NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

1.1 Ganaxolone is not recommended, within its 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 healthcare professional consider it appropriate to stop. For children and young people, this decision should be made jointly by the healthcare professional 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 it is uncertain how much ganaxolone reduces seizure frequency because there was a large increase in

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seizure frequency in the placebo group in the trial. There are also uncertainties in how well it works in the long term.

There are structural uncertainties in the economic model which mean that the cost-effectiveness estimates for ganaxolone are not reliable. There is not enough evidence to establish that ganaxolone is cost effective. So, ganaxolone is not recommended.

2 Information about ganaxolone

Marketing authorisation indication

2.1 Ganaxolone (Ztalmy, Orion and Marinus) is indicated 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 is 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 highlighted that CDD is rare, and that some people with CDD also have Lennox–Gastaut syndrome. The clinical expert noted that, for some people, CDD can be diagnosed later in life or may not be diagnosed. They considered that diagnosis usually takes around 2 years, but with better genetic testing and greater awareness of CDD this could improve to 1 year. The clinical expert added that people aged 2 years with CDD would have had multiple seizures and often tried more than 5 antiseizure medications, and would be able to try a new treatment at this point. The committee recognised the rarity of CDD and the associated limited evidence and difficulties with evidence generation 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 patient expert explained that CDD is unique, and that the impact of other paediatric epilepsies could not compare to the impact of CDD. 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. After consultation, the patient expert highlighted that most people with CDD also have profound learning disabilities. The clinical expert noted that these learning disabilities have a large impact on quality of life and result in full dependency on caregivers for daily activities. The clinical expert added that these learning disabilities increase the likelihood of mortality and also increased hospitalisations that affect quality of life. The patient expert and clinical expert agreed that reducing seizure frequency is important to improve quality of life. But they noted that cognitive abilities would still be affected and there would be an associated impact on quality of life because of dependency on caregivers. The committee concluded that seizures caused by CDD impact on quality of life for both people with the condition and their caregivers, and recognised the importance of seizure-free days. It also noted that learning disabilities and other comorbidities have a notable impact on quality of life.

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 regimen is individual and depends on response to medication and types of seizures. Because seizures are often refractory to treatment, people try many add-on treatments and some people have 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 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. They added that many people would use 3 or 4 antiseizure medications, to minimise the risks of 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 population in the NICE scope was people 2 years or over with seizures caused by CDD. The committee noted that the marketing authorisation for ganaxolone 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 start in people 18 years and over. 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 noted that the modelled starting age for treatment with ganaxolone may not reflect the entire marketing authorisation (see section 3.19). It also noted that there is a prevalent population of people with CDD, of varying ages. People in the prevalent population may start treatment with ganaxolone between 2 and 17 years. There will also be an incident population of people who are diagnosed with CDD and who become eligible for ganaxolone treatment. Many people in the incident population will have their condition diagnosed at a younger age and start treatment aged under 2 years (see section 3.1). In this group, ganaxolone may be considered for people aged 2 years and older. The incident population is likely to be, on average, younger than the prevalent population. 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 (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, however, this only affected a small number of people in the trial. 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 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. Therefore, the company focused on primary seizures, also known as major motor seizures, and this was reflected in its economic model (see section 3.9). 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. However, there is limited evidence on the natural progression of CDD that could explore how seizure frequency changes over time.

Reduction in seizure frequency

3.7 The primary outcome of the Marigold trial 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 calculated the Hodges–Lehmann statistic to estimate how far the responses in the ganaxolone arm are shifted from placebo. 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 (see section 3.9). 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, which was not statistically significant. The committee had concerns about the large increase in seizures in the placebo arm, and therefore the

benefit of ganaxolone. It was concerned the benefit of ganaxolone was largely because of the increase in seizure frequency in the placebo arm rather than the reduction in seizure frequency in the ganaxolone arm. The committee considered the following possible explanations for the large increase in seizures in the placebo arm:

- The maximum number of antiseizure medications in the trial: 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. However, the company noted that the median number of antiseizure medications at baseline was 2 in both treatment arms compared with a maximum of 5 concomitant medications used in clinical practice.
- The restriction on cannabidiol in the trial: The EAG explained that the restriction on cannabidiol (see section 3.5) in the double-blind period may have worsened seizure frequency for a small number of people. The company explained that these were unlikely reasons for the increase in seizures in the placebo arm, because 2 people used cannabidiol in the trial.
- Observation bias: The clinical expert highlighted that people having placebo also had usual care with antiseizure medications. They suggested that the increase may be from observation bias, because people may become more familiar with identifying and reporting seizures during the trial. The committee considered that an observation bias may explain the increase in mean seizure frequency in the placebo arm, but noted that any observation bias may be affected by absolute seizure frequency and would likely affect both treatment arms.
- A regression to the mean effect: The EAG noted that the increased seizures in the placebo arm may represent a regression to the mean effect by reflecting a natural exacerbation in seizure frequency over time. This is because people may choose to enter clinical trials during

an exacerbation of seizures. But, the EAG noted that there is limited evidence on how seizure frequency changes over time (see section 3.6). The committee noted that a regression to mean effect would more often be associated with an improvement in both arms rather than a deterioration. The company did not consider there would be a regression to the mean effect and 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 EAG added that the trial results were presented as total aggregate reductions in seizure frequency over the entire 17-week double-blind period, which is not informative for fully characterising individual changes in seizure frequency. Therefore, a time-series analysis of seizure frequency for every 28 days for each arm would be more informative.

- The results being driven by a few individuals with extreme worsening in seizure frequency: At consultation, the company explained that the increase in seizures in the placebo arm was driven by a few people who had extreme worsening in seizure frequency. So, it preferred using the median percentage change in seizure frequency rather than the mean, to mitigate the effects of a skewed seizure distribution. The company added that, for people who had an increase in seizure frequency, the median percentage change in seizure frequency from baseline was not statistically significantly different between treatment arms. The EAG agreed that an increase in the placebo arm may be driven by a small number of people who had extreme worsening and so using the median was reasonable.

The committee concluded that ganaxolone reduces the frequency of seizures 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 noted the high uncertainty around the seizure frequency results. It agreed that time-series results with confidence intervals would better inform the understanding of seizure variation in the trial and the treatment effect of ganaxolone. It would also better inform how clinical benefit in the trial is translated into benefit in the economic model.

Long-term effectiveness

3.8 The company used the Marigold open-label extension 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. This was 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 who discontinued did so 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. So, 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 attrition bias could have affected all outcomes. 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. The EAG also 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. After consultation, the company did a multiple imputation based on a mixed effects model to address the uncertainty with the last observation carried forward method. The company also clarified that the open-label extension was only used to assess a maintenance of treatment effect from the double-blind period. As a result, in the economic model the company assumed that a response to ganaxolone means that the reduction in seizure frequency is maintained for up to 2 years and the treatment effect is lost when not on treatment. The clinical expert considered that maintaining a treatment effect for 2 years or longer would be plausible in clinical practice, but there are a limited number of people using ganaxolone to inform this judgement. The EAG highlighted that it could not assess the validity and appropriateness of the company's approach to the multiple imputation method. This is because it is not commonly used and the company did not submit a thorough description of the methods. 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 structure

3.9 The company presented a 2-health state transition Markov model with a stopping rule applied at 6 months to estimate the cost effectiveness of ganaxolone plus usual care compared with established clinical management 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 focused on major motor seizures 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 seizure frequency for all people in the baseline period of the Marigold trial (see section 3.7) was expressed as a lognormal distribution and underpinned the estimated seizure frequencies in both arms of the model. The established clinical management arm was assumed to have the baseline period seizure frequency for the lifetime of the model. The ganaxolone arm seizure frequency was modelled by taking estimates of the relative effectiveness of ganaxolone (see sections 3.10 to 3.12) and applying them to the baseline period seizure frequency. Utilities were then applied to these seizure frequency distributions in bands based on number of seizures per month. Each model cycle was 28 days with a half-cycle correction and a 100-year lifetime time horizon. The committee noted that the quality-adjusted life year (QALY) benefit was 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 when people with CDD died. 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 the company's modelling of baseline seizure

