NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Contents:

The following documents are made available to consultees and commentators:

1. **Addendum to company submission post ACM2** from Zogenix

2. **ERG critique of addendum to company submission post ACM2**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

ID1109 Fenfluramine in Dravet syndrome (DS) – Addendum following the second Appraisal Committee meeting (AC2) on the 20 Jan 2022

We thank the Appraisal Committee Chair and NICE project team for the opportunity to provide a revised model in line with the committee's preferences expressed at ACM2 held 20th Jan 2022.

Revised base case

We have made the following changes to the model to develop revised base cases (Table 1, See Appendix for full details):

Table 1. Changes to the AC2 model in developing a revised base case reflecting the preferences of the committee

#	Changes to model	Rationale*	ICER	ICER with REVISED PAS
	Base case ICER at ACM2		£31,841	£27,673
1	Equalisation of short-term discontinuations for FFA and CBD	• Committee preference to equalise the short-term discontinuation rates during the trial period • Request by the Committee to incorporate this previous scenario analysis within the base case	£34,291	
2	Updating of long-term discontinuations for FFA and CBD	• Long-term discontinuation rates are updated in the model using the latest OLE study data available • Equalised for FFA and CBD in absence of equivalent data for the relevant CLB-treated subgroup of patients on CBD, and in line with Committee's preferred approach to short-term discontinuations	£31,947	
3	CBD real world dosing: 15mg/kg/day	• Consistent emergent evidence and clinical expert opinion supporting that real-world dosing of CBD is higher than the 12mg/kg/day initially assumed in TA614 and adopted in the previous AC2 model • Dose of CBD clearly underestimated in our original model	£16,779	
4	FFA real world dosing: 0.32mg/kg/day (with STP); 0.44mg/kg/day (without STP)	• Consistent emergent evidence and clinical opinion supporting that real-world dosing of FFA in practice is lower than the maximum licensed doses permitted and previously assumed in the previous AC2 model • Doses of FFA clearly overestimated in our original model • Consistent with the principle of using real world dosing for CBD	£21,995	
5	FFA: 50% stopping rule at 6 months	• Committee preference to explore alternative thresholds for discontinuation (after 6 months of treatment) if the patient fails to achieve a clinically meaningful improvement in seizure control with FFA. • It is noted in AC2 that a 50% reduction in seizure frequency from baseline seizures is a clearer indicator of benefit than 30% and is consistent with current NICE guidelines for other treatments in epilepsy. • Ensures that FFA will only be continued where a clinically meaningful benefit, that is greater than that required with CBD, is achieved and maintained – reduces uncertainty in clinical and cost effectiveness of FFA • Retained 30% stopping rule for CBD in line with TA614	£22,474	
6	Carer quality of life applied as disutilities	• Committee preference to use disutilities to represent carer QoL in model	£131,197	
7	Combined effect #1+#2+#6	• Cumulative impact of committee/ERG preferences	£119,061	£102,029

8	**Revised Base Case: Carer Disutilities model** (#1+#2+#3+#4+#5+#6)	• Revised base case in line with Committee preferences AND **incorporating carers' disutilities**, AND real world FFA or CBD dosing , AND company concession of a 50% FFA stopping rule	**FFA Dominates CBD⁻**	**FFA Dominates CBD⁻**
9	**Revised Base Case: No Carer QoL model** (#1+#2+#3+#4+#5+removal of carers)	• As per #8, but **removing carers' disutilities** (i.e. patient utilities only – no carer contribution) • Demonstrates that a carers disutilities model effectively eliminates any carer QoL benefit	**FFA Dominates CBD⁻**	**FFA Dominates CBD⁻**
10	**Revised Base Case: Carer Utilities model** (#1+#2+#3+#4+#5)	• As per #8, but replacing carer disutilities with **carers' utilities** • In absence of an accepted methodology for incorporating carer QoL, the carer utilities model remains relevant	**FFA Dominates CBD⁻**	**FFA Dominates CBD⁻**

ACM2, appraisal committee meeting 2; CBD, cannabidiol; clobazam: CLB; CSF, convulsive seizure frequency; DS, Dravet syndrome; FFA, fenfluramine; QoL, quality of life; STP, stiripentol; OLE: Open-label extension study. *Full details of changes and rationale provided in Appendix ⁻FFA has lower total costs and is more effective (see Table 2)

The revised base cases demonstrate fenfluramine (FFA) dominates (i.e. is both more effective and less costly than) cannabidiol plus clobazam (CBD+CLB).

