NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final evaluation document

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

1 Recommendations

1.1 Cerliponase alfa is recommended as an option for treating neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, only if the conditions in the managed access agreement are followed.

1.2 This recommendation is not intended to affect treatment with cerliponase alfa 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 or young people, this decision should be made jointly by the clinician and the child or young person, or the child's or young person's parents or carers.

Why the committee made these recommendations

CLN2 is a genetic disease that progresses rapidly, and leads to loss of speech, mobility and vision, progressive dementia and early death. Current treatment options are limited to symptomatic relief, and supportive and palliative care. Cerliponase alfa is expected to restore deficient TPP1 activity in the brain caused by the genetic mutation.

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Clinical evidence shows that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is only short-term clinical evidence, so assumptions about long-term disease stabilisation and mortality are very uncertain.

The cost-effectiveness estimates meet the criteria for a quality-adjusted life year weight of 3.0 (that is, show that cerliponase alfa provides substantial extra health and quality-of-life benefits), but are also very uncertain. However, they could plausibly be within the range that NICE normally considers an effective use of NHS resources for highly specialised technologies.

It is also recognised that CLN2 is a rare, devastating condition, that there is a substantial unmet need for an effective treatment, and that there are benefits beyond direct health benefits not captured in the economic analysis.

Taking all these factors into account, cerliponase alfa could provide value for money within the context of a highly specialised service. However, there is substantial clinical uncertainty and a high financial risk to the NHS. Therefore, a managed access agreement is needed to ensure the financial risk is addressed while allowing people expected to benefit most from cerliponase alfa access to it as further data are collected.

2 The condition

2.1 Neuronal ceroid lipofuscinosis type 2 (CLN2) is a rare genetic disease caused by deficiency of the enzyme called tripeptidyl peptidase 1 (TPP1). It is 1 form of neuronal ceroid lipofuscinosis, also known as Batten disease. CLN2 is inherited as an autosomal recessive disorder, which means that both chromosome copies carry mutations in the CLN2 gene, and both parents are unaffected carriers. A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells. Accumulation of these proteins and lipids prevent the cells from functioning as they should.

2.2 CLN2 progresses rapidly and predictably from presentation in late infancy to death by early adolescence. It is characterised clinically by a decline in mental and other capacities, epilepsy and sight loss because of retinal degeneration. Histopathologically, there is intracellular accumulation of ceroid lipofuscin in the neuronal cells of the brain and retina. Symptoms in children with CLN2 appear in the second year of life and can then progress rapidly with a decline in speech, the onset of seizures, loss of mobility, involuntary muscle spasms and, later on, visual impairment leading to blindness. Ultimately, the child will become totally dependent on families and carers for all their needs. Life expectancy is around 8 years to early adolescence.

2.3 The exact prevalence and incidence of CLN2 is unknown. It is estimated that, in the UK, around 3 to 6 children are diagnosed each year and currently around 30 to 50 children are living with the condition.

2.4 There is no cure or life-extending treatment option available for CLN2. Clinical management focuses on symptom control, monitoring and preventing complications, and palliative care. The aim is to maintain function for as long as possible and to improve quality of life. This involves a multidisciplinary and multiagency team working to control symptoms and complications such as malnutrition, gastroesophageal reflux, pneumonia, anxiety, Parkinsonian symptoms and dystonia, using medication and physical therapy. Children often need multiple medications, and clinicians need to balance symptom control with adverse effects and treatment interactions.

3 The technology

3.1 Cerliponase alfa (Brineura, BioMarin) is an enzyme replacement therapy consisting of a recombinant form of human tripeptidyl peptidase 1. It is expected to restore deficient tripeptidyl peptidase 1 (TPP1) activity in the brain caused by the genetic mutation. Cerliponase alfa has a UK

marketing authorisation granted under 'exceptional circumstances' for 'the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease', also known as TPP1 deficiency.

3.2 Cerliponase alfa is administered into the cerebrospinal fluid by infusion via a surgically implanted intracerebroventricular access device (reservoir and catheter). It must only be given in a healthcare setting by a trained healthcare professional knowledgeable in intracerebroventricular infusion administration. The recommended dose is 300 mg cerliponase alfa once every other week, but lower doses are recommended in patients under 2 years.

3.3 The adverse reactions listed as very common (that is, occurring in 1 in 10 people or more) in the summary of product characteristics for cerliponase alfa include: hypersensitivity, upper respiratory tract infection, seizures, headache, irritability, cerebrospinal fluid pleocytosis, vomiting and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 The list price of cerliponase alfa in England is £20,107 per 300 mg pack (excluding VAT), consisting of 2x150 mg vials. The recommended dosage for those over 2 years old is 300 mg every other week (at an annual cost of £522,782 per person).

