reduced by treatment, which could have a large benefit for patients and carers.

3.11 The committee discussed stopping fenfluramine in relation to waning of treatment effect in the model. The company did not assume waning of treatment effect in its model. It explained that no waning of treatment effect was assumed beyond the first 6 months. The company presented results from Study 1503 (n=330) to support the long-term treatment effect of fenfluramine, which had data from up to 3 years. Study 1503 included people who satisfactorily completed Study 1 and Study 1504, with a mean daily dosage between 0.3 mg/kg/day and 0.7 mg/kg/day for 70% of people (Study 1503 Fintepla.eu). Results indicated that the treatment effect on percentage change in convulsive seizure frequency per 28 days relative to baseline was largely maintained at 3-year follow up. The clinical expert noted that the inclusion criteria reflected clinical practice. They also noted that they did not see waning of treatment effect in practice and, if there is any, waning of treatment effect would appear in the first year of treatment. The committee appreciated that only people for whom fenfluramine was working would continue having it in practice. The company explained that the model also implemented ongoing treatment discontinuation probabilities as seen in Study 1503. Discontinuations seen in Study 1503 included stopping for all reasons, including loss of efficacy, as well as adverse events over the lifetime in the model. Evidence from Study 1503 indicated a 0.7% discontinuation probability for fenfluramine and a similar probability of 0.8% for cannabidiol plus clobazam per 28-day cycle. The committee concluded that it was appropriate for waning to be excluded from the model.

3.12 The committee appreciated that a stopping rule based on a less than 30% reduction in seizure frequency at 6 months might be applied in the model. However, it felt that this may not reflect all stopping caused by lack of efficacy because it knew that discontinuations were ongoing in Study 1503, including discontinuations caused by lack of efficacy in the longer-term follow up. The committee considered that there was some uncertainty in the company's stopping rule at 6 months, which assumed that a 30% reduction in seizure frequency at this timepoint already accounted for all loss of treatment effect in the model and was the most clinically appropriate threshold. The company presented a revised model which considered an alternative scenario using a stopping rule of a 50% reduction in seizures at 6 months. The clinical experts explained that a 30% reduction in seizures at 6 months is the minimum they would expect from a new treatment, but that it was unclear whether a 50% stopping rule at 6 months was a better threshold. They said that a 50% reduction in seizure frequency would not be a sensitive enough response criterion to take into account the potential benefit of reducing extremely severe seizures. And they said that a more moderate reduction in seizures (that is, between 30% and 50%) could still mean a valuable reduction in both severity of seizures and hospitalisations in people with Dravet syndrome. A 30% stopping rule would also align with the current stopping criteria for cannabidiol. The committee concluded that the stopping rule of at least 30% reduction in seizure frequency at 6 months was the most appropriate.

Modelling approach

The company's modelling structure is appropriate for decision making and overall the results are valid

3.13 The company presented a revised individual-patient state-transition model to estimate the cost effectiveness of fenfluramine during the consultation after discussions with the ERG and NICE. The model consisted of 3 health states: alive, on treatment; alive, treatment discontinued; and dead. Patient profiles including age, body weight, number of convulsive seizures per cycle, number of convulsive-free days per cycle, concomitant medication (receiving stiripentol or not), and

mortality risk were then assigned to individual patients. The model was run twice, once using baseline characteristic data from Study 1 without stiripentol and another using data from Study 1504 with stiripentol. The results were then combined and weighted based on an estimate of 58% of the population having stiripentol and 42% not having stiripentol, as informed by the European DISCUSS survey with UK data on carers of people with Dravet syndrome. The clinical experts noted that 58% of the population having stiripentol was largely in line with clinical practice in the NHS. For the merged population, the company's model focused on the comparison against cannabidiol plus clobazam as the second add-on therapies in the treatment pathway. The ERG noted that several validity issues raised at the first committee meeting were resolved during consultation, and that overall the model results were valid. However, it noted that, because of the design of the model, the company provided separate model files for scenario analyses and validating them would take longer than usual. For the same reasons, the ERG was not able run its preferred analyses. The ERG had noted an error in the updated base case of the company's model related to discontinuation probabilities. The company corrected its base case so that the discontinuation probabilities in the model for the trial titration and maintenance phases were the same as those in the company's submission, and equal for both treatments. The committee concluded that the company's model structure was appropriate for decision making, and overall the results were valid.

