National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over

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	Orion Pharma (UK) Ltd	Yes, Orion agree that ganaxolone should be referred to NICE for appraisal given the high unmet need in CDD (please see comments to "Background information" below). However, Orion believes that the appraisal is more suited to the highly specialised technology (HST) route rather than the proposed single technology appraisal route (STA). Please see below also Section "Questions for consultation" for further comment and justification. Further, as a consequence of the very low incidence of CDD, and thus the small number of patients with complex refractory seizures, scattered across the country, there is a lack of experience and extensive knowledge of the condition among neurologists/ paediatricians. Without national commissioning, this is likely to drive inequality between patients in different regions of the country, in obtaining appropriate treatment.	Thank you for your response. This topic has been routed to the technology appraisal programme.
	CDKL5 UK	Yes	Thank you for your response. No action needed.

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	Genetic Alliance UK	-	Thank you for your response. No action needed.
Wording	Orion Pharma (UK) Ltd	Orion agree with the specified remit	Thank you for your response. No action needed.
	CDKL5 UK	Yes	Thank you for your response. No action needed.
Timing Issues	Orion Pharma (UK) Ltd	There is an urgent unmet need for better therapies in CDD. [redacted]	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.
	CDKL5 UK	CDKL5 Deficiency is associated with difficult to control epileptic seizures, despite many children being prescribed multi anti-epileptic drugs (AED's). There is a strong view that uncontrolled epilepsy compromises development and reduces the quality of life for these individuals. Effective anti-seizure	Thank you for your comment. No action needed.

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		medication is therefore essential to help try and improve their development and quality of life.	
	Genetic Alliance UK	-	Thank you for your response. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Orion Pharma (UK) Ltd	Orion suggests to replace the section with the following text (changes/additions in italics): "Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a disease caused by mutations in the CDKL5 gene, which provides instructions for making proteins essential for normal brain and neuron development. The mutation results in a reduction in the amount of CDKL5 protein produced[1]. CDD is characterised by seizures and neurodevelopmental delay and can manifest in a broad range of clinical severity[2]. Often the first symptom of CDD is seizures that occur within the first few months of life with most children experiencing 1-5 seizures a day[3]. Other common symptoms include hypotonia, cortical visual impairment and learning and motor disabilities[4]. *CDD is classified as a developmental and epileptic encephalopathy, causing severe, chronic debilitation and high care burden for the families. High seizure burden in severe epilepsy can have a direct adverse effect on cognition (Epilepsia, 2005; 46(11):1780–1787), and could potentially have further negative contribution on the child´s overall development.* CDD occurs approximately in 1 in 40,000 to 1 in 60,000 live births[2]. Most CDKL5 mutations are not inherited, and instead usually occur spontaneously.	Thank you for your comments. The background section is intended to provide a brief summary of the condition. Therefore, these suggested changes have not been adapted verbatim. However, broader changes to the background section have been made in response to stakeholder comments received at consultation and during the workshop.

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		ONS figures show 613,936 live births in England and Wales in 2020, suggesting 10 to 15 people are born each year with CDD. CDD affects four times as many females as males (the CDKL5 gene is found on the X chromosome), but males may experience a more severe disease[2]. The genetic cause of CDD was first identified in 2004*, with diagnosis occurring in early childhood and only sporadic diagnosis* reported in the adult population in their 40s and 50s[5]. Data surrounding the long-term prognosis and survival is not available[5] and *therefore prevalence is not well understood*. *However, according to the Bristol Centre of Excellence for CDD* [redacted]*, there are currently only 50 to 60 diagnosed patients with CDD in England.* *Of the total CDD population those in need of adjunctive treatment would be in the target population of ganaxolone, as per the intended labelling. Thus, both CDD as well as the target indication of ganaxolone can be considered ultra-orphan conditions.* *Currently, there is no cure, nor any specifically approved treatments for patients with CDD. Frequent seizures are reported by caregivers to be among the most burdensome issues in caring for their child (https://www.cdkl5.com/wp-content/uploads/2020/06/CDD-VoP-REPORT.pdf). There are several anti-seizure therapies, which can be given either as a monotherapy or in combination. Some people might also try a ketogenic diet or steroids, and in absence of effective medications, vagal nerve stimulation or other surgical interventions.* *Unfortunately, improvement in seizure control with the currently available therapies may be short lived, and already within 6-12 months patients report diminished efficacy of ASMs (Müller A, et al. Eur J Paediatr Neurol. 2016;20(1):147-151). Indeed, in a significant share of CDD patients seizures become refractory to treatment with existing ASMs; approximately 84% of*	