4 Consideration of the evidence

The evaluation committee (see section 7) considered evidence submitted by BioMarin, the views of people with the condition or their carers, those who represent them, clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Course of CLN2 and current treatment options

4.1 The clinical and patient experts confirmed that neuronal ceroid lipofuscinosis type 2 (CLN2) is a progressive and devastating condition, and that there are currently no treatments available to treat the underlying cause of the condition. The committee heard that children with CLN2 are born seemingly healthy and develop normally in the first few years of life. Onset of symptoms typically starts in late infancy between the ages of 2 years and 4 years. Most children first present with delayed language development, followed by seizures and some loss of motor function (for example, increase in falls). Progression is then very rapid and predictable, leading to deterioration, and then loss of speech and walking ability. Most patients are unable to sit unsupported and become non-communicative by 6 years old. Children also have progressive difficulties with swallowing, constipation, hydration, respiratory function and sleep disturbance, and may need gastrostomy feeding. Visual acuity declines from around 4 years, leading to blindness within 3 years. Most children over 6 years with CLN2 become bedridden, and have myoclonus, epilepsy, dystonia, and ultimately blindness. Currently, there are no treatments for the underlying cause of the condition, and options focus on symptomatic relief, and supportive and palliative care. Children with CLN2 usually die at between 8 years and early adolescence; the average age of death is 10 years. The committee recognised that CLN2 is a devastating condition associated with very poor quality of life and a very short life expectancy, and that there is a significant unmet need in terms of effective treatment options.

Diagnosis of CLN2

4.2 The committee heard from the clinical experts that there is typically a delay of 2 years from the time of first seizure to diagnosis of CLN2. The experts explained that, currently, the earliest time point for laboratory

testing for CLN2 would be at the time of the first seizure. However, referral to a paediatric neurologist and specific testing often happens later, when the seizures are recurrent and found to be drug resistant, and motor and language delays are more pronounced. The clinical experts explained that most children with CLN2 first present with developmental delay, but that this alone is not sufficient to trigger suspicion of CLN2. This is because about 10% of all children in England have some developmental delay. This makes diagnosis at the earliest stage of the disease difficult. The patient experts agreed that, in an otherwise healthy and normal child, language delays are not generally seen as a cause of worry. However, they stressed that the pathway to diagnosis, even after children have had seizures and motor issues, can be long and uncertain.

Effect of the condition on parents and siblings

4.3 The patient experts stated that CLN2 has an adverse emotional, physical and financial effect on families. They explained that families' lives are altered as their children start developing symptoms, and that delay in diagnosis means they often have little or no support at the outset. Hearing about the lack of treatment options, and the rapid and severe course of the disease, has a huge emotional effect on families when CLN2 is diagnosed. As symptoms progress, children become increasingly reliant on their carers and are usually completely reliant by 6 years (see section 4.1). This increasingly, and severely, affects their carer's quality of life. Parents become full-time carers for their children, which places a financial burden on families. As children get older and heavier, the role of carer becomes physically burdensome. The parents explained that siblings who do not have the condition often find it difficult to process the changes to their lives, and parents struggle to provide a normal life for them. Moreover, often more than 1 child in a family is affected and this increases the burden on their parents. The committee acknowledged the emotional distress that comes with caring for a child with a life-limiting debilitating condition, and also recognised that CLN2 causes physical and

financial issues for families. It concluded that CLN2 severely affects the lives of families, carers and siblings.

Impact of the new technology

Clinical trial evidence

4.4 The main clinical evidence submitted by the company came from 3 studies (190-201, 190-202 and 190-901). Study 190-201 was a single-arm open-label study including 23 children aged 3 years to 16 years with late-infantile CLN2 treated with cerliponase alfa. Patients were enrolled from the US, Germany, Italy and the UK. Follow up was 48 weeks. After the completion of 190-201, patients were enrolled in an extension study (190-202) for long-term follow up. All patients who completed 190-201 transitioned to 190-202, in which data collection will continue for up to 240 weeks. Study 190-901 was a natural history study that retrospectively evaluated disease progression in patients with untreated CLN2 (included in the DEM-CHILD database). To provide comparative data for the efficacy outcomes in 190-201/202, the company matched the 190-901 cohort using a 1:1 matching algorithm. This matched patients on their CLN2 clinical rating score and age. The clinical experts stated that the populations across the studies were generalisable to patients seen in clinical practice in England. The committee recognised the limitations of developing an evidence base for an ultra-rare disease and was satisfied that it had been presented with the best available evidence.