The merged population is appropriate for decision making

3.14 During the first meeting, the committee noted that the cost-effectiveness estimates were substantially higher when stiripentol was used than when it was not, and asked for the reasons to be explored. During consultation, the company provided disaggregated results for the merged population: for the Study 1 population without stiripentol, and for the Study 1504 population with stiripentol. It explained that in Study 1 no one was taking stiripentol. So when people stopped fenfluramine or cannabidiol plus clobazam they reverted to standard care that was cheaper than standard care in Study 1504, which included stiripentol, which is an expensive drug. Consequently, the ongoing costs in Study 1 were much lower than in Study 1504. The committee also noted that fenfluramine 0.4 mg/kg/day with stiripentol in Study 1504 resulted in a

smaller incremental cost than fenfluramine 0.7 mg/kg/day without stiripentol in Study 1. Taking account of the quality-adjusted life year (QALY) differences between the 2 studies, the company explained that the net effect of stiripentol was to reduce the incremental cost-effectiveness ratio (ICER) in Study 1504 compared with Study 1. The ERG agreed with the company's explanation during the second meeting. The committee noted the difference in cost-effectiveness estimates when stiripentol is used compared with when it is not used in the company's base case. It recalled that stiripentol is not a treatment modifier for fenfluramine. The committee considered that grouping the population based on stiripentol use may be artificial and not feasible for clinical practice. This was because the treatment sequence for add-on therapies to control seizure frequencies is individualised to the patient (see section 3.4), and because stiripentol is used as either a first or second add-on treatment in the usual combination of 3 drugs to control seizure frequencies (see section 3.3). The committee was also aware that this grouping was not supported by the clinical evidence available. Taking into account the unmet need (see section 3.1), the complexities of the condition, and the individualised and unique treatment sequencing of adding treatments to first-line antiseizure drugs across patients, the committee concluded that the merged population is appropriate for decision making.

Basing the model on convulsive seizure-free days may be reasonable but there are uncertainties in the relationship between convulsive seizure frequency and seizure days

3.15 The company's network meta-analysis assessed the change (mean percentage reduction) in the frequency of convulsive seizures per 28 days from baseline compared with placebo for the fenfluramine and cannabidiol plus clobazam arms. The company reported that there was no information on the number of days people had convulsive seizures from the cannabidiol trials. It therefore assumed that the change (the mean percentage reduction) in the frequency of convulsive seizures per 28 days from baseline compared with placebo, as informed by the network meta-analysis, was the same as the change in days people had convulsive seizures per 28 days from baseline compared with placebo. The company then calculated seizure-free days by subtracting the

seizure days from 28 days per cycle. The ERG noted that, although there is a relationship between having fewer convulsive seizures and having fewer days with convulsive seizures in the 28-day cycle, the relationship was unlikely to be linear. During the first meeting, the committee noted that there were uncertainties in both the company's and ERG's approaches in deriving the relationship between the reduction in convulsive seizure frequencies and reduction in days having convulsive seizures. The committee concluded that basing the model on convulsive seizure frequency instead of convulsive seizure-free days would avoid the problem of determining the most appropriate relationship between them and the uncertainties. During consultation, the company explained that it modelled seizure-free days to adequately capture the impact of Dravet syndrome and therapies on patients and carers. The carer expert noted that both convulsive seizure frequency and seizure-free days are important. The carer expert explained that seizure freedom is relevant because with even just one night with no seizures, for example, the patient and their carers do not wake up exhausted. They have not needed to wake up to time a seizure and decide whether to administer rescue medication or call an ambulance during the night.