distribution to be simplistic. It considered the suitability of the lognormal distribution was uncertain and the distribution shift based on reductions in the trial may not fully represent how people's seizures change over time. This is because of the wide changes in seizure frequency that happened in both trial arms. These were simplified into a single reduction over 17 weeks from baseline, represented as a transformed distribution of seizure frequency, but could be better explored with a time series (see section 3.7). The EAG considered that a highly simplified model for CDD may not account for the whole treatment effect and that it was highly sensitive to the method used to estimate treatment effect. It noted that previous technology appraisals for conditions with childhood seizures have used other model types that could have also been used in this evaluation. The committee had some concerns on the validity of the model and whether it fully reflected the condition. It concluded that because the model is a simplified representation of CDD, it may not generate reliable cost-effectiveness estimates for ganaxolone.

Establishing relative treatment effect

Analyses for the first committee meeting

3.10 In the original model submitted for the first committee meeting, the company modelled the relative treatment effect of ganaxolone for the first 6 months using the Hodges–Lehmann shift estimate from the double-blind period of Marigold. After 6 months, for the subgroup of people who had a minimum 30% reduction in seizure frequency from baseline (responders), a separate Hodges–Lehmann shift estimate was calculated and used to model seizure frequency. The company had introduced a stopping rule after technical engagement which meant that people in the model who did not have a minimum 30% reduction in seizure frequency at 6 months stopped ganaxolone. 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 that 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 frequency 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 EAG noted that implementation of the stopping rule resulted in an increase in QALYs for ganaxolone. It considered that this lacked face validity because a substantial proportion of people stopped ganaxolone and it was not logical that this would lead to an increase in QALYs. It considered that there could be several plausible reasons for this result, including that differences in how utility values were modelled (see section 3.16) meant there could be a non-linear relationship between utility and seizure frequency. 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 Marigold, 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 also considered a stopping rule at 6 months would be appropriate in clinical practice. The

committee agreed that the concept of a stopping rule was appropriate. However, the committee considered that because of the issues with the face validity of this stopping rule, it may not have been implemented appropriately in the model. It considered that further analysis would have to ensure that the stopping rule was appropriately implemented before it could be accepted for decision making.

Analyses for the second committee meeting

3.11 After consultation, the company made several revisions to its original model (see sections 3.9 and 3.10). Firstly, it incorporated a gradual down-titration of ganaxolone over 8 weeks, with an additional 28-day treatment cycle cost as part of the stopping rule for anyone stopping ganaxolone. This was in response to the committee's conclusions on the stopping rule at the first committee meeting (see section 3.10). The EAG considered that this revision was appropriate after a correction to the costing of this titration period had been made. Secondly, the company updated its model to a response-based model. This new structure split the ganaxolone arm into 2 groups at baseline. These groups were people who had a minimum 30% reduction in seizure frequency from baseline (responders) and people who did not (non-responders). Responders were modelled to have a seizure frequency distribution based on the cohort-level Hodges–Lehmann shift in 28-day seizure frequency for responders in the Marigold trial (that is, difference in seizure frequency at the end of 17 weeks for responders compared with all people in the placebo arm at 17 weeks). Non-responders were modelled to have the same seizure distribution as the baseline seizure frequency distribution which was unchanged from the original model, and were modelled to stop treatment at 6 months (see section 3.10). So, the response-based model captured the relative effectiveness of ganaxolone based on a selected group of responders from the trial and the baseline seizure distribution, and not on a randomised comparison of ganaxolone with placebo. The EAG noted that the company's updated model may inflate the treatment effect because all responders are determined at the start of treatment, suggesting an

immediate response. It also noted that the face validity issue in which the stopping rule increased QALYs for ganaxolone (see section 3.10) remained in this updated version of the model. The company agreed that there were some issues with the modelling but did not consider that these would have a notable impact on the cost-effectiveness estimates. The committee commented that implementing the stopping rule has a large impact on the cost-effectiveness estimates and maintained its view that the impact on QALYs does not have face validity. It considered that the modelling of the stopping rule was not suitable for decision making in its current form. The committee considered that the response-based model raised issues with splitting the ganaxolone arm because it broke randomisation and because of the way it interacted with the non-linearity of seizure frequency and utility. The committee concluded that there was a high level of uncertainty in the updated model and that it was not robust for decision making because of issues related to face validity and issues related to how the clinical benefit of ganaxolone was implemented in the model.

