National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Fenfluramine for treating Dravet syndrome

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Zogenix	No supplementary comment.	Comment noted.
	Association of British Neurologists (ABN)	The wording is adequate.	Comment noted.
	Dravet Syndrome UK	We understand that the draft remit is to appraise the clinical and cost effectiveness of fenfluramine within its marketing authorisation for treating Dravet syndrome. We further understand that fenfluramine does not yet have a marketing authorisation and has been studied in placebo controlled trials as an 'adjuvant treatment for inadequately controlled Dravet syndrome in people taking one or more anti-epileptic drugs'.	Comment noted. The population considered in the appraisal is dependent on the wording of the marketing authorisation. The population has been left broad, the indicated population is

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		In absence of a marketing authorisation, we are assuming that the remit of the appraisal is aligned to the above description of placebo controlled trials and feel that this is appropriate. **However, we suggest that the final wording of the remit (and marketing authorisation) should in addition be clear regarding the age of the patients with Dravet Syndrome, so as not to unnecessarily restrict the use of fenfluramine to children e.g. 'from infants aged two to adults aged 18 years and older'.**	currently under review. No action required.
Timing Issues	Zogenix	No supplementary comment	Comment noted.
	Association of British Neurologists (ABN)	Important that this appraisal is undertaken soon. There are data available on fenfluramine in long term use; the data suggest that fenfluramine can be effective. People with Dravet syndrome with uncontrolled seizures are at continuous risk of SUDEP. Therefore there is a need to move ahead promptly, with at least the push that cannabidiol has received.	Comment noted. NICE aims to ensure the timely production of guidance and has scheduled this topic into its work programme.
	Dravet Syndrome UK	There is an urgent and significant unmet need for this NHS appraisal for the following reasons. • Dravet Syndrome (DS) is a devastating condition that places a huge burden on children/adults with the condition, their parents/carers and the entire family. • DS is characterised by prolonged recurrent seizures that usually start in the first year of life. As the condition progresses, other seizure types occur. Significantly, the risk of SUDEP in DS is up to 15 times higher than other childhood-onset epilepsies and 10% of children with DS die of SUDEP before their 20th birthday (see Cooper et al 2016). • It is also important to understand that unmet needs in DS are not limited to seizure control. DS is also characterised by a range of comorbidities that	Comment noted. NICE aims to ensure the timely production of guidance and has scheduled this topic into its work programme.

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		vary in range and severity. As children with DS become older, comorbidities can often be harder to manage than the seizures and lead to significant disabilities.
		• DS is a spectrum disorder. It's complex and not everyone responds the same way to treatments. Therefore, most of the currently approved treatments and treatment combinations are on a trial and error basis, which is taxing on the children and the carers.
		• Carers are always looking to improve the seizure control whilst balancing the drug side effects. Some children are better controlled than others but that can always change; the symptoms of the condition don't stay static for long.
		• Very few children/adults experience a seizure-free existence. Most are on three AED's, each of which bring with them side effects, such as suppression of appetite, aggression, insomnia, somnolence, etc. Side effects from treatments can also increase some of the symptoms of the comorbidities.
		• Many have tried the Ketogenic diet and VNS with limited success, again dependent on the child.
		• The burden of living with DS also has a significant impact on the quality of life of parent/carers. For example, a recent longitudinal 10-year follow up study on patients with DS in the UK (conducted by A Brunklaus et al; pending publication) found:
		  • 98% of parents/carers reported that their child/adult's condition had affected their own health
		  • Over 90% of parents/carers reported mental health difficulties (including feelings of depression, anxiety, stress disorders)
		In over 90% of families, at least one parent had to either quit their job or cut back on hours due to the burden of looking after a child that's very unwell; this has a significant financial impact on families	