3.16 In response to the consultation, the company did a regression analysis to estimate the proportionality between the percentage change in convulsive seizure frequency and the percentage change in convulsive seizure days. This analysis was of patient-level and combined data from all arms of Study 1 and Study 1504. The result indicated that the relationship was not 1:1 but close to linear (the data is confidential and cannot be reported here). The company used this assumption for both the fenfluramine and cannabidiol arms in the updated model. The committee appreciated that having fewer convulsive seizures and fewer days with convulsive seizures are both important for patient and carers, but that fewer days with convulsive seizures may be more meaningful for them. The committee concluded that basing the model on convulsive seizure-free days was reasonable but noted that this was an uncertainty in the model.

The strength of the relationship between convulsive seizure frequency and mortality is not clear

3.17 The company assumed in its base case that mortality is linked to the frequency of convulsive seizures. Total mortality in the model included background and seizure-related mortality: SUDEP, status epilepticus deaths and accidental deaths. The clinical expert noted that the association between convulsive seizure frequency and status epilepticus-related and accidental deaths is seen regardless of seizure cause. However, the clinical expert noted that the exact cause of SUDEP is unknown. The ongoing convulsive seizure frequency is a risk factor for SUDEP in Dravet syndrome although the relationship between reduction in convulsive seizure frequency and reduction in mortality is uncertain. There is little data on the association between convulsive seizure frequency and risk of SUDEP in Dravet syndrome. The company used Cooper et al. (2016), which is a retrospective uncontrolled cohort study including 100 children and young people with Dravet syndrome. Cooper et al. reports the incidence of Dravet-specific SUDEP and total mortality over a median follow up of 10 years. Because Cooper et al. did not report on the relationship between convulsive seizure frequency and SUDEP, the company took the risk estimates for SUDEP by seizure frequency from a case–control study of adults with general epilepsy (Nilsson et al. 1999). Because the SUDEP rate in Dravet syndrome reported by Cooper et al. was much higher than that in general epilepsy, the company calibrated the SUDEP rate reported by Nilsson et al. to the expected SUDEP rate from Cooper et al. using a multiplier of 8.38. During the first meeting, the ERG considered that strong assumptions were needed to link convulsive seizure frequency with SUDEP in Dravet syndrome. It was also concerned about the implausible estimates resulting from extrapolating. Given that there was no evidence of fenfluramine extending life, the ERG preferred to remove the link between seizure frequency and mortality, that is, to not assume in the model that treatment with fenfluramine prolongs life. People with Dravet syndrome have many comorbidities, which may also confound the association between frequency of seizures and death. The committee acknowledged that there may be an association between convulsive seizures and SUDEP. It also understood that the increased risk of death would not be necessarily reversed by treatment. So the committee concluded during

the first meeting that it would prefer to see scenario analyses testing different strengths of relationship between convulsive seizure frequency and SUDEP, including analyses in which fenfluramine did not prolong life.

3.18 During consultation, the company said that its survival curve based on Cooper et al. (SUDEP and status epilepticus-related mortality) and other published literature and expert opinion (accident-related mortality) was in line with the mortality expected in Dravet syndrome in the UK, and that this was confirmed by UK clinicians. The company also provided scenario analyses exploring the relationship between convulsive seizure frequency and SUDEP, but not for removing the link entirely from the model. The company argued that it would be unreasonable to remove the possibility of a mortality benefit from the model because of the lack of evidence from clinical trials. This is because Dravet syndrome is a rare condition and it is not possible for clinical trials to be powered enough to detect the difference in the risk of mortality between interventions. It also argued that modelling the relationship between convulsive seizure frequency and mortality was in line with clinical expectations. The 2 alternative scenarios the company provided assumed:

- the same mortality in Dravet syndrome as in the general epilepsy population

- mortality in Dravet syndrome to be calibrated midway between the company's base-case estimate in Dravet syndrome (Cooper et al. 2016) and general epilepsy mortality (Nilsson et al. 1999).

