NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ganaxolone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2023

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ganaxolone in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

Closing date for comments: 23 August 2023

Second evaluation committee meeting: 6 September 2023

Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Ganaxolone is not recommended, within its anticipated marketing authorisation, as an add-on treatment option for seizures caused by cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in children and young people aged 2 to 17 years and adults who turn 18 while on treatment.

1.2 This recommendation is not intended to affect treatment with ganaxolone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person, or their parents or carers.

Why the committee made these recommendations

Usual care for seizures caused by CDD includes antiseizure medications. There is no specific treatment for controlling seizures caused by CDD, so people often try several antiseizure medications and add-on treatments.

Clinical trial evidence suggests that ganaxolone plus usual care reduces seizure frequency compared with placebo plus usual care. But there are uncertainties in how well it works in the long term.

There are uncertainties in the economic model, including:

- its reflection of CDD
- the assumptions used to model quality of life
- how ganaxolone affects seizure frequency and quality of life
- if someone stops having ganaxolone, how this is modelled and how well it reflects clinical practice.

The cost-effectiveness estimates for ganaxolone are uncertain. Even when considering difficulties in collecting evidence for this rare condition, the severity of the condition, and potential benefits of ganaxolone not included in the economic model, the most likely cost-effectiveness estimates are above what NICE normally considers an acceptable use of NHS resources. So, ganaxolone is not recommended.

2 Information about ganaxolone

Anticipated marketing authorisation indication

2.1 Ganaxolone (Ztalmy, Orion) does not have a marketing authorisation in Great Britain yet. The Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product ganaxolone intended for the 'adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 to 17 years of age. Ztalmy may be continued in patients 18 years of age and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for ganaxolone.

Price

2.3 The list price for ganaxolone is confidential and cannot be reported here.

2.4 The company has a commercial arrangement, which would have applied if ganaxolone had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Orion, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

CDD is a rare condition

3.1 Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare condition caused by mutations in the CDKL5 gene, which affect proteins important for brain and neurone development. The genetic cause of CDD was first identified in 2004, so there is limited data on long-term prognosis and survival for people with the condition. The first symptom is often seizures within the first months of life, and CDD is differentiated from other paediatric epilepsies with a genetic test. The clinical expert considered that diagnosis would usually take an average of 2 years, but with better genetic testing and greater awareness of CDD this could improve to 1 year. They noted that, for some people, CDD can be diagnosed later in life or may not be diagnosed. The clinical expert highlighted that CDD is rare and that some people with CDD also have Lennox–Gastaut syndrome. The committee recognised the rarity of CDD and the associated limited evidence for this condition.

Effects on quality of life

3.2 CDD is characterised by multiple seizures a day and people with CDD may also have neurodevelopmental delay, hypotonia (decreased muscle tone), nutritional and gastrointestinal problems, sleep disturbances, visual impairment and speech impairment. CDD also impacts the quality of life of caregivers and families. The clinical expert explained that CDD can be more complex than other paediatric epilepsies, including Dravet syndrome and Lennox–Gastaut syndrome. This is because of the type and frequency of seizures, difficulty controlling seizures, adverse effects from polypharmacy, and frequency of hospital admissions. The impact of CDD on quality of life for people with CDD and their caregivers is associated with the frequency of seizures, and therefore how well seizures are controlled. However, the clinical expert explained that it is difficult to know how seizures specifically affect quality of life compared with comorbidities. They explained that better seizure control means that a person with CDD

is likely to spend less time recovering from seizures, and have fewer hospital admissions and improved quality of life, even if comorbidities are still present. The patient expert explained that the type of seizures (for example, tonic, myoclonic, spasms) and whether they happen in clusters are also important factors in addition to seizure frequency, and that some seizures are more visible than others. They added that seizure frequency may naturally change over time, including periods with fewer seizures, and that adults may have fewer seizures than children. The clinical expert added that having seizure-free days is an important factor for quality of life, because 1 seizure can impact an entire day. The patient expert agreed, and emphasised that having seizure-free days gives hope to parents and caregivers and allows rest and recovery around seizures. The committee concluded that seizures caused by CDD impact both people with the condition and their caregivers, and recognised the importance of seizure-free days.

