National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Fenfluramine for treating Dravet syndrome

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Zogenix	We believe it would be appropriate to refer this topic to NICE for appraisal	Comment noted.
	Association of British Neurologists (ABN)	An appropriate and timely referral to NICE.	Comment noted.
	Paediatric Neuroscience CRG	Yes	Comment noted.
	Dravet Syndrome UK	Yes	Comment noted.
	Epilepsy Nurses Association	This seems to be an appropriate remit given the Dravet population entering adulthood and the issues surrounding prescribing Steripental. It is essential to have alternative treanment options	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Zogenix	Yes, we believe it is appropriate.	Comment noted.
	Association of British Neurologists (ABN)	Appropriate.	Comment noted.
	Paediatric Neuroscience CRG	Yes	Comment noted.
	Dravet Syndrome UK	Yes	Comment noted.
	Epilepsy Nurses Association	Good background to Dravet	Comment noted.
Timing Issues	Zogenix	We would like to ensure that the appraisal is concluded as soon as possible following regulatory approval	Comment noted.
	Association of British Neurologists (ABN)	People with Dravet syndrome continue to have seizures despite available treatment. There is a pressing need for alternative treatment.	Comment noted.
	Paediatric Neuroscience CRG	No response	Response noted.
	Dravet	Urgently	Comment noted.

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	Syndrome UK		
	Epilepsy Nurses Association	May have some difficulty due to increased media coverage of Cannabidiol and the increase in parental requests for this treatment	Comment noted.
Additional comments on the draft remit	Zogenix	None	Response noted.
	Association of British Neurologists (ABN)	n/a	Response noted.
	Paediatric Neuroscience CRG	No response	Response noted.
	Dravet Syndrome UK	The Dravet community is in desperate need of more treatment options. The clinical trial results are very promising and where it may not help everyone it has proven to help some. We urgently need access and to see the affects Fenfluramine could have once licenced.	Comment noted.
	Epilepsy Nurses Association	No response	Response noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Zogenix	We would suggest revising the text to improve its accuracy and completeness. The suggested revised text is below:	Comment noted. The background section

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		Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy (SMEI), is a rare, severe, treatment-resistant, developmental epileptic encephalopathy (occurring I in 15,700-40,000 live births) commencing before the age of 12 months and continuing throughout the patient's life. Thus, there are both children and adults affected. In 80% of cases the condition is associated with a genetic mutation in the SCN1A gene, affecting the correct function of brain cells.[1-5] Seizures in Dravet syndrome begin within the first year of life, and are characterised by initial prolonged seizures accompanying a fever (febrile seizures), which are typically associated with one side of the brain (lateralisation). Subsequently affected children develop long-term refractory and multiple seizure types (including myoclonic, absence, focal and generalised tonic–clonic seizures) together with cognitive and motor impairments and other significant co-morbidities. Dravet syndrome is characterised by a high epilepsy-related premature mortality (around 20%) and a marked young age at death. Sudden unexpected death in epilepsy (SUDEP) accounts for nearly half of these deaths, most of the remainder by status epilepticus (SE).This state of continuous seizure requires frequent emergency care and hospital admission even when not leading to death..[3,5,6] *Dravet syndrome seizures are primarily manged with anti-epileptic drugs, and may also be supported by a ketogenic diet or vagus nerve stimulation. NICE clinical guideline 137 recommends sodium valproate or topiramate as first-line treatment options, and if seizures are inadequately controlled, clobazam or stiripentol are recommended as adjunctive treatment. Many children with Dravet syndrome seem to respond best to a specific combination of sodium valproate, stiripentol and clobazam.[5]* References:	is intended as a brief overview of the disease area, therefore few amendments required. To reflect the causes of mortality more clearly the final line of paragraph 2 has been amended to read "Sudden unexpected death in epilepsy (SUDEP) and status epilepticus cause around half and a third of deaths in this condition respectively."