Full revised base case results:

Table 2. Revised base case – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population when incorporating carers' disutilities, or carers' utilities, or removing carers' utilities in the model

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
8. Revised Base Case: Carer Disutilities model											
Cannabidiol +clobazam	£222,252	14.52	6.01	-5.40	0.61	-	-	-	-	-	-
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Fenfluramine Dominant***
9. Revised Base Case: No Carer QoL model											
Cannabidiol +clobazam	£222,252	14.52	6.01	0	0	-	-	-	-	-	-
Fenfluramine	[redacted]	[redacted]	[redacted]	0	0	[redacted]	[redacted]	[redacted]	0	[redacted]	**Fenfluramine Dominant***
10. Revised Base Case: Carer Utilities model											
Cannabidiol +clobazam	£222,252	14.52	6.01	11.66	17.66	-	-	-	-	-	-
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Fenfluramine Dominant***

***Fenfluramine is both more effective and less costly than cannabidiol. Detailed results are provided in the accompanying spreadsheet**

Scenario analyses

We have conducted scenario analyses exploring:

- the impact of a plausible range of confidential PAS discounts on the CBD list price (see **Error! Reference source not found.**) –
    - FFA dominates CBD up to an [redacted] discount on CBD list price when carer QoL is incorporated as either utilities or disutilities, and when carer QoL is excluded from the model
    - ICER for FFA vs CBD remains below £30,000/QALY up to a CBD PAS discount of
        - [redacted] when incorporate carers' QoL as disutilities
        - [redacted] when exclude carers' QoL from model
        - [redacted] when incorporate carers' QoL as utilities
- key changes implemented in the revised base case model that incorporates carer QoL as disutilities .

Table 3. Scenario analyses around revised base case when incorporating carers' QoL as disutilities in the model

#	Scenario analysis	Rationale	Result	Interpretation
	Revised Base case (Carer disutility model)	-	FFA Dominates CBD*	-
1	CBD PAS price. Testing 10-40% discount from list price	• Exploring plausible range of confidential PAS discounts on CBD list price	ICER <£30,000/QALY up to [redacted]% discount in CBD list price (see **Error! Reference source not found.**)	FFA is likely to be cost effective in clinical practice in the UK
2	"Best case" dosing for FFA, "worst case" dosing for CBD	• FFA dose 0.32 (w STP) and 0.40mg/kg/day (w/o STP) based on real-world dosing and first target doses in SmPC. • CBD dose 20mg/kg/day per its maximum licensed dose in SmPC	FFA dominates CBD* More effective by [redacted] QALYs. Less costly by [redacted]	The revised base case could plausibly be conservative
3	"Worst case" dosing for FFA, "best case" dosing for CBD	• FFA dose 0.4 (w STP) and 0.7mg/kg/day (w/o STP) based on maximum license-permitted doses (see SmPC) • CBD dose 12mg/kg/day per dosing assumed in TA614 is underestimated vs clinical practice	[redacted]	Provided for completeness – result is highly conservative and unlikely to reflect cost effectiveness of FFA across all patients in UK clinical practice
4	30% stopping rule for FFA at 6 months	• Aligned with stopping rule for CBD	FFA dominates CBD* More effective by [redacted] QALYs. Less costly by £[redacted]	Provided for completeness – we propose a 50% stopping rule for FFA
5	Population norm utility value for carers: 0.893	• Alternative population norm utility value for average age of carer 35-44 years	FFA dominates CBD* More effective by [redacted] QALYs. Less costly by [redacted]	Population norm utility value for carer not a key driver of results

CBD, cannabidiol (with clobazam); DS, Dravet syndrome; FFA, fenfluramine; QoL, quality of life; STP, stiripentol.
* FFA has lower total costs and is more effective

Figure 1. Sensitivity of the base case ICER when testing a plausible range of confidential price discounts (PAS) for CBD when incorporating carers' QoL as disutilities or utilities, or excluding carers' QoL in the model.