Clinical management

Treatment pathway

3.3 Ganaxolone is positioned as an add-on treatment to usual care with antiseizure medications. There are no specific treatments for seizures caused by CDD. The clinical expert explained that because most children with CDD have infantile spasms, standard treatment includes vigabatrin, clobazam, benzodiazepines, steroids, or a combination of these. They added that few people become seizure-free, so most people need further trials of antiseizure medication combinations. The choice of antiseizure medication regime is individual and could depend on response to medication and types of seizures. Because seizures are often refractory to treatment, many add-on treatments are tried with some people having high numbers of antiseizure medications at the same time. The clinical expert added that unlicensed or off-label treatments may also be used. Because treatment options are not CDD-specific, people usually try broad spectrum antiseizure medications and commonly used antiseizure

medications with well-established safety profiles before adding less commonly used antiseizure medications. The clinical expert added that people often try at least 8 different antiseizure medications, and this may be more than for other epileptic conditions. They explained that as the number of antiseizure medications that are needed increases, there is an increased risk of adverse effects from polypharmacy. The committee concluded that ganaxolone is positioned appropriately in the treatment pathway and considering it as an add-on to a broad range of antiseizure medications is appropriate because treatment regimens are individualised.

Treatment population

3.4 The decision problem in the NICE scope was people 2 years or over with seizures caused by CDD. The committee noted that the anticipated marketing authorisation includes people with CDD aged 2 to 17 years with an option for people 18 years and over to continue treatment. The company confirmed that this means treatment could not be started in people 18 years and over. The committee noted that the modelled starting age for treatment with ganaxolone may not reflect the entire marketing authorisation (see section 3.13). The patient expert considered there is significant unmet need for some people over 17 years because CDD can be diagnosed later in life (because its cause was recently identified). However, NICE is only able to evaluate ganaxolone within its marketing authorisation. The committee acknowledged that people over 17 years would likely have substantial unmet need for effective antiseizure medications but would not be included within the marketing authorisation for ganaxolone unless they started treatment with ganaxolone by age 17.

Clinical effectiveness

Trial design

3.5 The clinical-effectiveness evidence for ganaxolone came from the Marigold trial. This was an international, phase 3, double-blind,

randomised, placebo-controlled trial in people with CDD who previously had at least 2 antiseizure medications that did not control their seizures. It compared ganaxolone plus usual care (up to 4 other antiseizure medications) with placebo plus usual care. The trial comprised a 6-week period to collect baseline data on seizure frequency and a 17-week double-blind period that included a 4-week titration period to reach target dose and a 13-week treatment period. There were 101 people randomised (50 to ganaxolone plus usual care; 51 to placebo plus usual care) in the 17-week double-blind period. Cannabidiol was not permitted during the double-blind period unless there was a pre-existing stable prescription. The EAG noted that excluding cannabidiol may not reflect clinical practice. The trial included an open-label extension period in which people having placebo switched to ganaxolone. The company also provided supporting evidence from a phase 2a open-label proof-of-concept trial but this did not inform the economic model because of the small sample size (7 out of 30 people had CDD, of which 4 people continued in the extension period).

Seizure outcomes

3.6 In its economic model, the company focused on primary seizures, also known as major motor seizures. This was because they represented most seizures in the Marigold trial (see section 3.5), and they were considered to have the most impact on resource use and health-related quality of life. The primary seizures included the following focal (1 side of the brain) and generalised (both sides of the brain) types:

- bilateral tonic
- generalised tonic-clonic
- atonic (drop)
- bilateral clonic
- focal to bilateral tonic clonic.

The company also included secondary and tertiary seizures in an

analysis of all seizure types. The EAG considered that capturing seizure outcomes in clinical trials presented several challenges including:

- difficulties in accurately measuring seizure frequencies within seizure diaries (including visibility of the type of seizure)
- inability to capture severity or duration of seizures
- capturing the variation in seizure frequency rate (for example, around seizure clusters).

The committee considered that these issues exist in all evaluations of antiseizure medications, but noted the limitations and uncertainty in generalisability of the Marigold trial outputs. The EAG also noted a concern about a potential regression to the mean effect in the Marigold trial outcomes when considering the natural progression of the condition. This is because people may enter a clinical trial or start treatment for seizures after an exacerbation of seizures, so a natural reduction in seizure frequency would happen during follow-up.