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		1 European Medicines Agency (2014) Public summary of opinion on orphan designation Fenfluramine hydrochloride for the treatment of Dravet syndrome. Accessed May 2018 2 Dravet Syndrome UK (2016) What is Dravet syndrome. Accessed May 2018 3 Dravet Syndrome UK (2016) Facts about Dravet Syndrome. Accessed May 2018 4. Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011; 52:3-9 5. Scheffer IE. Diagnosis and long-term course of Dravet syndrome. Eur J Pediatr Neurol 2012; 16:S5-S8 6 Shmuely S (2016) Mortality in Dravet syndrome: A Review. Epilepsy & Behavior 64, 69–74 7 Epilepsy Action (2016) Dravet syndrome. Accessed May 2018	
	Association of British Neurologists (ABN)	Accurate.	Comment noted.
	Paediatric Neuroscience CRG	Yes	Comment noted.
	Dravet Syndrome UK	Dravet syndrome is extremely drug resilient and hard to control and manage. People with Dravet syndrome are at a higher risk of SUDEP than those with	Comment noted. The background section

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		other epilepsy conditions. . Dravet Syndrome is also not always a genetic diagnosis, it can also be diagnosed through clinical presentation	is intended as a brief overview of the disease area, therefore few amendments required. To reflect the causes of mortality more clearly the final line of paragraph 2 has been amended to read "Sudden unexpected death in epilepsy (SUDEP) and status epilepticus cause around half and a third of deaths in this condition respectively."
	Epilepsy Nurses Association	Good description of Dravet given	Comment noted.
The technology/ intervention	Zogenix	Yes	Comment noted.
	Association of British Neurologists (ABN)	Accurate.	Comment noted.
	Paediatric Neuroscience	Yes	Comment noted.

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	CRG		
	Dravet Syndrome UK	Yes	Comment noted.
	Epilepsy Nurses Association	No response	Response noted.
Population	Zogenix	All the medicines (and interventions) listed target seizures. We would suggest the wording is revised to more accurately state: People with Dravet syndrome *whose seizures are* inadequately controlled by current clinical management, which *may* include combinations of: …	Comment noted. The text in the population section has been amended as suggested.
	Association of British Neurologists (ABN)	Population is defined appropriately. There is no sub- population that needs separate consideration.	Comment noted.
	Paediatric Neuroscience CRG	Suggest add topiramate to the list of anti-convulsant medication given (ie the medications which have not led to adequate control of symptoms)..	Comment noted. Topiramate is currently included in the list of medication. No action required.
	Dravet Syndrome UK	Some of these drugs are spelt incorrectly. Stiripentol Topiramate	Comment noted. The typographical errors have been

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			corrected.
	Epilepsy Nurses Association	Population adults or Paeds?? Or both	Comment noted. The wording of the scope allows for consideration of both the adult and paediatric population. The population considered in the appraisal is dependent on the wording of the marketing authorisation.
Comparators	Zogenix	We agree on the approach of describing the comparator as 'established clinical management without fenfluramine' as there is no single established standard of care.	Comment noted.
	Association of British Neurologists (ABN)	Appropriate.	Comment noted.
	Paediatric Neuroscience CRG	Yes – standard treatment with anticonvulsant medications (valproate, stiripentol, clobazam combination +/- topiramate/ levetiracetm), non-medical treatments – VNS / ketogenic diet..	Comment noted.
	Dravet Syndrome UK	No response.	Response noted.

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	Epilepsy Nurses Association	List seems complete	Comment noted.
Outcomes	Zogenix	We would suggest addition of the following • Responder rate (the preferred endpoint of EMA for evaluation of AEDs (CHMP/EWP/566/98 Rev.2/Corr)) • Seizure free interval (in addition to proportion of patient seizure free) • Caregiver HRQoL (in addition to Patient HRQoL)	Comment noted. Responder rate has been included as an outcome, this encompasses patients who have a reduction in seizures or are seizure free. Seizure free interval could be considered under seizure frequency. Care giver-related quality could be considered under health-related quality of life or could be captured within the innovation section.
	Association of British Neurologists (ABN)	Appropriate but should also include those with episodes of status epilepticus.	Comment noted. “Incidence of status epilepticus” has been added as an outcome.