[redacted]

Clarifications to address other areas of uncertainty

- Relationship between convulsive seizure frequency and convulsive seizure days
  - We provided a detailed explanation of the approach to the regression analysis, including the choice of regression model and the data used, in our response to the ACD dated 28 October 2021.
  - In summary, the regression model was conducted on individual patient data from all patients in all treatment arms of the FFA RCTs, and a linear regression model was used given the the scatter plot of the change in seizure frequency vs the change in seizure days (a day with 1 or more seizures) indicates a linear relationship in that portion of the plot where the clear majority of points sit, corresponding to a reduction in seizure frequency.
  - Please see the full details contained in our response to the ACD dated 28 October 2021, Issue no. 11 on page 24-26, and Figure 8 on page 49 of the Appendix to that document, dated 01 December 2021.
  - As noted by the ERG, the ratio of convulsive seizure frequency to convulsive seizure days had a minor impact on the estimate of cost effectiveness.
- Relationship between convulsive seizure frequency and mortality with FFA treatment
  - We are pleased the Committee accepts that mortality is associated with convulsive seizure frequency and should be reflected in the model.
  - UK clinical experts agreed our underlying survival curve provides a reasonable representation of survival in DS patients in the UK.
  - We have previously explored adoption of alternative relationships between convulsive seizure frequency and mortality based on evidence from general epilepsy. However, the Committee in AC2 indicated it had not been provided with evidence to suggest an association between reduced convulsive seizure frequency and reduced risk of mortality in DS patients receiving FFA treatment.

- It is not possible to provide direct comparative trial evidence of a survival benefit with FFA or any other treatment for DS. However, a recently published analysis of 732 DS patients treated with FFA across the RCTs and real-world evidence studies (1185.3 person-years of exposure) indicates substantially reduced all cause and SUDEP mortality rates with FFA treatment (1.7 per 1000 person-years for both) compared with the most robust rates reported in the literature for all-cause mortality (15.8 per 1000 person-years) and SUDEP (9.3 per 1000 person-years). The internationally renowned DS expert authors note: "*It appears likely that the substantial reduction in convulsive seizure frequency, including GTCS frequency, coupled with significantly prolonged periods of seizure freedom reported in the clinical trials of FFA are the major contributors to the reduction in all-cause and SUDEP mortality reported here*." (Cross et al 2021).
- This supports our modelling of mortality based on convulsive seizure frequency, and provides the most robust evidence possible in DS of an association between reduced convulsive seizure frequency and reduced risk of mortality with FFA treatment.
- Given the interrelationship between mortality, seizure-frequency, treatment duration, accrued costs and QALYs in the model, it is not possible to decouple or modify the treatment effect of CBD and/or FFA from survival outcomes, without fundamentally changing the model in ways that would prevent a meaningful comparison of the results against the base case or other models.