Reduction in seizure frequency

3.7 The primary outcome of the Marigold trial was the percentage change from baseline in 28-day major motor seizure frequency during the 17-week double-blind treatment period. This showed a mean decrease of 14% in 28-day major motor seizure frequency from baseline in the ganaxolone arm, and a mean increase of 65% in the placebo arm. The company did a Hodges–Lehmann statistical test to estimate how far the responses in the ganaxolone arm are shifted from placebo, that is the median difference between the arms. The committee noted it was important to consider the Hodges–Lehmann estimation because clinical benefit was expressed in the economic model through changing the distribution of seizures in the population. The secondary outcome was the percentage of people with at least a 50% reduction from baseline in major motor seizure frequency. This showed that seizures reduced by more than

50% in 24.5% of people in the ganaxolone arm compared with 9.8% of people in the placebo arm. The committee had concerns about the large increase in seizures in the placebo arm, and therefore the benefit of ganaxolone. The EAG noted that the increased seizures in the placebo arm may represent natural exacerbations in seizures over time because people may choose to enter clinical trials when they are having an exacerbation of seizures (regression to the mean effect). The clinical expert highlighted that people having placebo also had usual care with antiseizure medications, and suggested that the increase may be from observation bias. The EAG explained that people could have a maximum of 4 antiseizure medications during the trial, which may be a substantial change for some people or a small change for others. It noted that the cap on antiseizure medications may have had more of an effect on the mean number of seizures for people with very frequent seizures. The EAG added that the restriction on cannabidiol (see section 3.5) in the double-blind period may have worsened seizure frequency for some people. The company considered that the 6-week baseline period (see section 3.5) would mitigate any risk of a sudden increase in seizure frequency. But the EAG considered that the 6-week baseline period may not be long enough because the duration of seizure exacerbations can vary and is not well characterised. The committee concluded that ganaxolone reduces the frequency of seizures for people with CDD compared with placebo, but there are limitations in the clinical evidence that raise uncertainty around the size of the treatment effect. It noted that few people in either arm had substantial reductions in seizures or became seizure-free, and there was substantial individual variation in seizure frequency for people in the trial. The committee added that the uncertainty about the reason for an increase in seizure frequency in the placebo arm should be explained.

Long-term effectiveness

3.8 The company used the open-label extension from Marigold to inform the long-term clinical effectiveness of ganaxolone. The EAG had concerns

about the long-term treatment effects of ganaxolone from the open-label extension because of:

- a high rate of missing data
- a possible regression to the mean effect after starting treatment.

The EAG explained that 88 out of 101 people randomised in the Marigold trial continued to the open-label extension. During the open-label extension, 12 out of 31 people discontinued because of lack of efficacy. However, the EAG considered it was plausible that a lack of efficacy could be related to more ambiguous reasons for discontinuation, such as clinician judgement, therefore there could be attrition bias that adds uncertainty in the treatment effect. The company reported that 28-day seizure frequency was reduced more after 12 months in the open-label extension compared with the 17-week double-blind period. After technical engagement, the company did an imputation of missing data method using the last observation of seizure frequency before discontinuation carried forward to all subsequent timepoints. This showed a maintenance of treatment effect for ganaxolone for up to 2 years, rather than a further reduction in 28-day seizure frequency. The EAG noted that this imputation was only done for the primary outcome, whereas all outcomes could have been affected by attrition bias. The EAG commented the observed continued efficacy would not necessarily be expected for other antiseizure medications. It also noted uncertainty with the last observation carried forward imputation method, for example, if treatment waning was not apparent in the last observation, or if there was treatment benefit but treatment was discontinued for other reasons. Additionally, the EAG explained that, because the open-label extension does not have a control arm, it is unknown if a proportion of the reduction in major motor seizure frequency is because of a regression to the mean effect or factors other than treatment effect. For example, reporting of seizure frequency in the open-label part of the study may differ from the

double-blind period. Therefore, the EAG had concerns about the validity of the long-term seizure frequency outcomes. The committee concluded that there is uncertainty associated with using data from the open-label extension to characterise longer-term treatment effects of ganaxolone.