  The company explained that both scenarios were likely to underestimate the actual risk of death in the model and may be biased against fenfluramine. The committee recalled that fenfluramine is likely more effective than cannabidiol plus clobazam in reducing convulsive seizure frequencies (see section 3.9). The ERG noted that the company's scenario analyses had a large impact on the cost-effectiveness estimate. During the second meeting, the committee noted that the company's overall survival projection in the model was in line with the literature and seemed reasonable. It noted that assuming that mortality in Dravet syndrome was a midpoint calibration between the Cooper et al. study and general epilepsy might be more probable than assuming it was the same as in the general epilepsy population. The committee recognised that convulsive seizure frequency is likely to be related to mortality in Dravet syndrome. However, it noted that it had not been presented with enough evidence to suggest an association between reduced convulsive seizure frequency and reduced risk of mortality in Dravet syndrome with fenfluramine treatment. Taking into account that Dravet syndrome is a rare condition, and the evidence available, the committee concluded that there may be a relationship between the reduced convulsive seizure frequency and mortality in Dravet syndrome but that the strength of this relationship was unclear.

The impact of excluding non-convulsive seizures from the model is not clear

3.19 The company explained that it excluded non-convulsive seizures from its model because it is difficult to measure them, being less noticeable and harder to record. It said that, had it included non-convulsive seizures, it is likely it would have improved fenfluramine's cost effectiveness compared with standard care drugs. To support this, the company cited a study (Gunning et al. 2020) comparing cannabidiol plus clobazam with placebo, which reported that cannabidiol plus clobazam may reduce the frequency of total seizures and convulsive seizures compared with placebo. The company explained that, because fenfluramine was likely to reduce convulsive seizure frequency compared with cannabidiol plus clobazam (see section 3.9), it was likely that fenfluramine would reduce

non-conclusive seizure frequency compared with cannabidiol plus clobazam as well. However, the ERG considered that including non-convulsive seizures could worsen cost effectiveness for fenfluramine and that there was uncertainty. This was because cannabidiol plus clobazam was compared with placebo instead of fenfluramine in Gunning et al. 2020. The clinical experts noted that non-convulsive seizures have a significant impact on day-to-day life, but acknowledged the difficulties in measuring them, particularly in adults who may be in residential care. Given the uncertainties, the committee concluded that the impact of excluding non-convulsive care in the model is unclear and took this into account during decision making.

Using real-world dosing evidence for fenfluramine and cannabidiol is appropriate for this appraisal

3.20 The company presented real-world evidence from studies that showed the average dosing of fenfluramine (see section 2.2) and cannabidiol (see section 3.9). The evidence suggested that the average dose for each treatment was below the licensed maximum dose. The clinical experts said that they titrate the treatment to a dose that reduces seizures while minimising the adverse effects of treatment. They added that most patients would not reach the maximum licensed dose. They said doses could start high but then be reduced if the patient had adverse effects, to a dose that still controlled seizures. In the preconsultation version of the company's model, the company used a dosage of 12 mg/kg/day for cannabidiol, which was in line with the dosage used in NICE's technology appraisal guidance on cannabidiol with clobazam. After consultation, the company argued that the typical maintenance dosage used in the UK was likely to be higher, and changed to a dosage of 15 mg/kg/day in its updated model. It justified this with the following:

- Evidence from a study on slow titration of cannabidiol add-on in drug-resistant epilepsies (D'Onofrio et al. 2020), which was done in France and included 48 people. It looked at slow titrations to improve safety without affecting the efficacy of cannabidiol. It showed that median dosages increased from 10 mg/kg/day to 18 mg/kg/day in people with Dravet syndrome from month 1 to month 6.

- Evidence from a study of 6 people with Dravet syndrome in 1 centre in the UK, which reported an average cannabidiol dose of 13.3 mg/kg/day over 7.5 months (Desai et al. 2021).
- The latest published data from an open-label extension study of add-on cannabidiol in patients with Dravet syndrome (n=315; Scheffer et al. 2021), which reported a median modal dose of over 20 mg/kg/day for a mean duration of 627 days.
- The company's clinical experts said that the average dose in the UK was 15 mg/kg/day or higher.

  The company said that there was no evidence of a significant difference in efficacy in the real-world studies compared with the trials. But it did not present the results of the studies in detail to enable the committee to assess this. The committee noted that the evidence from the open-label study was likely to be an overestimate because it was titrated for tolerability, and optimal efficacy was achieved at a lower dose. The committee noted that the study from the UK was very small so considered it supportive evidence for the French study. The clinical experts at the meeting noted that, particularly for children, 15 mg/kg/day seemed accurate. While the committee did not consider the evidence for the exact dosage of cannabidiol in the UK to be particularly clear, it was relatively confident from the French study, with support from the small UK-based study and clinical input, that the average UK dosage is higher than 12 mg/kg/day. It concluded that using a dose of 15 mg/kg/day of cannabidiol in the model was reasonable.