Discussion on the clinical and cost effectiveness of fenfluramine

- DS is a rare, lifelong and life-limiting disease that emerges in infancy and has high unmet needs for more effective treatments
  - If FFA was being appraised under the recently revised NICE methods process we would anticipate it to qualify for application of severity modifiers due to the significant shortfall in QALYs sufferers experience compared with age-matched population norms.
- The Committee acknowledges that FFA is likely to be more effective than CBD plus CLB in reducing convulsive seizures and may meet the criteria for an innovative treatment
  - Whilst there may be some uncertainties in the precision of the clinical effectiveness estimates – as a result of the rarity of the disease, heterogeneity of available trial populations, and inherent spontaneity of seizure events – there is little uncertainty in the magnitude of the clinical benefits of FFA versus CBD plus CLB
  - Clinical and patient experts have referred throughout the appraisal process to the unprecedented effectiveness of FFA in reducing seizures and improving QoL.
  - We therefore believe FFA should be considered an innovative therapy.
- We have addressed the Committee's preference for incorporating carer QoL in the economic model in the form of applying carer disutilities, which has a profound negative impact on the estimates of cost effectiveness of FFA
  - There is no agreed approach to inclusion of carer QoL into economic models, and we believe the preferred approach of the Committee to remove carer quality of life from an already impaired patient quality of life is clinically and technically inappropriate. Nonetheless, we have implemented this change in the model as requested.
  - A further analysis in which carer QoL is completely removed from the model serves to demonstrate that the disutility modelling approach effectively eliminates any carer QoL benefit.
  - Implementation of the revisions to the base case model in the utilities-based model indicates that the use of a disutility model may be highly conservative (see Table 1 and Figure 1).
- In an effort to secure patient access for this highly effective and innovative therapy, and to mitigate any residual uncertainties in the economic model, we have made additional and substantial concessions on our proposal

  - We have proposed a 50% stopping rule for FFA, which provides greater certainty that FFA will only be continued in patients who achieve and maintain a clinical meaningful benefit that is significantly greater than that required for continued treatment with the less effective CBD
  - We have increased the FFA PAS discount even further. [redacted].
- Our revised base case and scenario analyses demonstrate that FFA is highly likely to be a cost-effective treatment option in clinical practice
  - FFA dominates CBD in the base case analyses and the ICER remains <£30,000/QALY up to a CBD PAS discount of [redacted] when carers' QoL is incorporated as disutilities, [redacted] when carers' QoL is excluded, and >[redacted] when carers' QoL is incorporated as utilities.
- Several areas of our model remain clinically and economically conservative given the superior effectiveness of FFA over CBD plus CLB
  - The benefit of FFA in reducing the duration of convulsive seizures, and the benefit on the QoL of siblings of children or young people with DS are not included in the model
  - The model excludes the influence of non-convulsive seizures on QoL
  - Caregivers have noted that FFA improves children's intellectual development because fewer seizures means they can make progress in their speech. This and the value of other motor-functional (e.g. walking) and executive function improvements have not been included in the model.
  - We have assumed equal discontinuations for FFA and CBD in the absence of publicly available data for the relevant CBD plus CLB subgroup
  - We do not include the greater potential of FFA to reduce the dose or number of concomitant AEDs, which could simplify treatment regimens, reduce the potential for adverse events with other AEDs and would reduce the overall costs of the FFA strategy in the model.
  - Over time, we anticipate that FFA will be used in a higher proportion of adult patients, which based on the capped dosing of FFA (at a weight approximating an average 13 year old) will improve its cost effectiveness compared with the uncapped dosing of CBD plus CLB.
  - A high proportion of the total costs of managing DS, and the daily burden of this, are borne by patient families and caregivers. Whilst not included in our model, the value of FFA in alleviating these costs and burden to the DS community should not be ignored in the Committee's decision-making.

Conclusion

- We thank the Committee and NICE project team for considering this addendum in a closed meeting in April.
- With limited available treatment options for DS patients, there is little doubt that FFA is highly clinically effective in this rare, life limiting disease, and should be viewed as an innovative therapy.
- Our revised economic model, in which we have made substantial concessions to accommodate the Committee's preferred assumptions, indicates FFA is also highly likely to be a cost-effective treatment option.
- Following a very protracted appraisal process, we respectfully request the Committee recommends FFA as a clinically and cost-effective treatment option to avoid further delaying patient, caregiver and clinician access to this much needed, innovative therapy.