Economic model

Company model

3.9 In its submission, the company presented a 2-health state transition Markov model to estimate the cost effectiveness of ganaxolone plus usual care compared with placebo plus usual care for people with seizures caused by CDD. The 2 health states in each arm were alive (in which people having ganaxolone could stop it and have usual care) and dead. The model cycle was 28 days with a half-cycle correction and a 100-year lifetime time horizon. The Hodges–Lehmann shift estimate from the double-blind period of Marigold and the mean reduction in 28-day seizure frequency from the open-label extension were used to model efficacy of ganaxolone. The committee noted that the quality-adjusted life years (QALYs) were accrued from an improved quality of life through reduced seizure frequency. The company modelled caregivers separately to people with CDD and assumed caregivers were removed from the analysis alongside people with CDD. It modelled 1.8 caregivers until the person with CDD turned 18 (based on the average number of parents during childhood) and reduced this to 1 caregiver after 18 years. Other NICE technology appraisal guidance for similar indications has included 1.8 carers. The EAG acknowledged that evidence for CDD is limited but considered that the company's model was highly simplified for the condition and may not account for the whole treatment effect. The committee had some concerns on the validity of the model and whether it fully reflected the condition. It concluded that the model may introduce uncertainty by being simplified.

Introducing a stopping rule

3.10 After technical engagement, the company introduced a stopping rule at 6 months for people who did not have a minimum 30% reduction in seizure frequency from baseline. The EAG noted that the company did not give a clear justification on the clinical decision making for assessing treatment continuation at 6 months. The clinical expert agreed that a stopping rule is appropriate to include, so that people are not taking unnecessary treatments, which increase the likelihood of adverse effects from polypharmacy (see section 3.3). Also, that 6 months is an appropriate time to review the efficacy of ganaxolone because of its mechanism of action. The clinical expert added that a stopping rule could be implemented in clinical practice by monitoring seizures with a diary, as done for other antiseizure medications. They noted that although seizure count would be the most reliable measure to record, poor quality of life could result from seizures that are less frequent too. The clinical expert explained that many people with CDD have frequent seizures so any change is likely to have a notable impact, and a minimum 30% reduction in seizure frequency is reasonable. The committee noted a minimum 30% reduction in seizures was also used in other NICE technology appraisal guidance for similar indications. The committee questioned whether stopping treatment would happen immediately at 6 months as in the economic model or over a longer period of time. The clinical expert noted that treatment was stopped over 4 weeks in the Marigold trial, and in clinical practice there is a gradual discontinuation which may be between 6 to 8 weeks. This is because people can have withdrawal symptoms if antiseizure medication is stopped immediately. The committee considered that a gradual treatment discontinuation over an appropriate timeframe should be modelled for all people stopping treatment. This is to align with NHS clinical practice and to reduce the risk of seizures and negative impacts on health-related quality of life from abruptly stopping treatment. It concluded that a stopping rule at 6 months would be appropriate in clinical

practice, and the model should include a gradual discontinuation that reflects clinical practice.

Implementation of the stopping rule in the model

3.11 The EAG noted concerns with the implementation of the stopping rule in the company model. In particular, that stopping ganaxolone results in an increase in QALYs. It considered this concept lacked face validity because a considerable proportion of people stop treatment (the exact proportion is considered confidential by the company and cannot be reported here) and this should not result in health-related benefits. The company noted that the data source used to inform health-related quality of life (see section 3.12) affected the outcomes of the stopping rule. This was because the reduction in seizure frequency that is applied to responders does not correspond exactly to the proportion shifting between seizure frequency categories. The EAG considered that a possible explanation is that a weighted average of those alive and on treatment may increase utility. Also, because of differences in how the utility values were modelled (see section 3.12), there could be a non-linear relationship between seizure frequency and utility. However, the EAG also considered that the results could be caused by an error in the modelling. The EAG noted that changing the model structure (for example, to a decision tree) may be needed to appropriately incorporate the stopping rule. The committee also considered that the results lacked face validity and had significant concerns that the stopping rule may not have been implemented appropriately in the model. It concluded further analysis would be required to ensure that the stopping rule is implemented appropriately in the model and provides plausible results.

Health-related quality of life

Utility data source

3.12 The Marigold trial did not collect EQ-5D data, and there were no direct health-related quality of life outcomes reported from people with CDD.