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Additional comments on the draft remit	Zogenix	No response	Response noted.
	Association of British Neurologists (ABN)	No response	Response noted.
	Dravet Syndrome UK	No response	Response noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Zogenix	Background: Para1, lines 7-9. Consider adding “progressive” “Subsequently infants develop multiple seizure types (including myoclonic, absence, focal and generalised tonic–clonic seizures) and are affected by [add: “progressive”] developmental delay or regression” • Background. Para 2, lines 2-4. Consider rewording Current: “Dravet syndrome-related mortality is estimated to be around 20%, with most deaths occurring before 10 years of age.” Proposed: “Dravet syndrome-related mortality is estimated to have a 15% risk of death after 10 years of follow-up post diagnosis of Dravet syndrome” These data by Shumley et al., (referenced in the scope and figures below) identified a cohort of predominately younger patients, with a prior diagnosis of Dravet syndrome, and which had died. Given the physiological and genetic nature of the condition and that many adult patients are currently	Comment noted. The background section has been updated to reflect the progressive nature of developmental delays. Comment noted. The background section of the scope is intended to provide a brief summary of the disease and how it is managed. It is not designed to be exhaustive. Where

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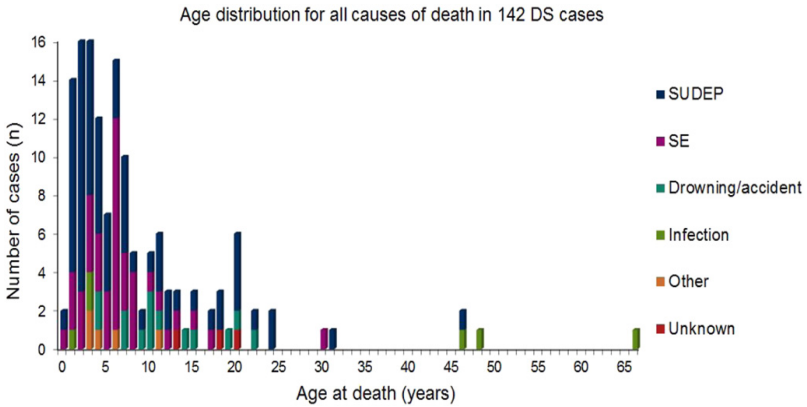
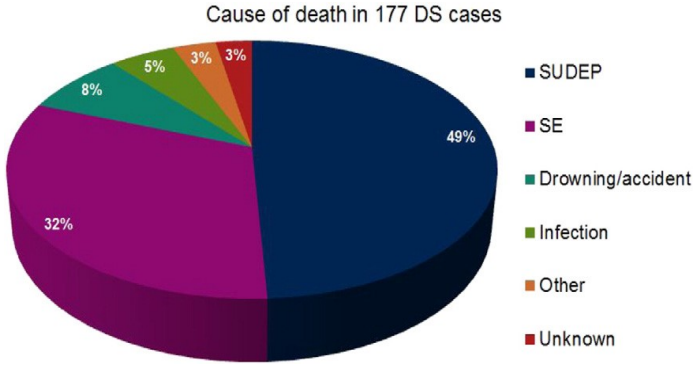
		undiagnosed with Dravet syndrome, the mortality risks associated with seizures is likely to continue into adulthood. Cooper et al., derived: “a Dravet-specific mortality rate of 15.84 per 1000-person years which translates to an almost 15% risk of death after 10 years of follow-up post diagnosis of DS [Dravet syndrome]”   Source: Shumley et al (No. 4 in the scope).	relevant and appropriate, evidence on the nature and epidemiology of the condition will be considered in any appraisal of fenfluramine. No action required.