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		patients experience treatment-resistant, refractory seizures (Int J Genomics. 2019:6956934). *Thus, there is an urgent unmet need for better seizure control in this population, and access to improved medication is considered essential for the children and families affected.*	
	CDKL5 UK	"Often the first symptom of CDD is seizures that occur within the first few months of life with most children experiencing 1-5 seizures a day3" "1-5 seizures" downplays the severity of the seizures in CDD. They are often clusters of many spasms in one seizure and can be prolonged.	Thank you for your comment. The background section has been amended following discussions at the scoping workshop to reflect the uncertainty surrounding how seizures are categorised and recorded.
	Genetic Alliance UK	Following discussions with CDKL5 UK, we feel that the background information doesn't accurately reflect the severity of the condition. The background states that most children experience 1-5 seizures a day however we have been informed by CDKL5 UK that parents often do not report all seizure types, for example cluster spasms. Parents and individuals often only report the full body tonic-clonic seizures as that is what is widely understood to be a seizure.	Thank you for your comment. The background section has been amended following discussions at the scoping workshop to reflect the uncertainty surrounding how seizures are

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		CDKL5 UK gave an example of a child with the condition who experienced approximately 75 seizures a day, varying in type. Spasms are seen to be less severe but frequent spasms throughout the day, every day, has a huge impact on a person's ability to carry out daily tasks and therefore impact their quality of life. It is also worth noting that the unpredictable timing, length, severity and type of a seizure means that families are not only affected by them while they are occurring. The anticipation of seizures also has an impact.	categorised and recorded.
The technology/ intervention	Orion Pharma (UK) Ltd	Yes	Thank you for your response. No action needed.
	CDKL5 UK	Yes	Thank you for your response. No action needed.
Population	Orion Pharma (UK) Ltd	Yes, the population definition is appropriate. Please note that due to the relatively small pivotal study in an orphan population any strong conclusions regarding subgroups may not be feasible.	Thank you for your response. No action needed.
	CDKL5 UK	Yes	Thank you for your response. No action needed.
Comparators	Orion Pharma (UK) Ltd	Yes, the proposed comparator definition is appropriate.	Thank you for your comment. No action needed.

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	CDKL5 UK	Standard clinical pathway for Epilepsy is used in the NHS for CDD, this isn't always the best course of action due to the severity of the seizure disorder in CDKL5 and impact on quality of life.	Thank you for your comment. No action needed.
Outcomes	Orion Pharma (UK) Ltd	Orion proposes that the outcome measures should also include change in seizure intensity and duration.	Thank you for your comment. The suggested outcomes are considered to be relevant to broader outcomes already included within the scope. No action needed
	CDKL5 UK	Yes	Thank you for your comment. No action needed.
Economic analysis	Orion Pharma (UK) Ltd	Orion considers that the cost effectiveness threshold generally used by NICE within STAs would not be appropriate to assess ganaxolone given (i) the rarity of the disease and the consequent limited evidence base, both with and without ganaxolone treatment, and (ii) important benefits provided will not be captured by the quality adjusted life years measure of health benefit (e.g. benefit to carers). Orion requests NICE to reconsider its proposal to assess ganaxolone under the STA programme and rather assess it under the HST programme. We agree with the principle of life-time modelling in chronic disease.	Thank you for your response. This topic has been routed to the technology appraisal programme. Cost assumptions in the model will be

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		Within the cost-effectiveness or the budget impact analyses Orion believes that no additional costs for genetic testing should be associated with a prescription for ganaxolone. In NHS England genomic testing is generally offered to patients with rare early onset or syndromic epilepsy (https://www.england.nhs.uk/publication/national-genomic-test-directories/). CDD presents with seizures in infancy, that quickly become challenging to manage and other features of the complex disease start to become apparent as well.	considered in detail as part of the full appraisal.
Equality and Diversity	Orion Pharma (UK) Ltd	No additional comment.	Thank you for your response. No action needed.
Other considerations	Orion Pharma (UK) Ltd	No additional comment	Thank you for your response. No action needed.
	Genetic Alliance UK	Individuals affected by CDKL5 experience sleeping difficulties which is not mentioned in the draft scope. Sleeping disturbances have a large impact on quality of life not just for the individual but also for parents and therefore should be included in the scope.	Thank you for your comment. The background section has been amended following discussions at the scoping workshop to include sleeping difficulties.
Innovation	Orion Pharma (UK) Ltd	The complexity of CDD and the refractory nature of the seizures has meant there are few effective therapeutic options available for patients with CDD. At present, there are no curative, or other treatments specifically developed and	Thank you for your comment. During the development of the appraisal, the