References:

Cross JH et al. Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome. Seizure: European J. Epilepsy 93 (2021) 154–159
Desai I et al. UK Northwest Profile of Epidyolex use for Refractory Seizures in Children. BPNA 2021 (Poster)
D'Onofrio G et al. Slow Titration of Cannabidiol Add-On in Drug-Resistant Epilepsies Can Improve Safety With Maintained Efficacy in an Open-Label Study. Frontiers in Neurology. August 2020; Volume 11: Article 829
NICE. CHTE methods review: Health-related quality of life - Task and finish group report; July 2020
Scheffer IE et al. Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial. Epilepsia. 2021;62:2505–2517.
Scheffer IE et al. Efficacy and Tolerability of Adjunctive FINTEPLA (Fenfluramine Hydrochloride) in an Open-Label Extension Study of Dravet Syndrome Patients Treated for Up to 3 Years. AMCP 2021 (Poster)
Specchio N et al. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. Epilepsia 2020: DOI: 10.1111/epi.16690.

Strzelczyk A et al. Efficacy, tolerability, and retention of fenfluramine for the treatment of seizures in patients with Dravet syndrome: Compassionate use program in Germany. Epilepsia 2021: DOI: 10.1111/epi.17034
Sullivan J et al. Fenfluramine HCl (Fintepla®) provides long-term clinically meaningful reduction in seizure frequency: Analysis of an ongoing open-label extension study. Epilepsia 2020: DOI: 10.1111/epi.16722

Attachments:

- ACIC checklist
- Model base case (original from AC2 and the revised base case model)
- Excel spreadsheet of results and code changes

Appendix: Full description of changes made to model

1. Equalisation of short-term discontinuations for FFA and CBD

- We have equalised the trial-based discontinuations for FFA and CBD in line with the approach taken by the ERG and the committee's preference to see this in a revised base case.

2. Updating of long-term discontinuations for FFA and CBD

- We have updated the probabilities of long-term treatment discontinuations (which include discontinuations for any loss of effect) using the latest data from the open-label extension (OLE) study (n=330) that includes follow-up for up to 3 years, as reported in the latest FFA SmPC. In the absence of equivalent data for CBD plus CLB, and in line with the committee's preferred approach to the trial-based discontinuations, we have assumed the same long-term discontinuations for FFA and CBD plus CLB in the revised base case.
- It should be noted these data include all patients in the OLE study, including de novo patients who previously received placebo in the core RCTs. The overall probability of discontinuation with FFA based on these data is therefore likely to be overestimated compared with what would be observed in FFA-experienced patients in clinical practice; however, as these data are applied equally to both arms of the model, this is considered a clinically conservative decision without favouring either treatment strategy.

3. CBD real world dosing: 15mg/kg/day

- With more real-world use of CBD plus CLB since TA614 was published, there is increasing published evidence on its dosing in DS patients. These data consistently report of routine CBD dosing being greater than the 12mg/kg/day dosing assumed in TA614, and used in our model presented during the AC2 meeting, without a corresponding increase in efficacy:
  - Desai et al (2021) reported an average CBD dose of 13.3mg/kg/day over 7.5 months, in a small study of DS patients (n=6) at a single UK centre.
  - In a much larger, prospective, multicentre study in France (n=48) based on the nominative Temporary Authorisation for Use (ATU) programme, in which doses were titrated by efficacy and safety and deliberately more slowly than recommended in the CBD SmPC, the median CBD dose increased from 10mg/kg/day to 15.5mg/kg/day over 1 month, and at 6 months was 18mg/kg/day (D'Onforio et al 2020).
  - In the latest published data from the CBD open-label extension study (n=315, mean duration of CBD dosing 626.8 days), in which dose titration based on efficacy and safety was permitted up to a maximum of 30mg/kg/day (i.e. above the licensed dose stated in the European SmPC), the mean modal dose of CBD (irrespective of clobazam use) was 22mg/kg/day (Scheffer et al 2021a).
- Clinical opinion shared with Zogenix from highly-respected UK experts, also agreed that CBD would typically be dosed at 15mg/kg/day in DS [redacted] has confirmed that average CBD doses are ≥15mg/kg/day (personal communication).
- As there is no evidence of a significant difference in efficacy in these real-world studies versus that observed in the trials, this collective evidence supports a CBD dose of 15mg/kg/day in the model to reflect the dosing of CBD in routine UK clinical practice.
- A "best/worst case" for CBA and FFA dosing is explored in scenario analyses.