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		Cooper et al., Epilepsy Research 128 (2016) 43–47	
	Association of British Neurologists (ABN)	Adequate, but the references should be to original peer-reviewed scientific output. The reported incidence figures are outdated.	Comment noted.
	Dravet Syndrome UK	The background information is incomplete in describing DS as "a severe form of epilepsy that affects children and adults". As the UK patient group for DS, we feel it is more accurate and complete to describe DS as a life-limiting neurological condition that causes severe, difficult to control seizures, alongside varying degrees of learning disabilities and other comorbidities, such as autism, gait and mobility problems, speech difficulties, nutrition and feeding problems, dysautonomia and sleep disturbances. For more information see www.dravet.org.uk/about-dravet-syndrome/comorbidities) and the following references: • Gataullinaa and Dulac, *Seizure,* 2017 - 'SCN1A positive DS is more than an epilepsy syndrome, it should be considered as a disease' (p65). • Villas et al, *Epilepsy & Behaviour,* 2017 (US study) - 'Our findings support the concept of Dravet syndrome as a disease of the central nervous system with far-reaching effects' (p85) • Lagae et al, *Developmental Medicine & Child Neurology,* 2018 - 'Patients with Dravet syndrome with the highest current seizure frequency suffer from more comorbidities and have a lower QoL' (p63) In order to fully appraise the impact of a new treatment such as fenfluramine, it's important to recognise that DS is not limited to epilepsy and seizures. The comorbidities associated with DS can often be harder to manage than the seizures and, as children become older, these can lead to significant disabilities.	Comment noted. The background section of the scope is intended to provide a brief summary of the disease and how it is managed. It is not designed to be exhaustive. Where relevant and appropriate, burdens associated with Dravet Syndrome in people with the condition will be considered in the appraisal of fenfluramine. No action required.

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		It is the combination of repeated, prolonged, difficult-to-control seizures with debilitating comorbidities that causes DS to have such a devastating impact not only on health-related quality of life but overall quality of life - for the person with the condition and their family. If a child has fewer seizures and fewer side effects from medication, this will positively affect their development, improve their comorbidities and ultimately improve their quality of life. Which can often be quite poor. Fewer seizures also will reduce the time patients spend at hospital which will improve the lives of the whole family as well as reducing the burden on in-hospital NHS resources. Simply put, if seizure control can be achieved or improved it affect the whole aspect of looking after a child with this devastating condition, leading to significant improvements in overall outcomes for patients and their families. Please note also that the incidence figure given in the background information '1 in 19,000 to 1 in 40,000 live births' is now out of date. The UK incidence of the incidence of SCN1A-related DS is now considered to be 1 per 15 500 live births (see Symonds et al, *Brain* 2019, p8).	
The technology/ intervention	Zogenix	• The Technology: Para1, lines 1. Correction Proposed: "Fenfluramine (FINTEPLA, Zogenix International Ltd)" At this time, the indicated population is currently under review by the EMA	Comment noted. The technology section has been updated.
	Association of British Neurologists (ABN)	Yes	Comment noted.
	Dravet Syndrome UK	The description given is in line with our understanding of the technology.	Comment noted.

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Population	Zogenix	At this time, the indicated population is currently under review by the EMA	Comment noted.
	Association of British Neurologists (ABN)	Yes. It is vital that adults are not excluded from this process – most children with Dravet syndrome survive into adulthood. We already have the nonsensical situation where stiripentol, an effective drug, cannot be initiated in the same disease in adulthood, but can in childhood. The distinction between the two is arbitrary: the disease is the same.	Comment noted. The population considered in the appraisal is dependent on the wording of the marketing authorisation. No action required.
	Dravet Syndrome UK	Any child/adult with DS whose seizures are not controlled could benefit from trying this new medication. Most of these children/adults have tried many drugs before and still have seizures. Any reduction in seizure activity is a benefit. For example, if you have a child who has five seizures a night and the medication reduced the number of seizures to three a night, that would be considered by a family to an improvement. Or if a child was having daily seizures and the medication reduced this to two seizures a week, then that would be considered a success. One factor that needs consideration is the reduction in length of seizure. For example, if a child has three seizures a week, and each seizure normally last five minutes; if after starting treatment they still have those three seizures week, but the length of seizures has reduced to one minute each, that is a huge difference.	Comment noted. The population considered in the appraisal is dependent on the wording of the marketing authorisation. No action required.
Comparators	Zogenix	In the UK, the current therapeutic pathway for patients with Dravet syndrome is formed of the listed 'comparator' treatments, in conjunction with combinations of treatments that form a 'background standard of care': **Comparators** **Background standard of care**	Comment noted. The comparators included in the scope reflect those that are relevant to the proposed licensed indication. The