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		approved for patients with CDD. Ganaxolone will represent the first treatment specifically indicated for use in this patient group. Ganaxolone has been shown to have a significant and clinically meaningful impact by reducing the monthly major motor seizure frequency in people with CDD (Marigold Study), with little additional side effect burden. It also appears to provide prolonged maintenance of the effect, if comparing the Marigold open-label extension data to literature (see "Background information"). Ganaxolone offers transformational change for people and their families towards a life with a reduced burden of seizures and associated sequelae.	committee will consider the degree to which ganaxolone is an innovative technology when making its recommendations. No action needed
	CDKL5 UK	Yes – seizure management in CDD remains problematic despite children and adults being prescribed multiple AED's which can have a significant impact on Quality of Life. Reference Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. Müller, A., Helbig, I., Jansen, C., Bast, T., Guerrini, R., Jähn, J., Muhle, H., Auvin, S., Korenke, G. C., Philip, S., Keimer, R., Striano, P., Wolf, N. I., Püst, B., Thiels, C. h., Fogarasi, A., Waltz, S., Kurlemann, G., Kovacevic-Preradovic, T., Ceulemans, B., … Kluger, G. European journal of paediatric neurology, 20(1), 147–151. (2016) https://doi.org/10.1016/j.ejpn.2015.09.001	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which ganaxolone is an innovative technology when making its recommendations. No action needed
Questions for consultation	Orion Pharma (UK) Ltd	**How should best supportive care be defined?** Best supportive care has not been defined for CDD, as there is no CDD specific guideline available and CDD is not specifically identified in the current NICE epilepsy diagnosis and management guidelines. At present, there are	Thank you for your comments. The appraisal committee will discuss

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		no treatments specifically developed and approved for patients with CDD. The current consists of non-specific ASM treatments as well as ketogenic diet and vagal nerve stimulation. These were all permitted during the Marigold study. The CDKL5 Centre of Excellence works in partnership with regional medical teams, by providing specialist clinical input as well as focused pastoral care and support. **Where do you consider ganaxolone will fit into the existing NICE epilepsy pathway?** It is likely that treatment will be initiated under the guidance of expert centres due to the complex nature of CDD. Patients with CDD will be treated according to section '1.10 Referral for complex or refractory epilepsy'. Management of CDD requires input from a multi-disciplinary team of experts. **Do you consider that the use of ganaxolone can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** CDD is a complex and chronically debilitating condition that places a huge burden not only on the person with the condition, but also their parents/carers and the entire family. Benefits such as impact on carers may not be fully captured by the quality adjusted life years measure of health benefit. **Comments on the appropriateness of NICEs intention to appraise the technology in the STA process:**	the appropriate definition of "established clinical management without ganaxolone" during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence, and current clinical practice. Where possible, evidence should be provided that shows CDD has a substantial effect on carer's health-related quality of life and how ganaxolone affects carers. This topic has been routed to the technology appraisal programme.

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		In our view the technology fulfils the current criteria for selection into HST process (See: https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies) as follows: 1) *The disease is very rare, defined as a disease that has a prevalence in England lower than 1 in 50,000 people, or about 1,100 people.* As indicated above the known, diagnosed CDD cases (prevalence) is currently 70-100 patients in the UK (currently 50 to 60 in England), with an estimated ~10-15 more children being born each year in England and Wales. 2) *Normally, no more than 300 people in England are eligible for the technology in its licensed indication.* [redacted] Therefore, the target population is likely to be well below the 300 threshold (as per point 1 above). 3) *The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life* CDD is a rare complex and chronically debilitating condition characterized by refractory seizures, severe global developmental impairment, and multiple comorbidities. All patients with CDD experience intellectual disability and severe global developmental impairment (Pediatr Neurol. 2019 Aug; 97: 18–25). See “Background Information” for further justification. 4) *There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options*	

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		Caregivers paint a bleak picture of current treatment options for children and young people with CDD, who early on are cycled through anti-epileptic drugs, sometimes combined with diets (ketogenic or Atkins) which at best work only for a short time and yield only partial benefits, often at a cost of making some of the child's other symptoms worse and decreasing engagement and skill acquisition.(The Voice of the Patient Report: CDKL5 Deficiency Disorder (CDD) 2020 https://www.cdkl5.com/wp-content/uploads/2020/06/CDD-VoP-REPORT.pdf) There is a high unmet need for improved therapy options. It is Orion´s view that ganaxolone should be included in the HST process, rather than STA.	
	CDKL5 UK	Which treatments are considered to be established clinical practice in the NHS for seizures caused by CDKL5 deficiency disorder? Specifically, which anti-seizure drugs are used? **Many individuals are taking multiple AED's and continue to have significant seizures. Vigabatrin which is used in infantile spasms appears to have a good efficacy, but it is not always prescribed in older children who may not present with hypsarrhythmia.** **Vagus nerve stimulation is used in this population of children**. Do you consider ganaxolone to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might	Thank you for your response. No action needed.

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		improve the way that current need is met (is this a 'step-change' in the management of the condition)? **As discussed currently there are no CDD specific pathways to control epilepsy in these patients. Ganaxolone has the potential to substantially impact on health-related benefits provided patients are able to reduce the amount of concurrent seizure medications that they take.** Do you consider that the use of ganaxolone can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Concurrent use of AED's can impact significantly on patients, particular where they may also suffer with respiratory problems, as some AED's increase secretions and increase the risk of aspiration and pneumonia. Ganaxalone has the potential to reduce the number of AED's being prescribed in some patients which could improve overall health, and morbidity	

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

N/A