4. FFA real world dosing: 0.32mg/kg/day (with STP); 0.44mg/kg/day (without STP)

- With increasing real-world use of FFA for patients with DS, there is also published evidence on the doses of FFA used in routine clinical practice. Consistently, in patients comparable to the trial populations, these doses are lower in practice than the maximum licensed doses of 0.4mg/kg/day (with stiripentol) and 0.7mg/kg/day (without stiripentol) assumed in our model presented at the AC2 meeting, without a corresponding decrease in efficacy to that observed in the RCTs:
  - In a multicenter study of patients receiving FFA in a German compassionate use programme (n=78, median follow-up 255.5 days), the mean dose of FFA, irrespective of stiripentol use, was 0.40mg/kg/day (Strzelczyk et al 2021).
  - In a multicentre study of patients receiving FFA in an Italian expanded access programme (n=52, 9.0 months median follow-up), the mean dose of FFA, irrespective of stiripentol use, was 0.46mg/kg/day (Specchio et al 2020).
  - In the FFA OLE study, at a median treatment duration of 256 days (n=252), the mean dose of FFA irrespective of stiripentol use was 0.40mg/kg/day (Sullivan et al 2020). The dose at a later follow-up (median treatment duration 631 days, n=330) was highly consistent (Scheffer et al 2021b). When taken with stiripentol the mean FFA dose was 0.32mg/kg/day, and without stiripentol was 0.44mg/kg/day (Sullivan et al 2020).
- UK clinical expert opinion shared with Zogenix agreed there was little reason to believe the dosing observed in the OLE study would be expected to differ from that in practice.
- As there is no evidence of a reduction in efficacy in these real-world studies versus that observed in the trials, this collective evidence supports FFA dosing of 0.32mg/kg/day (with stiripentol) and 0.44mg/kg/day (without stiripentol) in the model to reflect the dosing of FFA in UK clinical practice. “Best/worst case” CBA and FFA dosing is explored in scenario analyses.

5. FFA: 50% stopping rule at 6 months

- Clinical expert opinion at the AC2 meeting indicated that a 50% reduction in seizure frequency would be a clearer indication of benefit than a 30% reduction.
- Feedback from the AC2 meeting indicated the Committee wished to explore alternative thresholds of response for a stopping rule.
- Adopting a 50% stopping rule at 6 months for FFA in the base case ensures FFA will only be continued when a clinically meaningful benefit is achieved, and reduces uncertainty in the clinical and cost effectiveness of FFA. It is also consistent with NICE guidelines for the continued use of other therapies in epilepsy.
- The 30% stopping rule for CBD has been retained in line with its recommendation in TA614.
- Scenario analysis has been conducted exploring the original 30% stopping rule in the revised base case model.
- Although the stopping rule is applied at the first 6 months, the model incorporates monitoring and management every 3-6 months in line with routine clinical practice over the lifetime of the patient. Consistent with typical management practices for DS, patients would be withdrawn from a treatment if not achieving a minimally effective response. This is captured in the ongoing discontinuations beyond 6 months.

6. Implemented carer QoL as disutilities

- Although there is no agreed method for incorporating carer QoL into economic models, the Committee preferred the use of a disutilities-based method rather than the utilities-based method we had employed. We have therefore implemented a disutilities-based method in the revised base case.
- To estimate disutilities for carers in the model it was necessary to establish a population norm utility value for carers, from which to subtract the individual trial-based utility values for carers.
- To establish a population norm utility value for carers

- Zogenix approached Dravet Syndrome UK for any information they could provide on the age of its carer members. Based on these anonymised summary data, we estimate that the average age of a carer in the UK would be 41.5 years.
- The *NICE CHTE Methods review: Health-related Quality of Life Task and Finish Group Report* published July 2020 listed several sources of general population utility data. From this report we obtained a utility value of 0.91 for an adult aged 41 years, based on consistent values from two recommended and cited sources: *Health Survey for England*, and UK data from *A compendium of populations norms across a number of European countries collected on behalf of the EuroQol working group*.
- Scenario analysis has been conducted to explore an alternative population norm utility value for an adult aged 35-44, using data for England from the compendium of populations norms.