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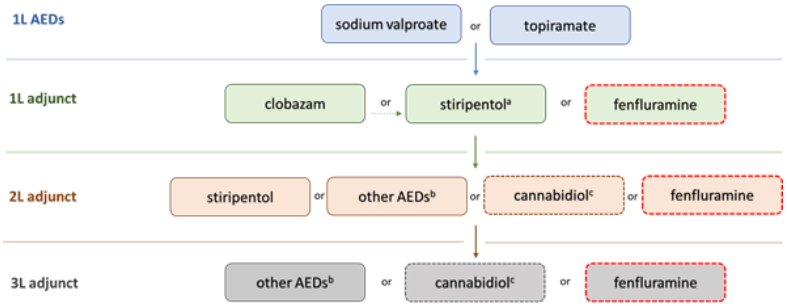
		• stiripentol • cannabidiol with clobazam *(Combinations of AEDs, diet and devices)* • levetiracetam • ketogenic diet • vagus nerve stimulation • sodium valproate • topiramate • clobazam The proposed positioning of fenfluramine in the UK pathway is presented in Figure 1. **Figure 1: Proposed position of fenfluramine within the treatment pathway for Dravet syndrome**  **KEY:** 1L, first-line; 2L, second-line; 3L, third-line; AEDs, anti-epileptic drugs **a)** Stiripentol is not licensed for use as 1L adjunct therapy in Dravet syndrome, however, NICE guidelines recommend considering stiripentol as an alternative to clobazam if seizure control is not achieved on 1L treatment alone	appraisal committee will further discuss the most relevant comparators and treatment pathway during the development of this appraisal. No action required.

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		b) Anti-epileptic drugs licensed for general epilepsy are used in Dravet syndrome on an experimental or off-label basis **c** Cannabidiol, requiring co-administered with clobazam per EMA granted license, has only been recently approved by NICE in the UK for the treatment of Dravet syndrome and is expected to become a clinical option at the time of the fenfluramine NICE review **d)** Fenfluramine may be considered as a 1L adjunct option for a small group of patients clinically considered not suitable to receive clobazam and would be compared to against maintaining a background standard of care without clobazam, stiripentol, or Epidyolex. **NOTE:** In addition to AEDs, ketogenic diet and vagal nerve stimulation are also considered as additional adjunct treatments in the management of seizures in Dravet syndrome. Based on the patient population recruited into the fenfluramine clinical development programme, the proposed product label and existing UK guidelines in the context of discussions with the Dravet Syndrome community, it is anticipated that fenfluramine will be used at various stages of the treatment pathway, including as a 1st line add-on therapy following initial treatment with valproate or topiramate in a few patients not clinically suitable to receive clobazam, and as an alternative and/or add-on to stiripentol, or cannabidiol with clobazam, to form a 2nd and/or 3rd line adjunct therapy option (Figure 1). In the two registration RCTs, fenfluramine was compared against placebo; with (Study 1504) or without (Study 1) stiripentol, on top of a background standard of care that included the patient's existing combinations of AEDs, diet and devices. In these trials, clobazam was included as an option within the patient's background standard of care. However, given the proposed pathway positioning of fenfluramine in the UK, it is plausible that fenfluramine may be	

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		clinically considered after topiramate and/or valproate in patients that are not clinically suitable to receive clobazam (or Epidyolex with clobazam; or stiripentol with clobazam and valproate, per licensed indications). Therefore, fenfluramine could be considered as an alternative first-line add-on treatment option in these patients (Figure 1), and so would be compared against maintaining a background standard of care without clobazam, stiripentol, or Epidyolex. Only a small sub-population of patients within the trials received clobazam without stiripentol (i.e. 1st line adjunct or add on) to enable comparative evidence for a trial-based comparison. At the time of conducting the trials, cannabidiol was not commercially available in Europe or the US and so was not able to be included as a comparator in these trials. However, following the recent NICE recommendation, Epidyolex would now be considered a therapeutic comparator to fenfluramine in UK clinical practice (Figure 1). ***NICE guidance - 1.9.9 Pharmacological treatment of Dravet syndrome*** ***First-line treatment for Dravet syndrome*** *1.9.9.1 Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Dravet syndrome.* ***[new 2012]*** *1.9.9.2 For first-line treatment of Dravet syndrome:* *• Consider topiramate for women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years).* *• Consider sodium valproate or topiramate[14] for boys, men and women who are not of childbearing potential.* *• Do not offer sodium valproate as first-line treatment to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless other options are ineffective or not*	