Therefore, the company estimated health-related quality of life using utility values from the Lo et al. (2022) vignette study of people with a similar severe paediatric epilepsy, tuberous sclerosis complex, and their caregivers. The EAG provided an alternative scenario using utility values from the Auvin et al. (2021) vignette study of people with Lennox–Gastaut syndrome and their caregivers. The company considered that tuberous sclerosis complex is more closely aligned with the types and frequency of seizures in CDD, whereas Lennox–Gastaut syndrome has more atonic seizures than generalised seizures. The company also noted that the major motor seizure frequency burden is higher in CDD than in Lennox–Gastaut and Dravet syndromes, which have better quality of life in the most severe health states. The EAG highlighted that applying vignette studies from different populations to the CDD population introduces substantial uncertainty because the utility values that are elicited are very specific to the population in the study. For example, the Lo et al. study included references to skin abnormalities and the need for frequent surgery which does not apply to people with CDD. The EAG preferred to use estimates from Auvin et al. because it had more granular health states that incorporated seizure-free days and it was consistent with the disease area used to inform resource use and mortality (Chin et al. [2021]; see section 3.14). The EAG noted that there is some overlap with the Lennox–Gastaut syndrome population used in Auvin et al. and CDD (see section 3.1). The committee considered the importance of seizure-free days on patient and caregiver quality of life (see section 3.2) and noted that the utility values from Lo et al. would not be sensitive to changes in quality of life from seizure-free days. It also noted that the potential range of quality of life from Lo et al. (including negative utility values for the most severe health states) was substantially wider than in Auvin et al. However, because Auvin et al. has more granular health states, any number of seizures can have a large impact on the health-related quality of life. The patient expert explained that the impact of seizures on health-related quality of life would vary because CDD is a multisystem condition. For

example, fewer seizures may not necessarily correspond with substantially better health status, as aspects of the condition other than seizures can substantially affect quality of life. The committee considered that both Lo et al. and Auvin et al. have substantial limitations associated with being vignette studies for proxy conditions. It concluded that, on balance, the utility values from Auvin et al. may better reflect the impact on health-related quality of life from changes in seizure frequency, and therefore may be more appropriate to estimate utility values for CDD.

Costs in the economic model

Treatment costs

3.13 The dosing for ganaxolone is weight-based and split into 3 equal doses per day. For people up to 28 kg, the recommended dose is 63 mg/kg/day, and for people over 28 kg, the recommended dose is 1,800 mg/day. The committee noted that because dosing for ganaxolone is weight-based, older people have the maximum dose and therefore increased costs. But the model assumptions on starting age and discontinuation do not reflect this, because few people reach the maximum dose in the model. In addition, the company assumed no wastage during treatment with ganaxolone in its model. The EAG preferred to include 10% wastage based on clinical expert opinion. The company suggested a more realistic estimate may be 0.47% wastage, a hypothetical estimate based on the size of a pack and the proportion of people with CDD that would miss a dose. It also noted that the summary of product characteristics is likely to advise against redosing. The clinical expert agreed that wastage is likely during treatment, but that it is unlikely to be notable, especially if the person with CDD has a feeding tube. The patient expert explained that children can go through phases in which they refuse food and drink, which makes it difficult to give medication. Also, that children can respond in a variety of ways to being given medication, which may depend on behavioural problems. The patient expert added that losing medication when administering (for example, when drawing it up, from spilling,

spitting, human error) is likely. The committee agreed that it is appropriate to include wastage in the model. It concluded that the level of wastage to include is uncertain and scenarios should include different levels of wastage for ganaxolone. It also concluded that modelling scenarios for the prevalent population that are likely to have the maximum dose of ganaxolone would be useful to reflect treatment costs.

Health-state resource costs

3.14 The company used Chin et al. (2021), which used data from a population with Lennox–Gastaut syndrome, to inform its health-state resource costs. In the company model, only epilepsy-related hospital inpatient admissions and A&E visits differed between the ganaxolone and usual care arms. The company assumed that the median reduction in major motor seizure frequency would also mean an equivalent reduction to length of hospital stays and A&E visits. The clinical expert clarified that not all seizure types would result in hospitalisation or A&E visits, such as short seizures or non-motor seizures which could be treated at home. But, they noted that hospital admissions are more likely with major motor seizures because they can last a prolonged period. The EAG had concerns that the median length of hospital stay used by the company was from an international CDD registry, which may not reflect people from the UK. The clinical expert said that the international CDD registry reflects people from the UK to an extent and there is currently no specific UK registry. The company added that, in the registry, the subset of people from the UK had a median length of stay in line with the model (the exact numbers are considered confidential by the company and cannot be reported here). The committee noted that over time, people become more familiar with seizures caused by CDD, which may mean that some seizures could be treated at home rather than the hospital. It also considered that the assumption that any reduction in major motor seizure frequency would be directly proportional to a reduction in hospitalisation or A&E visits was uncertain. This is because resource use is unlikely to be evenly distributed between people.