Analyses for the third committee meeting

3.12 For the third committee meeting the company updated its modelling of treatment effect with the intention of resolving some of the uncertainties identified at the previous committee meetings. The changes included:

- implementing response status at model entry regardless of whether the stopping rule is active
- modelling an up-titration and utility correction factor so that people in the model did not start on the target dose from the first cycle (see section 3.17)
- changing from a cohort-level to individual-level Hodges–Lehmann shift.

This new approach calculated the Hodges–Lehmann shift individually for each participant in Marigold compared with the entire placebo arm, producing a distribution of Hodges–Lehmann shifts for responders and

non-responders. The Hodges–Lehmann shift distributions were then applied to the modelled baseline seizure frequency curve to estimate post-baseline seizure frequency. The company fitted a distribution to the frequency of Hodges–Lehmann shift reductions. The EAG noted that values for this new approach taken for estimating treatment effect were hard coded into the model which made it impossible to verify the calculations or validate the choice of distribution. The EAG was also concerned about splitting responders and non-responders from baseline (see section 3.11) and considered that the response-based model was conceptually inappropriate. The committee recognised that the individual Hodges–Lehmann shift analysis had a limited impact on the seizure frequency distribution. It noted that the outputs could not be validated. It also considered that the updated approach retained the uncertainties which had been identified in previous meetings.

Updated stopping rule

3.13 The company highlighted that the changes to modelling of treatment effect were prompted by an issue with the stopping rule identified at the second committee meeting whereby implementing the stopping rule resulted in an increase in QALYs for the ganaxolone arm (see section 3.10). The company's updated submission for the third committee meeting considered that this was because of the non-linearity of utility values and seizure frequency. The EAG noted that under the new treatment effect modelling approach, implementing the stopping rule only reduced costs of ganaxolone, not QALYs. It commented that a stopping rule should generally result in a reduction in costs, QALYs and incremental cost-effectiveness ratios (ICERs; with the fall in costs offsetting the fall in QALYs). The committee acknowledged that the updated stopping rule no longer resulted in a QALY gain for ganaxolone. However, it considered that it was counterintuitive that the stopping rule had no effect on QALYs. This is because it would be expected that some people who have a response to treatment below a 30% reduction in seizure frequency would stop treatment under the stopping rule but would otherwise have a small

QALY gain with continued treatment. The committee concluded that the implementation of the stopping rule was structurally uncertain.

Treatment effect waning

3.14 The updated treatment effect modelling that the company submitted for the third committee meeting showed that some people in the ganaxolone responders group experienced a lower than 30% reduction in seizure frequency, or even an increase in seizure frequency. The company also submitted time-series data showing the median difference between the ganaxolone responders group and the placebo group over the first 5 cycles. The EAG considered that both of these sets of data suggested that a waning of treatment effect was possible and noted that the model included no modelling of treatment effect waning for people who remain on treatment. The company responded that the confidence intervals on the time-series data were very wide and that it considered this did not offer strong support for an assumption of treatment effect waning. The committee noted that it had not seen any time-series data for the total ganaxolone group compared with placebo. The committee noted the EAG's position and considered there was limited evidence on treatment waning. It considered that the modelling did not account for possible treatment waning and this added to the uncertainty because if there were treatment effect waning in practice this would not be captured in the model. The committee considered the evidence and concluded that it was plausible that the treatment effect could wane over time for responders, given the large changes seen in both arms of Marigold over a relatively short time period. The committee concluded that the failure to explore any treatment effect waning added substantial uncertainty to the model structure and that there was a potential risk that the health benefits of ganaxolone had been overestimated.