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		tolerated and the pregnancy prevention programme is in place. Follow the MHRA safety advice on valproate use by women and girls. ***[amended 2020]*** ***Adjunctive treatment in children, young people and adults with Dravet syndrome*** *1.9.9.3 Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 1.9.9.2) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam[14] or stiripentol as adjunctive treatment.* ***[new 2012]*** ***1.9.9.4*** *Do not offer carbamazepine, gabapentin[15], lamotrigine, oxcarbazepine, phenytoin, pregabalin[15], tiagabine or vigabatrin.* ***[new 2012]***	
	Association of British Neurologists (ABN)	Yes, this is reasonable.	Comment noted.
	Dravet Syndrome UK	Comparators reflect our experience of established clinical practice for the treatment of DS.	Comment noted.
Outcomes	Zogenix	The primary and key secondary endpoints in the registration trials for fenfluramine measured 'changes in seizure frequency from baseline' and '% of patients achieving a % reduction (responders) from baseline'. Whilst fulfilling standard regulatory requirements and providing a single metric of effect, these metrics alone have some limitations in clinically and economically characterising the seizure components of the condition in a group of patients with a spectrum of inherently spontaneous and variable seizure frequencies on both a population and patient level. For example, a	Comment noted. The list of outcomes is not exhaustive, therefore information on those specific outcome measures can be submitted.

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		50% reduction from baseline seizures per month, would have different clinical, economic and patient (parent/carer) QoL implications, if patients had experienced 2 or 60 seizures per month at baseline. The following additions to the scope are therefore proposed to assist with characterising the seizures and the effectiveness / meaningfulness of a treatment. Items added in **bold** text are proposed to be added to the scope:. •Seizure frequency (overall & by type): - **Convulsive seizures** **- Non-convulsive seizures** •Response rate **(% and number) relative to the patient's seizures at baseline** (overall & by type) •**Convulsive** seizure severity* •**Seizure free intervals (days), over a defined period of time** **- Cumulative convulsive seizure-free days** **- Average longest convulsive seizure-free period** **- Convulsive seizure-freedom** **•Time to convulsive seizure event (relative between treatments)** •Incidence of status epilepticus •Mortality •Adverse effects of treatment •Health-related quality of life: **- Patient HR-QoL**	Frequency of seizure by type could be considered under seizure frequency. No action required. Absolute and relative changes of seizure severity from baseline could be considered under seizure severity. No action required. Seizure free intervals could be considered under seizure frequency. No action required.

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		- Parent/carer and family HR-QoL It is considered and well-demonstrated (Lagae et al 2018, Baily et al 2018) that parents, carers and the broader family unit (e.g. siblings) also experience a substantial impact on their QoL attributed to the patient's condition. Therefore, in effectively treating the patient, a broader health-related QoL benefit is plausibly experienced (and demonstrated) by a wider group of the patient's care providers and the family unit. In both registration trials (Study 1 and Study 1504), in addition to results on the individual patient's QoL, the change from baseline EQ-5D-5L throughout the studies was also measured for the parents/carer. **Footnotes:** *Whilst contained in the existing draft scope, clarification on 'seizure severity' is sought. The seizure event data collected in the RCTs do not allow for an accurate measurement of seizure duration, only type and time of day. It is proposed that the frequency of the most severe seizure type (generalised tonic clonic seizures) could be derived from the trial dataset and also modelled in the CUA; alongside use of rescue medication as a proxy for a 'severe' seizure event requiring emergency intervention. _____ ***Source:*** *Lagae, L., et al., Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol, 2018.* ***60****(1): p. 63-72.* Bailey et al., *www.zogenix.com/wp-content/uploads/2018/11/2.423_AES-Sibling-QOL.pdf; and www.zogenix.com/wp-content/uploads/2018/11/2.424_AES-Sibling-Psych.pdf*	Carer's quality of life could be considered under health-related quality of life. No action required.