However, in the absence of evidence, this was considered acceptable for decision making.

Severity

3.15 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company estimated that a weight of 1.7 should apply based on a calculation of absolute shortfall for patients. The company considered caregivers as living with the condition and impacted by the same severity as people with CDD because of the need for constant support and the impact from comorbidities (see section 3.2). Therefore, the weight of 1.7 was applied to both patient and caregiver incremental QALY gains for ganaxolone. The EAG-preferred utility values (from Auvin et al., see section 3.12) reduced the absolute shortfall to a range that would give a weighting of 1.2. The EAG also considered that the weight of 1.2 should only be applied to people with CDD and not to caregivers. The EAG noted that the choice of utility source is important when determining the severity weighting. But, it noted both Auvin et al. and Lo et al. are vignette studies for proxy conditions, with no external data that could indicate the true health-related quality of life estimates for people with CDD and their caregivers. The committee noted that the severity modifier reflects the additional value that society places on health gains in more severe conditions. It considered that there may be a conceptual overlap between the reason for this societal preference in severe conditions and the effects of severe conditions on caregivers. The committee therefore considered that applying the severity modifier to caregivers may result in double-counting of societal preference. The committee noted the limited data on prognosis and survival in the long term in CDD (see section 3.1). In addition, the committee noted that model may not reflect the condition

over the lifetime of a person with CDD, because the model may be simplified (see section 3.9). The committee understood that the QALY shortfall calculation was strongly affected by the source of utility data chosen (see section 3.12). Because of its preference for the Auvin et al. utility source, the committee concluded that a severity weight of 1.2 applied to the QALYs is appropriate, and that the severity weighting should be only applied to people with CDD.

Cost-effectiveness estimates

3.16 The committee noted the high level of uncertainty, specifically the:

- validation of seizure frequency outcomes (see section 3.7)
- uncertainty in the long-term clinical-effectiveness evidence for ganaxolone from the open-label extension of the Marigold trial (see section 3.8)
- model structure may simplify the complexity of the disease area and the validity of model outcomes (see section 3.9)
- implementation of the stopping rule (see sections 3.10 and 3.11)
- level of wastage to include in the model (see section 3.13)
- uncertainty of utility values from vignette studies of proxy conditions (see section 3.12).

The committee's preferred assumptions included:

- implementing a stopping rule that incorporates a gradual stopping of ganaxolone over a period that reflects clinical practice (see sections 3.10 and 3.11)
- plausible health-related quality of life outcomes after implementing a stopping rule (see section 3.11)
- using Auvin et al. (2021) to inform utility values for people with CDD and their caregivers (see section 3.12)
- modelling scenarios for the prevalent population that are likely to have the maximum dose of ganaxolone (see section 3.13)

- scenarios on different levels of treatment wastage for ganaxolone (see section 3.13)
- applying a 1.2 severity modifier for people with CDD only (see section 3.15).

The committee noted that some of these uncertainties are related to how the rarity of the condition could affect evidence generation. It also noted that there may be uncaptured benefits of ganaxolone related to the type and severity of seizures and potential reduction in risk for mortality. It considered these potential benefits when considering the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). However, when taking into account its preferred assumptions and the effect of uncertainties not appropriately captured in the economic modelling, the most likely incremental cost-effectiveness ratio for ganaxolone was above £30,000.

Other factors

Equality issues

3.17 No equality or social value judgement issues were identified.

Conclusion

3.18 The committee's preferred cost-effectiveness estimates for ganaxolone were above the range that NICE considers an acceptable use of NHS resources. So, the committee concluded that it could not recommend ganaxolone for treating seizures caused by CDD.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Baljit Singh

Vice chair, technology appraisal committee B

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Summaya Mohammad

Technical lead

Adam Brooke

Technical adviser

Jeremy Powell

Project manager

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