Highly Specialised Technologies (HST) criteria checklist

**Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over ID3988**

### Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see [section 7 of NICE health technology evaluation topic selection: the manual](https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies)

### Key – does the technology meet the criteria? Please use the colour key to advise if the technology meets the criteria

|  |  |
| --- | --- |
| Met  | There is clear and strong evidence that this criterion is met |
| Unclear | There is some evidence, or the evidence available is unclear. |
| Not met | There is no evidence or limited evidence that the criterion is met.  |

### MA wording: \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

| **Number** | **Criterion** | **Description of how the technology meets the criteria**  | **Does the technology meet the criteria?** |
| --- | --- | --- | --- |
|  | The condition is very rare defined by 1:50,000 in England  | **Company comments on HST checklist:*** Company provided two references for reported incidence
	+ 1.77 per 100,000 births *(Brain 2020: 143; 1099–1105)*
	+ 1 in 40,000 to 1 in 60,000 live births *(Pediatr Neurol. 2019 Aug; 97: 18–25)*
* ONS figures show 613,936 live births in England and Wales in 2020 based on this figure.
	+ Brain 2020- 10.9 people born each year with CDD
	+ Pediatr Neurol 2019 -10.2 to 15.3 people born each year with CDD

For prevalence, the company stated that currently less than 100 people diagnosed with CDD in the UK, with an estimate of 50 to 60 patients in England **Scoping workshop and consultation comments:*** A clinical expert suggested that the Brain paper might not be reliable as it only looked at the Scottish population and was based on only 2 to 3 cases of CDD.
* Clinical and patient experts commented that it is difficult to arrive at an exact figure but that the 10-15 people a year (1 in 40,000 to 1 in 60,000) figure is reasonable.

**Summary** Based on the above, this criterion is very likely met.  | **Met** |
|  | Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications  | **Company comments on HST checklist:*** Diagnosed CDD cases (prevalence) is currently less than 100 case in the UK, with an estimate of 50 to 60 patients in England (Bristol Centre of Excellence for CDD
* The target population of ganaxolone as per intended indication \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Therefore, the target population is likely to be well below the 300 threshold, considering the information above

**Scoping workshop and consultation comments:*** Clinical and patient experts were not able to provide an exact figure for the eligible patient number.
* The clinical experts explained that most people with CDD do experience seizures.
* The clinical experts explained that historically not everyone with CDD will have received a diagnosis, but now all children presenting with seizures will receive an epilepsy gene panel.
* The clinical and patient experts agreed that the total CDD population could be ≈200, but there is a lot of uncertainty.
* The clinical experts suggested that a high proportion of those with CDD would be eligible to receive ganaxolone, but there are other treatments that would be tried first.
* Although \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

**Summary** The disease is very rare and likely to be well below 300. Although the drug has been studied in other indications, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.  | **Met** |
|  | The very rare condition significantly shortens life or severely impairs its quality  | **Company comments on HST checklist:*** “All patients with CDD experience intellectual disability and severe global developmental impairment”.
* “Daily seizures are reported in approximately 80% of patients, with 20% experiencing weekly to monthly seizures”.
* “Approximately 84% of patients with CDD will ultimately experience treatment-resistant, refractory seizures”.
* “High seizure burden in severe epilepsy can have a direct adverse effect on cognition and could potentially have further negative contribution to the child´s overall development”.
* “Beyond the seizures, the vast majority of patients also experience generalized hypotonia, cortical vision disorders, hand stereotypies and sleep-related disorders, spreading the entire sleep spectrum”.

**Scoping workshop and consultation comments:*** Patient/carer groups stated how severe and frequent the seizures experienced by people with CDD can be as well as how anticipating the seizures can impact families.
* The patient expert explained that there are some people with mild to moderate CDD who are in mainstream education and that they often experience less severe seizures but can experience other symptoms related to CDD.
* However, the clinical experts explained that mild CDD is uncommon and that at least 90% of people with CDD could be classed as severe or profound.
* The clinical experts explained that given the heterogeneity, rarity, and recent discovery of CDD it is currently very difficult to quantity average life expectancy.

**Summary** From the data above it is not possible to make a judgement on the impact of the disease on length of life. However, CDD does severely impact quality of life.  | **Met** |
|  | There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. | **Top-line MARIGOLD trial results:*** Ganaxolone showed a median reduction of 30.7% in 28-day major motor seizure frequency compared with 6.9% for placebo, which achieved the primary end point (P = .0036)”.

**Company comments on HST checklist:*** “Currently, there is no cure, nor any specifically approved treatments for patients with CDD. Ganaxolone will represent the first treatment specifically indicated for use in this patient group”.
* “Currently available anti-epileptic drugs (AEDs) 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”.
* “Frequent seizures are reported by caregivers to be among the most burdensome issues in caring for their child”.
* “Improvement in seizure control with the currently available therapies may be short lived, and already within 6-12 months patients report diminished efficacy of anti-seizure medications”.
* “Approximately 84% of patients experience treatment-resistant, refractory seizures”
* “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 the literature”.

**Scoping workshop and consultation comments:*** Consultation comments from patient/carer group suggested ganaxolone could be innovative. CDKL5 UK “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.”
* CDKL5 UK “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. Ganaxolone has the potential to reduce the number of AED’s being prescribed in some patients which could improve overall health, and morbidity”
* The impact of ganaxolone on the use of other anti-seizure therapies is uncertain.
* The long-term impact of improved infantile seizure management is uncertain but clinical experts assume it would improve lifetime neurodevelopment.

**Summary** The large range of antiseizure treatments available and actively used in this population suggests that ganaxolone does not meet this criterion. Although the company state that current treatments are not satisfactory, the company has not clearly demonstrated that ganaxolone would offer significant additional benefit compared with these many existing treatments. The HST checklist categorises a criterion as “not met” if there is “no evidence or limited evidence that this criterion is met”.The MARIGOLD trial shows a benefit in the primary outcome for ganaxolone (plus background therapy) compared with placebo (plus background therapy). Placebo plus background therapy is not a relevant existing treatment option within the NHS. Relevant existing treatments in this context are active anti-seizure medications. Had there been a comparison with an active anti-seizure medication included as comparator instead of placebo, clear additional benefit could have been established. Furthermore, considering that the comparison in MARIGOLD resulted in an improvement of -27.1% vs placebo in reduction in 28 day seizure frequency, it is likely that the difference in 28-day seizure frequency would be less if an active comparator had been included. There are other antiseizure treatments that have a similar mechanism of action to ganaxolone. Like other antiseizure treatments, ganaxolone modulates the GABAA receptor complex (albeit using a distinct recognition site). This suggests that ganaxolone is not necessarily offering a unique or innovative mechanism of action specifically for CDD.  | **Not met** |