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	Association of British Neurologists (ABN)	Reasonable list. But it is also clear that some measures will not capture important nuances –for example, seizure control may lead to meaningful improvements in cognitive function though these may not be captured using standard crude tools. The paper uses a composite endpoint of mean convulsive seizure frequency (MCSF) which avoids the issue of severity.	Comment noted. Both frequency and severity of seizure are outcomes that will be considered. The list of outcomes is not exhaustive, therefore information on those specific outcome measures can be submitted. No action required.

	Dravet Syndrome UK	Health-related quality of life is included as a QoL measure in the list of outcomes. However, given the burden that living with DS places on families, 'health-related quality of life' may be too narrow a measure to fully capture all quality of life benefits.
		For example:
		• Licheni et al, 2018, highlights the burden of sleep problems, affecting more than 70% of Dravet individuals: 'These sleep problems exacerbate issues such as increasing the likelihood of seizures due to sleep deprivation, impact on the child's learning, and effect on the family's overall quality of life' (p194).
		• A recent longitudinal 10-year follow up study on patients with DS in the UK (conducted by A Brunklaus et al; publication ending) found:
		  • 98% of parents/carers reported that their child/adult's condition had affected their own health
		  • Over 90% of parents/carers reported mental health difficulties (including feelings of depression, anxiety, stress disorders)
			Comment noted. Carer's quality of life could be considered under health-related quality of life. No action required.

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		• In over 90% of families, at least one parent had to either quit their job or cut back on hours due to the burden of looking after a child that's very unwell; this has a significant financial impact on families **We therefore recommend including additional quality of life measures in the list of outcomes that reflect the reduced burden on families e.g. 'Caregiver quality of life'.**	
Economic analysis	Zogenix	Consistent with the reference case: • The time horizon will be life-long • Cost-effectiveness between strategies will be expressed in terms of incremental cost per quality-adjusted life years. • Costs will be considered from an NHS and Personal Social Services perspective. A patient-level microsimulation approach with individual patients modelled (no transitioning through defined health state) is proposed. Each patient has an applied utility and cost associated with their individual experience in the model. Upon discontinuation patients return to their baseline seizure frequency. Seizure-free days (alongside seizures) can be derived and a respective utility can be assigned on a patient-level basis.	Comment noted.
	Association of British Neurologists (ABN)	If fenfluramine is effective, it may need to be used for life. Important cost aspects to include are that of echocardiography/ECG, and the benefits of withdrawal of other antiseizure drugs, that may be expensive – eg stiripentol, cannabidiol.	Comment noted.
	Dravet Syndrome UK	We support the economic analysis described in the draft scope, particularly that costs will be considered from an NHS and Personal Social Services perspective.	Comment noted.

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Equality and Diversity	Zogenix	**Older and adult patients with undiagnosed Dravet syndrome** The diagnosis of Dravet syndrome was initially clinically characterised in the mid-1970s and has only relatively recently been confirmed with genetic testing alongside a clinical diagnosis. At this time an ICD 9/10 code has not been assigned to Dravet syndrome. Today, an estimated 80-95% of children in the UK receive a genetic diagnosis of Dravet syndrome, however, many young adults and adults remain undiagnosed due to their condition not being diagnosed in their early years. These vulnerable, older (mainly adult) patients may currently exist undiagnosed and consequently are not receiving the benefits of optimal care or appropriate treatment; or even treatment that may do them harm*. NICE should consider in their guidance how these patients may be identified to ensure they are not overlooked by current care arrangements. *See also section above. NICE guidance *1.9.9.4 Do not offer carbamazepine, gabapentin[15], lamotrigine, oxcarbazepine, phenytoin, pregabalin[15], tiagabine or vigabatrin* **Weighting a Dravet syndrome patient's Quality of life in the context of 'norms'** Whilst a method to derive and determine a seizure-specific impact to QoL for patients with Dravet syndrome has been used in the RCTs, it is considered that given the potential for patients and their carers to 'cope' with the day-to-day complexities of the patient's condition, as well as the individualised and progressive nature of the syndrome to affect a spectrum of comorbities impacting overall QoL (each with differing severity), the QoL impact from the seizure component of the syndrome is likely to be somewhat muted due to	Comment noted. The appraisal committee can only make recommendations for patient population covered by the marketing authorisation of the technology. It will consider any potential equality considerations identified throughout the appraisal process and whether the recommendations make it more difficult for a particular group to access treatment. No action required. We encourage companies to submit all