Conclusion on modelling of relative treatment effect

3.15 The committee considered the various methods that had been used to establish the relative treatment effect of ganaxolone, noting that each one

relied in some form on splitting the modelled ganaxolone arm into responders and non-responders.

The committee considered that:

- the response-based model broke the randomisation established in Marigold
- the implementation of the stopping rule produced counterintuitive results and was structurally uncertain
- it was unclear whether the baseline seizure distribution and transformations of that using the Hodges–Lehmann shift appropriately captured the effect of ganaxolone on individual patients
- it was concerned about the inability to validate the results of the model against clinical evidence.

The committee also noted that the non-linear relationship between utility and seizure frequency exacerbated the issues with the response-based model. Based on these considerations, the committee concluded that there was structural uncertainty at the core of the modelling of relative treatment effect which made the cost-effectiveness analyses unreliable for decision making.

Health-related quality of life

Utility data source

3.16 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, Lo et al. 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 3.21). The EAG noted that there is some overlap with Lennox–Gastaut syndrome, the population 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). It noted that the estimate of utility of 0.73 from Lo et al. for the lowest seizure frequency band (0 to 27 seizures a month) was plausible for someone who is seizure-free. The company provided evidence to show that people in the ganaxolone arm had numerous seizure-free days on average. The exact numbers are considered confidential and cannot be provided here. The committee noted that having a proportion of seizure-free days in a month did not equate to seizure freedom and considered that the utility estimate of 0.73 may be an overestimate. It also noted that the utility values from Lo et al. would not be sensitive to changes in quality of life from seizure-free days and 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, because 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 considered that the relative difference in the utility values associated with a change in seizure frequency from Auvin et al. may better reflect the impact on health-related quality of life from changes in the seizure frequency component of CDD.

After consultation, the company used interim data from an ongoing international caregiver survey that assessed the burden of illness in CDD to support its preference for Lo et al. This survey used the EQ-5D-5L proxy version 1 and had a mean EQ-5D-5L index that was lower than the mean utility value calculated for CDD using the Lennox–Gastaut syndrome and tuberous sclerosis complex utility values (the exact value is considered confidential by the company and cannot be reported here). The patient expert emphasised that no proxy condition could accurately reflect the impact on quality of life for people with CDD and their families (see section 3.2). The company also presented alternative cost-effectiveness estimates, using both Lo et al. and Auvin et al., by averaging the expected lifetime costs and lifetime QALYs in both arms. However, at the second committee meeting the company introduced a new argument that it did not consider Auvin et al. provided a valid measure of utility because the values were not preference-based. The EAG acknowledged that the interim results from the international caregiver survey suggested that the average utility may be worse than in Lennox–Gastaut syndrome and tuberous sclerosis complex. However, the EAG maintained a preference for using Auvin et al. for the reasons described previously and recognising that both data sources have limitations. The EAG noted that the company's cost-effectiveness results using the averaged utilities may help decision making. The committee accepted that the methods of

obtaining utility estimates from Lo et al. were more consistent with the NICE reference case, but highlighted the lack of available data and the need to use proxy conditions. For example, it noted that Lo et al. included other factors around daily functioning that could result in an increase in utility from improved functioning and independence that is attributed to reduced seizure frequency, but this may not be the case for CDD (see section 3.2). It noted that the absolute utility values from proxy conditions were less important for the modelling than the relative differences between health states based on seizure frequency, for which there was no specific information for CDD. It considered that the caregiver survey may suggest that CDD is more severe than other paediatric epilepsy conditions. But, this would not mean that reducing seizures in CDD would correspond to a quality of life benefit similar to improving health states in other proxy conditions. The committee concluded that all sources of utility values had substantial limitations but, on balance, Lo et al. would be a more appropriate source for utility values than Auvin et al. However, the benefit of reducing seizures is likely to be overestimated so there remains substantial uncertainty in the utility data.

