NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ganaxolone within its marketing authorisation for treating seizures caused by CDKL5 deficiency disorder (CDD) in people aged 2 years and over.

Background

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]. The genetic cause of CDD was first identified in 2004 so data surrounding the long-term prognosis and survival is not available[5]. However, it has been reported that some adults have been diagnosed with CDD in their 40s and 50s[5].

Most CDKL5 mutations are not inherited, and instead usually occur spontaneously. Mutations are believed to occur in approximately 1 in 40,000-60,000 live births[2], suggesting 11-17 people are born with CDD a year in England and Wales. CDD effects 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].

There is currently no specific treatment or cure for CCD. Instead, early intervention with a multidisciplinary approach to manage symptoms is recommended[1]. 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. If people are refractory to anti-seizure therapies, they may benefit from vagus nerve stimulation or other surgical interventions.

The technology

Ganaxolone (brand name unknown, Orion Pharma) is a synthetic analogue of the natural neurosteroid allopregnanolone that is a positive allosteric modulator of the γ-aminobutyric acid type A receptor. It is administered as an oral suspension.

Ganaxolone does not currently have a marketing authorisation in the UK for treating seizures caused by CDD. It has been studied in clinical trials in people two and over with CDD related seizures in combination with existing anti-seizure treatment.

Intervention	Ganaxolone
Population	People two years of age or older with seizures caused by CDD
Comparators	Established clinical management without ganaxolone
Outcomes	The outcome measures to be considered include: • seizure frequency (overall and by seizure type) • proportion of people seizure-free (overall and by seizure type) • seizure severity • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing for CDKL5 gene mutations in people with CDD who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** None **Related Guidelines:** 'Epilepsies: diagnosis and management' (2012). NICE guidelines CG137 Expected updated publication date April 2023, consultation Dec 2021. **Related Interventional Procedures:** 'Deep brain stimulation for refractory epilepsy in adults' (2020). NICE interventional procedures guidance IPG678. 'MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy' (2020). NICE interventional procedures guidance IPG671. 'Vagus nerve stimulation for refractory epilepsy in children' (2004). NICE interventional procedures guidance IPG50. **Related Quality Standards:** 'Epilepsy in adults' (2013). NICE quality standard QS26 'Epilepsy in children and young people' (2013). NICE quality

	standard QS27 **Related NICE Pathways:** Epilepsy (2016) NICE pathway
Related National Policy	Department of Health & Social Care (2021) The UK Rare Diseases Framework NHS England (2020) Implementation Plan for the UK Strategy for Rare Diseases – progress report. The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapters 11,78,119 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 2 and 4.

Questions for consultation

Have all relevant comparators for ganaxolone been included in the scope?

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?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom ganaxolone is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ganaxolone will fit into the existing NICE epilepsy pathway?

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 ganaxolone will be licensed;
- 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 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 ganaxolone 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)?

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?

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.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1- National Organization for Rare Disorders (2020). CDKL5 Deficiency Disorder. Accessed December 2021

2- Jakimiec M, Paprocka J and Smigiel R (2020). CDKL5 Deficiency Disorder—A Complex Epileptic Encephalopathy. Accessed December 2021

3- Genetic and Rare Diseases Information Center (2021). CDKL5 deficiency disorder. Accessed December 2021

4- Olson HE et al. (2019). Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review. Accessed December 2021

5- The International Foundation for CDKL5 Research (2021). About CDKL5. Accessed December 2021