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		respective 'progressive ceiling' effects and 'noise' from the complexities of the patient's condition. Despite a dramatic improvement in seizures, in consequence to the underlying and progressive nature of comorbidities associated with the syndrome, patients will experience a progressive deterioration in health and QoL. Patients are therefore unlikely to experience a comparatively 'normal' quality of life to their peers of their same age. It is also unlikely that a 'normal' person experiencing the level of seizures that patients (and their parents/carers/siblings) deal with on a day-to-day basis, would have only a muted impacted to their QoL as observed in trials. A form of adjustment should therefore be provided to enable equality in assessing these QoL data in the context of a population 'norms'. In addition, given the substantial burden of seizures on the carer/parent and broader family unit's QoL, these perspectives should also be fully taken into consideration when appraising the health related benefits of a new treatment for Dravet syndrome.	relevant and available evidence for committee's consideration. Where appropriate and relevant, benefits not fully captured in measures of QoL may be considered by the appraisal committee. No action required.
	Association of British Neurologists (ABN)	Adults without capacity to consent on related matters must not be excluded.	Comment noted.
	Dravet Syndrome UK	No comments.	Comment noted.
Other considerations	Zogenix	No response	Response noted.
	Association of British	No response	Response noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Neurologists (ABN)		
	Dravet Syndrome UK	No comments	Comment noted.
Innovation	Zogenix	The complex and pharmaco-refractory nature of the seizures (as well as the condition more broadly) has meant there are few effective therapeutic options available for patients with Dravet syndrome. In RCTs, open-label extension studies, expanded access programmes and long-term follow up studies, fenfluramine has consistently been shown to have a profound, clinically meaningful and sustained impact to reduce seizures in patients with Dravet syndrome. Fenfluramine therefore provides a transformational change for patients, their parents/carers as well as their siblings, towards living a life without the burden and daily anxiety of seizures and their associated mortality risk. Fenfluramine does provide a substantial step change in the treatment of Dravet syndrome.	Comment noted. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology. No action required.
	Association of British Neurologists (ABN)	Yes, evidence to date suggests fenfluramine is innovative, with potential to make significant and substantial impact in a group of people for whom treatments currently are insufficient. Benefits: see above – meaningful cognitive benefits may not be captured by existing tools. Original peer-reviewed publications should be included in the evaluation, not just references to data summarised on support group websites (good though that might be). e.g.	Comments noted. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology. No action required.