Starting treatment

3.17 In response to concerns about responders being defined at the start of the model and having the full treatment effect for ganaxolone response (see section 3.11) the company applied a correction factor of 0.64 to patient utility for all responders in the first cycle. This was to reflect that the full treatment effect was unlikely to occur immediately after starting ganaxolone, and that it may accrue gradually during start of treatment, particularly as the dose is up-titrated. The EAG agreed with the principle of adjusting utility by applying a reduction to responders in the first cycle however it noted that no rationale was given to explain how the value of 0.64 was calculated. The EAG also considered that the correction factor could reflect the fact that people titrated slowly onto the target dose of ganaxolone during the first cycle (see section 3.5). However, it noted that the time-series data submitted by the company (see section 3.12)

suggested that the full treatment effect may take 3 months to manifest once the target dose had been reached. The EAG offered a scenario which interpolated the treatment effect in the first 3 cycles which might better reflect the time taken for the full treatment effect to manifest in reality, noting that this would have limited effect on the cost-effectiveness analyses. The committee considered that it was reasonable to consider that the treatment effect would not apply immediately because of the up-titration to target dose and a delay once the target dose was reached. The committee concluded that the concept of reducing the modelled treatment effect in initial cycles might better reflect how ganaxolone worked in clinical practice.

Costs in the economic model

Wastage

3.18 The company assumed there is no drug wastage associated with ganaxolone treatment. 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 a proportion of people with CDD who would miss a dose. 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. After consultation, the company included scenarios that modelled 2.5% and 5.0% wastage. From this, the company suggested that wastage between

2% to 3% is the most plausible, and assumed zero wastage for people who were tube-fed. The company estimated that 40% of people with CDD would be tube-fed, based on a 21% to 56% range from an international consensus recommendation for CDD by Amin et al. (2022). However, the company maintained the assumption of zero wastage in its model. The EAG noted that there is no robust evidence on wastage, and considered 5% plausible from the range of wastage levels explored by the company and EAG (0% to 10%). The clinical expert noted that ganaxolone is in a liquid formulation and a proportion of people with CDD do not use a feeding tube, meaning that zero wastage is unlikely. The committee concluded that, within the context of a reliable model, it would be appropriate to consider wastage in modelling of ganaxolone for this indication and that a 5% level would be plausible.

Treatment starting age

3.19 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 dosing for ganaxolone is weight based, so older people have the maximum dose and therefore increased costs. As people with CDD move through the model, their weight increases, with the starting weight depending on the starting age at baseline. But the model assumptions on starting age and discontinuation do not reflect the full effect of increasing weight because few people reach the maximum dose in the model. Also, the different potential starting age ranges for people that may have ganaxolone impact on costs (see section 3.4). These are the:

- incident population, that is people aged between 2 years and the starting age in the model
- prevalent population, that is people aged 2 to 17 years, covering the marketing authorisation population who can start ganaxolone (see section 2.1).

The committee concluded that modelling scenarios for the prevalent population that is likely to have the maximum dose of ganaxolone would be useful to reflect treatment costs. After consultation, the company and EAG maintained its mean treatment starting age (the exact number is considered confidential by the company and cannot be reported here). The company based this on clinical expert opinion that the latest diagnosis is by 2 years. The company did scenario analyses using the median starting age of 6 years in Marigold to reflect the prevalent population in which a larger proportion of people have the maximum dose of ganaxolone. The company also did a scenario analysis using a starting age of 2 years, which it considered may reflect future use of ganaxolone with increased awareness of the condition and earlier diagnosis. The clinical expert explained that ganaxolone would be used at 2 years because people with CDD would have had seizures by this age, including onset in the first few weeks of life, and tried more than 5 antiseizure medications at this point. The committee considered it was unclear what the average age of the prevalent population would be because the trial may not be representative of the UK population. It considered both the prevalent and incident populations and agreed that it would be conceptually more appropriate to base costs in an economic model for a novel treatment on the prevalent population. However, it acknowledged that, in the future, people may start ganaxolone at an earlier age and therefore costs may decrease.