3.21 The committee noted that the evidence for the real-world use of cannabidiol was predominantly from France, with a smaller amount of supportive evidence from the UK. The evidence for fenfluramine was from real-world use in Germany and Italy, and an international open-label extension study in which the mean daily dose for fenfluramine was 0.32 mg/kg/day with stiripentol and 0.40 mg/kg/day without stiripentol. The clinical experts said that there was no reason to expect that patients in the UK would be treated differently to patients in Europe because genetically they would be similar, and Dravet syndrome is managed in the same way as it is managed in the UK. The committee noted that using the real-world expected dose for both treatment and comparator had a considerable impact on the ICER but considered it would better reflect

the cost of these treatments to the NHS. The committee noted that, while it would prefer not to disconnect the effects from the drug from the amount of drug given, it considered this to be an exceptional situation. It noted that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose. And it heard from clinical experts that the dose used would be a balance between seizure reductions and adverse effects of treatment. In this case, the committee concluded that it was reasonable to use the real-world evidence presented by the company to determine the dosages of both treatments in the model.

Adverse events

Fenfluramine is associated with manageable adverse events but there is uncertainty in modelling

3.22 The company excluded from its model treatment-emergent adverse events on the basis that the incidence was low and similar across fenfluramine and placebo arms. The company made a pragmatic assumption that adverse events would be similar for cannabidiol so excluded them from the model. The company also provided evidence supporting the assumption that there is little difference in the incidence of treatment-emergent adverse events between fenfluramine and cannabidiol plus clobazam. However, the ERG noted that in Study 1, 12.5% of people having fenfluramine 0.7 mg/kg/day stopped treatment because of adverse events, compared with none in the placebo arm. While the ERG agreed that the impact in the model was likely to be small, the clinical expert considered that the impact of adverse events should be included in the model. During consultation, the company explained that the monitoring for adverse events was fully captured in routine management, and that additional costs related to monitoring were appropriately captured in the model as well. The ERG noted that the impact of adverse events and additional monitoring were not reflected in event costs or corresponding disutilities, although this was likely to have a minor impact on the cost-effectiveness estimate. The committee concluded that fenfluramine was associated with manageable adverse events, although there was uncertainty in its modelling, and it took this

into account in its decision making.

Utility values in the economic model

Incorporating carers' quality of life in the model is appropriate but this should be done by applying a carer disutility

3.23 The company estimated that 1.8 carers (2 carers minus 0.2 to account for sharing) would apply to all patients. Carer utility was added to the patient utility to obtain the overall quality of life in the model. However, the ERG noted that the company's model removes the carer's utility when the patient dies, which overestimates the impact of mortality because the carer does not die with the patient. The clinical and carer experts noted that comorbidities and learning disabilities need care, which was not a direct function of seizure frequency. They explained that remaining alert for a seizure has a significant impact on a carer's quality of life. They also noted that many people with Dravet syndrome are cared for in the family home, with a big impact on parents and siblings, and that at least one parent needed to give up work. The ERG considered that applying a carer decrement (disutility), as in NICE's technology appraisal guidance on cannabidiol with clobazam, rather than adding a carer utility may address these problems. The ERG explored this approach by applying 1.8 carers, but only to people with the highest seizure frequencies (more than 8 seizures a month). The company argued that the ERG's approach was based on arbitrary categories and was not appropriate for a model based on carer-level data from clinical trials. The company also noted that individual carer-level data shows that seizure-free days also affect carers' quality of life. During the first meeting, the committee concluded that there was no agreed way to incorporate carer utilities in the model. However, it was concerned that the company's approach was not implemented appropriately because it included implausible assumptions for carers' utilities.