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	Paediatric Neuroscience CRG	Suggest identify proxy measures of seizure severity – eg number of doses of rescue medication needed over defined period, number of hospital admissions because of seizures, number of episodes of status epielpeticus.	Comment noted. "Incidence of status epilepticus" has been added as an outcome. Proxy measures of seizure severity could be considered under seizure severity.
	Dravet Syndrome UK	Reduced seizure control and a positive affect on cognitive function	Comment noted. Reduced seizure control could be considered under seizure frequency. Effect on cognitive function could be considered under health-related quality of life.
	Epilepsy Nurses Association	Outcomes seem to be easily measurable and what is commonly used to measure effectiveness	Comment noted.
Economic analysis	Zogenix	No comment	Comment noted.
	Association of British Neurologists (ABN)	No response	Response noted.

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	Paediatric Neuroscience CRG	No response	Response noted.
	Dravet Syndrome UK	No response	Response noted.
	Epilepsy Nurses Association	Would need to be clear of cost of drug compared to current treatments as this would determine prescribing	Comment note
Equality and Diversity	Zogenix	No issues identified.	Comment noted.
	Association of British Neurologists (ABN)	Adults with Dravet syndrome should not be excluded from consideration.	Comment noted. The population under consideration in the appraisal is dependent on the marketing authorisation of the intervention.
	Paediatric Neuroscience CRG	No problem foreseen	Comment noted.
	Dravet Syndrome UK	No response	Response noted.
	Epilepsy Nurses Association	No response	Response noted.

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Other considerations	Zogenix	None	Comment noted.
	Association of British Neurologists (ABN)	No response	Response noted.
	Paediatric Neuroscience CRG	No response	Response noted.
	Dravet Syndrome UK	No response	Response noted.
	Epilepsy Nurses Association	No response	Response noted.
Innovation	Zogenix	Do you consider fenfluramine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *Dravet Syndrome seizures are highly treatment resistant and fenfluramine has demonstrated significant seizure reduction and seizure freedom in excess of those observed with other therapies* Do you consider that the use of fenfluramine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *It's likely that the use of fenfluramine will have HRQoL benefits that extend to*	Comments noted. Carer HRQoL will be considered by the committee at the appraisal committee meeting.

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		caregivers. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. *We have included measures of caregiver HRQoL in our Phase 3 programme.*	
	Association of British Neurologists (ABN)	We consider that the technology is a step change.	Comment noted.
	Paediatric Neuroscience CRG	Yes. Trial data presented at international meetings with fenfluramine as add on treatment with and without stiripentol.	Comment noted.
	Dravet Syndrome UK	If the results continue to be positive then this could be a very important treatment for many of the Dravet community	Comment noted.
	Epilepsy Nurses Association	No response	Response noted.
Questions for consultation	Zogenix	Have all relevant comparators for fenfluramine been included in the scope? Which treatments are considered to be established clinical practice in the NHS for the treatment of Dravet syndrome? *The seizures associated with Dravet Syndrome are recognised as being treatment resistant. Currently only one medicine is licensed by EMA for the treatment of the seizures associated with Dravet Syndrome (Stiripentol). Most patients are treated with sodium valproate, topiramate, clobazam, stiripentol, levetiracetam used in various combinations. In addition, patients*	Comments noted.