Discontinuation of ganaxolone

3.20 In the company's model for the second meeting, a continuous discontinuation was applied until 6 months at which point non-responders stopped (because of the stopping rule) and responders continued with a new, higher rate of discontinuation. At the third committee meeting the company updated its modelling of discontinuation stating that it had identified an error in the previous analyses. The updated modelling had different discontinuation rates applied to responders and non-responders

both before and after month 6 (non-responders continued treatment after month 6 when the stopping rule was not active). The company explained that these rates were derived from the Marigold trial. The rates are considered confidential by the company and cannot be reported here. At the third committee meeting, the company also submitted scenarios exploring a lower discontinuation rate from cycle 29 and a fixed plateau representing a proportion of the population who would not discontinue. The EAG noted that the new rates modelled for the third committee meeting would result in an overall increase in discontinuation compared with the analysis submitted for the second meeting and that this would benefit ganaxolone. The EAG explained that if the number of people remaining on treatment did not fall, the costs of ganaxolone would increase at a greater rate than the benefits. The clinical expert at the second meeting did not think it was plausible that discontinuation rates would increase for responders after month 6, stating that generally if the condition responds to treatment, people will continue treatment. The patient expert explained that some of the discontinuation would be because of adverse effects such as sleepiness and drooling, and some because of trial-specific reasons. The patient expert explained that the trial took place in the US and people might discontinue because they had to travel long distances to trial locations or because of 'trial hopping' (leaving a trial to get treatment in another). The committee considered that there was a contradiction between the lack of treatment effect waning in the modelling (see section 3.14) and the substantial discontinuation rate in responders. It therefore also considered that it was implausible for responder discontinuation to increase after 6 months. It understood that discontinuation caused by the trial itself or 'trial hopping' would not apply in NHS clinical practice. The committee considered that the discontinuation in the company base case was likely an overestimate. It concluded that alternative scenarios that modelled lower discontinuation rates for ganaxolone could be more appropriate, in the context of a reliable model, but that there was limited evidence to inform this. It

understood that lower discontinuation rates for ganaxolone would worsen the cost effectiveness of ganaxolone.

Health-state resource costs

3.21 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. In its submission, 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. But, in the response-based model, this is based on the mean reduction for people that have a minimum 30% reduction in seizure frequency. 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 for 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. The committee considered this to be a problem when only using a higher seizure frequency reduction for responders. The committee considered that there was uncertainty around the healthcare

resource use and costs applied in the current modelling, but that the assumptions used would be acceptable for decision making within the context of a reliable model.

Severity

3.22 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. At the second committee meeting the EAG-preferred utility values (from Auvin et al., see section 3.16) which 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 because it affects the total QALY gain in the comparator arm. 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 agreed that any severity weighting should only be applied to QALY gains in people with CDD. 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 the 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 3.16). Because of its initial preference for the Auvin et al. utility source, the committee concluded that a severity weight of 1.2 applied to the QALYs would be appropriate. At the second meeting, the committee considered all the evidence around Auvin et al. and Lo et al., including the:

- interim mean EQ-5D-5L proxy index from the international caregiver survey in the CDD population
- model results that used the averaging of QALYs estimated from the Auvin et al. and Lo et al. studies
- patient expert comments on the impact on health-related quality of life.

It also recalled that Lo et al., while uncertain, was a more appropriate source for utility values than Auvin et al. (see section 3.16), and considered that this might be particularly the case for encapsulating the severity of the condition. The committee acknowledged the rarity of CDD and therefore, the difficulties in capturing quality of life estimates. Overall, it acknowledged that the currently available modelling implied a severity weighting of 1.7 could be appropriate, if the modelling were reliable for decision making. However, the committee recalled the important uncertainties in the modelling, including that it showed a highly simplified representation of CDD over a lifetime horizon (see section 3.9 and sections 3.11 and 3.12). It concluded that the limitations in the modelling result in substantial uncertainties in calculating and applying a severity modifier.