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		Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, Devinsky O, Cross JH, Guerrini R, Talwar D, Miller I, Farfel G, Galer BS, Gammaitoni A, Mistry A, Morrison G, Lock M, Agarwal A, Lai WW, Ceulemans B; FAiRE DS Study Group. Lancet. 2020 Dec 21;394(10216):2243-2254. doi: 10.1016/S0140-6736(19)32500-0. Epub 2019 Dec 17. PMID: 31862249 Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S; FAiRE, DS Study Group. JAMA Neurol. 2019 Dec 2. doi: 10.1001/jamaneurol.2019.4113. [Epub ahead of print]. PMID: 31790543	
	Dravet Syndrome UK	From the published clinical trial data and from the anecdotal feedback of families with DS participating in these trials and/or patient access programmes, we absolutely view fenfluramine as offering a step-change in the management of DS. There have been many very positive stories from our community about children becoming seizure-free or having dramatically improved seizure control, with several families reporting that fenfluramine has transformed their lives* Here are some verbatim examples: • A x-year old boy with DS: '[he] went from having 5-6 tonic clonics a night to having maybe 1-2…We know we will never be seizure free, it's about getting a balance of seizures and life. Fenfluramine has enabled him to take part in days out, and be more involved in activities, no sleepiness in the day.	Comments noted. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		We were very close to putting a lift in our house, he couldn't walk out the front door without getting in a wheelchair, he can now climb the stairs quite happily, stands more upright, walks and runs a small distance. It has helped the whole family feel better about enjoying things and less stressed parents. He does still have nights with maybe 3 seizures, but we know he'll get some nights with 1 or sometimes even none! His schoolwork is better, his overall happiness is better, as he's not being asked to do things when he's trying to recover from loads of seizures. He's on the highest dose. At first his appetite did suffer, and that was hard as he had always eaten well, but now it's totally fine'. • An 11-year old girl with DS: 'Before the study started, she was suffering with 30-60 seizures a day and was unable to walk, only communicated with 1 or 2 words together in a sentence, and was on the verge of having to be tube fed , as her appetite declined so drastically, she barely ate anything. Within 48 hours of being on the trial and during the 'blind testing' her seizures decreased significantly. 1 year & 9 months later, she is now only having between 10-15 seizures a month - compared to her 30-60 a day!! Recovery time from these shortened seizures are also within minutes and not needing rescue medication on many occasions. Her speech has improved and she is recalling information too. She can now count to 20, recognise shapes, colours, and some numbers and letters. She is able to hold a basic conversation and is repeating songs. She is able to walk unattended for short distances and has much improved lower body strength. Her appetite has improved and she is eating full meals'. • Another example is a child with DS whose photosensitivity seizures had previously made it difficult to leave the house. With fenfluramine the photosensitivity was significantly reduced to the extent that the family was able to take a trip together to Disneyland, something they could not have attempted before. Families have reported some side effects including one report of an increase in aggressive behavior, although we cannot confirm if this was drug related.	

Section	Consultee/ Commentator	Comments [sic]	Action
		However generally fenfluramine appears well-tolerated. We're aware that there may be potential for cardiac side effects, but these have not been reported to us as an issue to date. The combination of these improvements - reduction in seizures and side effects, and better health-related quality of life - has a huge impact on overall quality of life for families. Children/adults with DS are able to participate more fully in family life and stress/worry is lessened for parents/carers, potentially improving their mental health. **This data is drawn from comments emailed to DSUK or posted on our closed Facebook group. We can provide anonymised copies if required. Note more than 500 families with a diagnosis of DS are currently registered with DSUK.*	
Questions for consultation	Zogenix	**"Will people with Dravet syndrome continue to use fenfluramine in adulthood?"** -It is anticipated that fenfluramine will receive an indication *as an add on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults.* Transitioning or newly identified adult patients with Dravet syndrome that require treatment, should not be stopped from receiving treatment or prevented from having access to it, for no other reason than on the basis of their age. *-Please also see 'Equality section' above* **Is fenfluramine likely to require additional monitoring for the risk of adverse cardiovascular outcomes such as heart valve disease?** At this time, a risk-benefit assessment of fenfluramine is currently under review by the EMA, alongside any requirements for post-marketing obligations.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Would it be appropriate to use the cost comparison methodology for this topic? Fenfluramine is not similar in its therapeutic class, costs or effects to other available agents in the treatment of Dravet syndrome and so a cost-(utility) effectiveness analysis is appropriate.	
	Association of British Neurologists (ABN)	No response	Response noted.
	Dravet Syndrome UK	No comments	Comment noted.
Additional comments on the draft scope	Zogenix	No response	Response noted.
	Association of British Neurologists (ABN)	Clinicians are likely to consider fenfluramine a better option than cannabidiol. The opportunity to be able to try fenfluramine ahead of cannabidiol should be made available as soon as possible for patient benefit.	Comment noted.
	Dravet Syndrome UK	In summary: • Seizure control is very poor in most people living with DS • People living with DS are in desperate need of more treatment options • DS is not just seizures – co-morbidities can often be more a problematic to manage than the seizures • DS is a devastating condition that effects quality of life for the entire family • A treatment that improves seizure control and quality of life without a high burden of side effects will provide a much needed and welcomed treatment option for Dravet patients of all ages	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

ESNA - Epilepsy specialist Nurses association