- The trial-based utilities data for carers are estimated based on EQ-5D-5L data mapped to EQ-5D-3L, as previously described in our submission.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Fenfluramine for treating Dravet syndrome

Third response to company's ACD comments (March 2022)

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Date completed	30/03/2022

Following the Appraisal Committee (AC) meeting discussions on 20th Jan 2022, the company submitted additional information in March 2022. An updated model was submitted that incorporated several changes in response to the 2nd ACM. See below for the ERG comments on the submission of March 2022.

Cost effectiveness evidence

The company has increased the fenfluramine PAS discount. Furthermore, although the company made some changes to the model in line with the preferences of the AC and ERG, the company implemented additional changes to the model. These changes were not requested by either the AC or ERG.

The company has now implemented the following changes in its revised base case:

1. Equalisation of short-term discontinuations for FFA and CBD (requested by ERG)
2. Updating of long-term discontinuations for FFA and CBD
3. CBD real world dosing: 15mg/kg/day
4. FFA real world dosing: 0.32mg/kg/day (with STP); 0.44mg/kg/day (without STP)
5. FFA: 50% stopping rule at 6 months
6. Carer quality of life applied as disutilities (requested by ERG)

Moreover, the company did not provide an adaptable model including all changes in the revised base case (i.e. the revised model does not contain "switches" to run the model without (some of) the revisions). The use of different model versions for all separate analyses, instead of one adaptable model file (as is commonly done) hinders the validation of individual adjustments made by the company.

Relationship between convulsive seizure frequency and convulsive seizure days

The ERG would like to emphasize that the ratio of convulsive seizure frequency to convulsive seizure days had a minor impact on the estimate of cost effectiveness in the model provided after the 1st ACM. However, it is unclear how big the impact of this assumed relationship is in the current (revised/updated) company base case.

Relationship between convulsive seizure frequency and mortality with FFA treatment

It is unclear what the preferences of the AC are regarding this assumption.

Incorporating carer QoL in the economic model in the form of applying carer disutilities (i.e. Model change #6)

The ERG welcomes the implementation of carer quality of life by using disutilities instead of the previous approach adopted by the company. The calculation of disutilities was done by establishing a population norm utility value from which the trial-based utilities data from carers was subtracted. The company extracted a population norm utility of 0.91 for an adult aged 41 years (assumed to be the average age of a caregiver). While this value was taken from the *NICE CHTE Methods review: Health-related Quality of Life Task and Finish Group Report*, it is on the high end of the spectrum. The company explored a scenario in which an alternative population norm utility value for average age of carer 35-44 years was assumed (which is also mentioned in the NICE CHTE report). This favourably impacted the incremental QALY gains (i.e. higher QALYs for fenfluramine compared to CBD), which feel counterintuitive to the ERG and was not explained by the company.

Revised stopping rule for fenfluramine (i.e. Model change #5)

The ERG would like to emphasize that it is unclear whether the adjusted stopping rule is in line with committee preference and UK clinical practice. Furthermore, the ERG questions the implementation of

two different stopping rules for fenfluramine (at least 50% reduction in convulsive seizures frequency) and cannabidiol (at least 30% reduction in convulsive seizures frequency).