Cost-effectiveness estimates

3.23 The company's deterministic base-case ICER for ganaxolone compared with usual care was £20,045 per QALY gained. The EAG proposed several changes to the modelling to best describe its preferences that resulted in an exploratory base-case ICER of £37,774 per QALY gained. The company base case and EAG exploratory base case included a severity modifier using a QALY weighting of 1.7.

The committee considered that these ICERs did not reflect the uncertainty in the modelling. It recalled its conclusions that the model is a simplified representation of CDD, and that there was structural uncertainty at the core of the modelling of relative treatment effect which made the cost-effectiveness analyses unreliable for decision making. It noted that the stopping rule was included in the company's base case but had substantial limitations (see section 3.13), but removing the stopping rule (as in the EAG's analysis) may be a conservative assumption. The committee noted other important uncertainties in the economic modelling, including treatment effect waning, utility values and health state resource costs. It was aware that several of the structural uncertainties, including treatment effect waning (see section 3.14) and discontinuation (see section 3.20), would likely favour ganaxolone. So, the cost effectiveness estimates, if they were suitable for decision making, may be underestimates. But it did not see alternative structures or validation to explore this uncertainty. The committee recalled that it had previously considered ICERs based on earlier versions of the modelling and had identified that the best available ICERs based on plausible assumptions were above £30,000 per QALY gained. However, the committee further recalled that that modelling had a high level of uncertainty, and that it had not been able to specify a precise cost-effectiveness estimate. It considered that those estimates were not reliable for decision-making.

The committee concluded that the structural uncertainty in the model meant the cost-effectiveness estimates were unreliable for decision-making.

Other factors

Equality issues

3.24 The patient submission highlighted that people with CDD have comorbidities that include a learning disability. The committee noted that learning disabilities can affect quality of life, and that people with a learning disability have worse health outcomes (see section 3.2). The committee considered whether a recommendation could discriminate against those with a learning disability. It considered that access to the treatment would not differ for people with a learning disability. The committee acknowledged the difficulties in evidence generation for health-related quality of life for people with a learning disability, and the committee considered health-related quality of life data from vignette studies of proxy conditions (see section 3.16).

Uncertainty and uncaptured benefits

3.25 The committee noted that some of the uncertainties in the model are related to how the rarity of the condition could affect evidence generation. The NICE health technology evaluations manual specifies that committees may be able to make recommendations accepting a higher degree of uncertainty in circumstances where evidence generation is particularly difficult. The committee 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. The committee may take into account aspects that relate to uncaptured benefits, alongside considerations of uncertainty, when considering ICERs above £20,000 per QALY gained. The committee therefore considered these factors in its deliberations on the evidence for ganaxolone. However, it concluded that the nature and scale of the uncertainties in the evidence, in particular the

structural uncertainties in the economic model, were such that even after considering these factors the model results remained unsuitable for decision making.

Conclusion

3.26 The committee could not be confident in specifying a precise cost-effectiveness estimate for ganaxolone compared with established clinical management because of critical uncertainties in the economic modelling. The committee noted its concerns about how the model did not fully capture the relative treatment effect of ganaxolone, how well health-related quality of life was reflected, and how long people continue having treatment with ganaxolone. It recalled that the model results, if they were suitable for decision making, might be biased towards ganaxolone. The committee also noted the uncertainty in the clinical effectiveness of ganaxolone. It recalled the potential uncaptured benefits of ganaxolone and the severity of the condition, and noted that some of the uncertainties in the model are related to how the rarity of the condition could affect evidence generation. However, the committee concluded that even with these additional considerations, the cost effectiveness estimates were not reliable enough for decision making because of the important uncertainties in the modelling approach. The NICE Principles state that NICE's guidance uses evidence that is relevant, reliable and robust, and that a committee should not recommend an intervention if there is not enough evidence on which to make a clear decision. The committee concluded that it had not seen enough evidence that ganaxolone represented a cost-effective use of NHS resources, so 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 and Samuel Slayen

Technical leads

Adam Brooke

Technical adviser

Jeremy Powell

Project manager

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