3.24 During the consultation, the company explained that it set carer utility at zero when the patients dies in its base case. The company also provided a scenario analysis retaining the carer's utilities when the patient dies, but at the lowest quality-of-life estimate for carers when the patient was

alive. The ERG commented that this assumption was debatable but had a large impact on the cost-effectiveness estimate. If applying carers' utilities when the patient dies, the ERG preferred to retain the carer utility in the model at the highest quality-of-life estimate the carer experienced when the patient was alive. However, it was unable to implement this analysis. The committee was concerned that the company's technique for including carer utility – whereby carers are modelled to die at the same time as the patient – is unusual and would result in biased results. The committee understood that there was no consensus method when incorporating carers' quality of life in a model, but, mathematically, the carer disutility approach may be more appropriate in this case. The committee concluded that it was appropriate to incorporate carers' quality of life in the model but said this should be done by applying a carer disutility. In response, the company revised its model to incorporate carer disutility and presented it alongside a scenario analysis showing the impact of using both approaches. Using the carer disutility approach had a large impact on the ICER. The committee noted that both approaches had limitations and that the true ICER may lie between both approaches. But it concluded that using the disutility approach had more face validity because it did not result in the unexpected assumption that carers would die at the same time as the patient.

Cost-effectiveness estimate

The ICERs are within the range considered cost effective and take into account the committee's preferred assumptions

3.25 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, decisions 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. There is a patient access scheme for the comparator treatment cannabidiol. Therefore costs and ICERs are confidential and cannot be presented. When the committee's preferred assumptions were taken into account, the ICER was within the range normally considered a cost-effective use of NHS resources

(£20,000 to £30,000 per QALY gained). The committee's preferred assumptions included the following assumptions and approaches:

- Correcting the error for discontinuations as identified and adopted by the ERG (see section 3.13).
- Using the merged population including people taking and not taking stiripentol (see section 3.14).
- Basing the model on convulsive seizure-free days (see section 3.15 and section 3.16).
- A relationship between convulsive seizure frequency and mortality in Dravet syndrome (see section 3.17).
- Using real-world dosing evidence for fenfluramine and cannabidiol (see section 3.20 and section 3.21).
- Incorporating carer's quality of life into the model by applying carer disutility (see section 3.23 and section 3.24).

Other factors

Equality issues

3.26 No equality issues relevant to the committee's preliminary recommendations were raised.

There are likely to be additional benefits of fenfluramine not captured in the model

3.27 A clinical expert said that they considered fenfluramine to be a step change in managing Dravet syndrome because the same benefits have not been seen in trials of other drugs. A carer expert said fenfluramine has significantly improved their quality of life. They also noted that fenfluramine can improve a child's intellectual development because fewer seizures means, for example, that they can make progress in their speech. During the second meeting, the committee noted that there may be potential benefits of fenfluramine which were not captured in the

modelling. These included, for example, the benefit of fenfluramine in reducing the duration of convulsive seizures (see section 3.10), the benefits on non-convulsive seizures (see section 3.19) and the benefit on the quality of life of the siblings of children or young people with Dravet syndrome (see section 3.23). The company also highlighted that its model is likely to be conservative because it does not capture the value of:

- other motor functional (for example walking) and executive function improvements
- the potential for fewer discontinuations and adverse events with fenfluramine
- that fenfluramine is likely to be used in a higher proportion of adults, which is likely to improve cost effectiveness compared with the uncapped dosing of cannabidiol.

The committee concluded that that there are likely to be additional benefits of fenfluramine that were not captured in the model.

Fenfluramine is recommended

3.28 The committee acknowledged that Dravet syndrome has a substantial effect on the quality of life of people with the condition, and their families and carers. It noted that the clinical evidence suggested fenfluramine is clinically effective in reducing the number of convulsive seizures, and that it may be more effective than cannabidiol plus clobazam in reducing convulsive seizure frequency. There were some uncertainties around the assumptions in the model. However, the committee considered that the most plausible ICER for fenfluramine compared with cannabidiol plus clobazam was likely to be within the range normally considered an effective use of NHS resources. So, fenfluramine is recommended as an add-on to 2 other antiseizure medicines for treating seizures associated with Dravet syndrome in people aged 2 years and older in the NHS.

4 Implementation

4.1 Section 7 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 fenfluramine 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.

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