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		some patients follow a ketogenic diet and/or receive vagal nerve stimulation. Are the outcomes listed appropriate? *We would suggest a modified list of outcomes* • *Responder rate* • *seizure frequency* • *proportion of people seizure-free* • *seizure free interval* • *mortality* • *adverse effects of treatment* • *Patient HRQoL* • *Caregiver HRQoL* *We consider these to be appropriate and have been validated with EMA for inclusion in our Phase 3 trials* Are there any subgroups of people in whom fenfluramine is expected to be more clinically effective and cost effective or other groups that should be examined separately? *No, we consider that fenfluramine may be an appropriate therapeutic option for all patients experiencing seizures associated with Dravet Syndrome.*	

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		Will people with Dravet syndrome continue to use fenfluramine in adulthood? *Its likely that any patients initiated on fenfluramine in childhood will continue on therapy depending on clinical need.* Where do you consider fenfluramine will fit into the existing NICE pathway, 'Epilepsy (2016)'? *We consider that fenfluramine would be included as an adjunctive treatment option as per clobazam or stiripentol in the current guideline.* Is fenfluramine likely to require additional monitoring for the risk of adverse cardiovascular outcomes such as heart valve disease? *Yes, we expect that patients will require periodic echocardiographic monitoring during treatment.*	
	Association of British Neurologists (ABN)	**Please see responses to questions (highlighted) from Appendix B, pages 3 + 4.** **Page 3: Questions for consultation** 'Have all relevant comparators for fenfluramine been included in the scope? Which treatments are considered to be established clinical practice in the NHS for the treatment of Dravet syndrome?' **Yes.**	Comments noted.

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		'Are the outcomes listed appropriate?' **Yes and should also include status episodes.** Are there any subgroups of people in whom fenfluramine is expected to be more clinically effective and cost effective or other groups that should be examined separately? **No subgroup beyond Dravet syndrome.** Will people with Dravet syndrome continue to use fenfluramine in adulthood? **Absolutely.** Where do you consider fenfluramine will fit into the existing NICE pathway, 'Epilepsy (2016)'? **For Dravet syndrome only, after failure of the first line.** Is fenfluramine likely to require additional monitoring for the risk of adverse cardiovascular outcomes such as heart valve disease? **Yes** **Page 4 questions:** NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Fenfluramine will be licensed; **Adults** • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the	

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		technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Do you consider fenfluramine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Yes** Do you consider that the use of fenfluramine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Should include measures of alertness, interaction and behaviour change** Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. **Cost, processes, difficulties with obtaining echo.**	
	Paediatric Neuroscience CRG	Continuation in adults – yes, if symptoms controlled with treatment. How this will fit in existing NICE pathways – this would probably be used after failure of symptom control with existing anticonvulsant combinations.	Comments noted.

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		No barriers to putting treatment into practice are anticipated if it is adopted.	
	Dravet Syndrome UK	No response	Response noted.
	Epilepsy Nurses Association	1) Reviewing one clinical trial paper the results were positive although the study was small in numbers 2) Cost of the drug I cannot locate the cost anywhere so no comparison to current treatments although I know Stiripentol is expensive 3) Usual therapy Valproate and Clobazam 4) Stiripentol often also prescribed via tertiary centres but funding not always agreed at CCG level so can be disputes re ongoing treatment 5) Who would initiate the prescribing of the drug . Specialist Consultants, Tertiary centres 6) Would secondary care/GP's continue with the prescriptions 7) Given the cost of the drug who would pay for ongoing treatment tertiary centres or an individual basis from CCG's approved funding 8) Given population group receiving the drug those with-Intellectual Disabilities cardio checks are likely to be required due to side effects previously highlighted hence why it was withdrawn from the market previously. Who would be responsible to ensure the cardio checks 9) Consideration of side effects loss of appetite given the initial indication of the drug	Comments noted.
Additional	Zogenix	None	Comment noted.

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comments on the draft scope	Association of British Neurologists (ABN)	No response	Response noted.
	Paediatric Neuroscience CRG	No response	Response noted.
	Dravet Syndrome UK	No response	Response noted.
	Epilepsy Nurses Association	If effective, fenfluramine would be continued, or perhaps, in some cases, initiated in adulthood	Comment noted.

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

Department of Health and Social Care