Dose adjustments for cannabidiol in the model (i.e. Model change #3)

The company has proved additional references to justify an increase in the dose of cannabidiol assumed in the model. The presented evidence reported average CBD doses ranging from 13.3 mg/kg/day (no further details, Desai et al. 2021) to 18 mg/kg/day (median, D´Onforio et al. 2020) to 22 mg/kg/day (mean modal, 22 mg/kg/day). Therefore, it is likely that CBD routinely used in clinical practice might be greater than 12 mg/kg/day assumed in TA614 and used in the economic model. However, the company did not share details on the "clinical opinion shared with Zogenix from highly-respected UK experts". It should be noted that the referred studies are either based on a low number of participants and/or not conducted (solely) in the UK. For example, the study of Scheffer et al 2021a was based on the OLE study of the GWPCARE studies in which investigators could increase the CBD dose to a maximum of 30 mg/kg/day if they considered it may be of benefit. This is not in line with TA614, in which the marketing authorisation states that for cannabidiol "Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg taken twice daily up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day)". It is therefore unclear to what extent the presented results are applicable to the UK clinical practice.

Dose adjustments for fenfluramine in the model (i.e. Model change #4)

The model presented at ACM 2 assumed FFA doses of 0.4 mg/kg/day (with stiripentol) and 0.7 mg/kg/day (without stiripentol). The evidence presented in the addendum following ACM 2 reported lower doses of FFA. While lower doses of FFA (compared to the ACM 2 model) are supported by the presented evidence, it should be noted that:

a) There is some concern regarding the applicability of the findings, e.g. all participants included in Speechio et al. 2020 had a SCN1A mutation, compared to approx. 80% of participants in the trials reported in the CS;
b) The company did not share any details regarding the "UK clinical expert opinion shared with Zogenix"; and
c) There is some uncertainty in the results, e.g. the SD is roughly a third of the estimate reported in Sullivan et al. 2020.

It is therefore unclear to what extent the presented results are applicable to the UK clinical practice.

Updates to the company's base case following the 2nd ACM

See below and overview of the company's adjustments along with ERG comments.

Table 1. Updates to the company's base case following the 2nd ACM (source company submission)

#	Company update	ERG comment
1	Equalisation of short-term discontinuations for FFA and CBD	In line with ERG preferences. Small impact on the ICER (i.e. ICER increases with ±£3,000).
2	Updating of long-term discontinuations for FFA and CBD	In line with ERG preferences. Minimal impact on the ICER (i.e. ICER increases with ±£100).
3	CBD real world dosing: 15mg/kg/day	This change was not requested by the ERG and initiated by the company. It is unclear to what extent this dose is applicable to the UK clinical practice. Large impact on the ICER (i.e. ICER decreases with ±£15,000).
4	FFA real world dosing: 0.32mg/kg/day (with STP); 0.44mg/kg/day (without STP)	This change was not requested by the ERG and initiated by the company. It is unclear to what extent this dose is applicable to the UK clinical practice. Large impact on the ICER (i.e. ICER decreases with ±£12,500).
5	FFA: 50% stopping rule at 6 months.	This change was not requested by the ERG and initiated by the company. The ERG questions the implementation of two different stopping rules for fenfluramine (at least 50% reduction in convulsive seizures) and cannabidiol (at least 50% reduction in convulsive seizures). Large impact on the ICER (i.e. ICER decreases with ±£9,000).
6	Carer quality of life applied as disutilities.	The implementation of disutilities is in line with Committee's and ERG preferred approach. Very large impact on the ICER (i.e. ICER increases with ±£100,000).

Additional ERG analyses

The ERG would have liked to run an additional ERG scenario which only incorporated changes #1, #2, and #6 from the revised company base case as these changes were in line with the committee's or ERG preferences. However, this analysis was not performed given that the company did not provide an adaptable model including all changes in the revised base case (i.e. the revised model does not contain

"switches" to run the model without (some of) the revisions). As a result, implementing alternative scenarios is particularly challenging and time consuming due the opaqueness of the economic model.

Conclusion

Although the company did implement changes in accordance with the ACM, some additional changes were implemented in the model which were not requested by the ERG or ACM and were not fully justified. Hence, there remains uncertainty related to the estimated cost effectiveness (as highlighted above).