CLN2 clinical rating scale

4.5 The primary efficacy outcome in the clinical studies was change in the CLN2 clinical rating scale score. The committee understood that this scale had been adapted by the company from the Hamburg and Weill Cornell scales, 2 validated CLN2-specific instruments. This had been done to focus on the motor and language domains, but it excluded other domains (such as visual function, seizures, myoclonus, and feeding and

swallowing). Both domains are scored from 3 (normal or near-normal condition) to 0 (complete loss of function); a total range of 6 to 0. The company and a clinical expert explained that walking ability (motor function) and language are key functional health domains that are closely linked to the progression of CLN2. The ERG stated that the European Medicines Agency (EMA) had confirmed the scale was acceptable as a primary outcome in the short-term context of 190-201/202. However, the EMA expressed reservations that focusing on language and motor domains prevented a more comprehensive evaluation of a patient's clinical situation. The committee was aware that vision and seizure domains were also presented in secondary analyses using the full Hamburg scale. It concluded that, on balance, the CLN2 clinical rating score was an acceptable instrument to inform efficacy outcomes in the short term, but that it would also consider any broader measures presented in its considerations of clinical effectiveness.

Mixed-effect model to estimate rate of decline in CLN2 scores in the natural history population

4.6 The committee was aware that the company had estimated the mean rate of decline in CLN2 scores in the untreated population in study 190-901. It did this to form a reference point against which to compare observed outcomes in the patients who had cerliponase alfa. The company explained that the estimated mean rate of decline in CLN2 scores in the untreated natural history study was 2 points per 48 weeks (in which each 1-point change in score represented a clinically meaningful change in motor function and speech, and in quality of life). The ERG noted that estimates of mean decline in the natural history controls varied depending on the statistical method used. More sophisticated methods, such as mixed models for repeated measures, resulted in lower estimates (a 1.29- to 1.46-point decline per 48 weeks). The ERG explained that the more sophisticated statistical methods were superior to the company's simplistic approach because they made better use of all the available data

points. The committee concluded that all available data should be used when possible. It also concluded that the mixed effects model used by the ERG was more appropriate to estimate the rate of decline in CLN2 scores in the natural history population.

Results

4.7 The committee discussed the results presented for CLN2 clinical rating scale scores, noting that the company conducted a number of analyses on this endpoint. Originally, data were provided from the 48-week analysis of the pivotal clinical trial, study 190-201, which included:

- Responder analysis (the percentage of patients with less than a 2-point decline on the CLN2 clinical rating scale per 48 weeks): this showed that, in 65% (15/23) of patients who had cerliponase alfa, there was no change or an improvement in score (stabilisation) at week 48. Additionally, there was a 1-point (or better) decline in 87% of patients, which was statistically significantly better than the expected rate of 50% in the untreated population.
- Slope analysis (mean rate of decline in CLN2 scores): this suggested that patients who had cerliponase alfa had a slower rate of decline in CLN2 scores than patients who had no treatment (0.48 points per 48 weeks in the treatment group compared with 2.09 points in the natural history population estimated by the company).
- Time-to-event analysis (time taken to have a 2-point scale score change) comparing the full natural history cohort (not the matched natural history cohort): this showed that the natural history population was more likely to have an unreversed 2-point decline in CLN2 score compared with patients who had cerliponase alfa (results are academic in confidence).

The committee agreed that CLN2 scores showed that cerliponase alfa was effective in slowing disease progression in 2 key functional

domains (motor and language). This was the case even when compared with rates of decline in CLN2 scores in the untreated population, as estimated by the ERG using its preferred mixed effects model (a 1.29- to 1.46-point decline per 48 weeks; see section 4.6).

4.8 After consultation, the company submitted further clinical data. These data are deemed to be academic in confidence by the company, so cannot be presented. However, the company stated that the results were supportive of an effect with cerliponase alfa, and indicated a trend towards long-term disease stabilisation.

4.9 The committee discussed the results (academic in confidence) from the secondary endpoint analyses including the Hamburg scale. It noted the company's statement that the results showed a durable treatment effect and broad-based disease stabilisation that was not domain specific. In particular, the committee discussed the effects on seizure and vision domains:

- Seizures: the committee noted the improvement in scores in the seizure domain. It also heard from a patient expert that their child, who started having cerliponase alfa at a later stage in the disease (having lost mobility), had gone from having multiple seizures to 1 seizure in the 18 months after starting treatment. Their younger sibling, who had treatment at an earlier stage in the disease, had not had a seizure in the 15 months since starting treatment. However, the ERG highlighted that the seizure domain of the Hamburg scale reflects only frequency of tonic-clonic seizures and does not take into account other seizure types. A clinical expert confirmed that the CLN2 scale captures the tonic-clonic seizures needing rescue medication and hospitalisation, and which therefore substantially affect quality of life, but there is the possibility that other events may not be captured. The committee discussed the ERG's interpretation that new electroencephalography (EEG) activity could be suggestive of new seizures activity. The clinical

experts confirmed that EEG activity is not interpreted in this way. One clinical expert noted that EEG activity can be used to guide treatment, with spikes in EEGs reducing the probability that people will stop seizure-controlling treatment. The company stated that the evidence showed that treatment with cerliponase alfa slows the deterioration of myoclonus-related symptoms. The ERG noted that slowing deterioration does not imply that myoclonus symptoms are fully controlled. A clinical expert stated that continuous myoclonus is characteristic of later stages of the disease, and is very painful and difficult to treat. The expert highlighted that people having treatment with cerliponase alfa have not had disease progression to a point where there are continuous myoclonus symptoms. The committee concluded that the long-term effect of cerliponase alfa on seizures remained uncertain. However, it agreed that some seizure control with treatment, with a subsequent effect on quality of life, was plausible.

- Vision: the company stated that patients having treatment with cerliponase alfa had a slower decline in vision (as measured by the vision domain in the Hamburg rating scale) than patients who had not had treatment. The ERG noted that baseline vision scores were higher for the cerliponase alfa group than for the natural history group, so the comparability was limited. The ERG also noted that the vision domain of the Hamburg scale may not have been the most appropriate scale to measure deterioration in vision because the scale wording necessitates a certain level of motor function (for example, grabbing objects). It stated that other more specialised ophthalmological endpoints would have been more appropriate for assessing vision decline. The company stated that the vision domain score of the Hamburg scale is a validated measure of visual function in the people with CLN2 disease. The ERG also noted concerns relating to the lack of biological plausibility for cerliponase alfa slowing vision deterioration. This is because cerliponase alfa is administered by intracerebroventricular infusion and may not reach therapeutic levels in the retina because of the blood-

retinal barrier. The company acknowledged the physiological mechanism to explain that the treatment effect on vision was uncertain. However, it stated that central brain function also affects vision, so some improvement in vision was biologically plausible through the effect of treatment directly on the brain. It noted that it did not expect treatment with cerliponase alfa to prevent vision loss. However, based on the trial results, the committee thought that a slowing of visual deterioration was plausible. In the EMA's clinical assessment of cerliponase alfa, it noted that an effect on retinal tissue could not be totally excluded with intracerebroventricular infusion administration. However, it suggested that further data collection was necessary to determine clinical plausibility. The committee concluded that there was insufficient evidence to suggest that cerliponase alfa would prevent vision loss in people with CLN2.

4.10 The parents stated that cerliponase alfa has had great effect on the physical health of their children and an immeasurable effect on their lives as a family. In their experience, the children had not had any further deterioration in their health, in a usually rapidly progressive disease. This contrasted with other children who did not take part in the cerliponase alfa trials, who had deteriorated a lot and some of whom had died. The experts confirmed that cerliponase alfa was also not associated with adverse events that could not be easily managed. The committee queried whether administrating cerliponase alfa via intracerebroventricular infusion posed any additional risks or burden for patients. The clinical experts stated that it is associated with a risk of infection but, because it is carried out exclusively in specialist settings, the risk is reduced and there were no infection-related deaths in the trials. The committee heard that treatment in England would continue to be delivered in specialist centres. The parents noted the burden of travelling for treatment, but emphasised that it was insignificant compared with the benefits of treatment to their children. The committee concluded that substantial benefits had been shown with

cerliponase alfa in the short term for treating the key neurological aspects of CLN2.

Long-term effectiveness

4.11 The committee was aware that the assumptions about long-term disease stabilisation were key drivers for the results from the economic model. The company categorised patients having cerliponase alfa into 2 groups. Patients who did not have an unreversed CLN2 score-point decline after week 16 were classified as 'early stabilisers'. Those patients having an unreversed points decline after week 16 were classified as 'late stabilisers'. The company assumed that early stabilisers would have no further decline in CLN2 score after week 16, and that late stabilisers would not have a decline after week 96. The ERG stated that there were a number of limitations related to these assumptions:

- These definitions were determined after the studies, which was inappropriate because differences in response may be because of sampling error rather than a genuine difference in response patterns to cerliponase alfa treatment.
- Trial data were not sufficiently long enough (96 weeks) to make long-term judgements about disease stabilisation.
- Long-term trends in CLN2 scores (data academic in confidence) implied that scores will continue to decline for late stabilisers beyond 96 weeks, so contradicting the assumption that disease stabilises in all patients.
- Relative to baseline, there was a trend of new epileptiform activity on EEG, suggesting that disease progression had not halted completely.

The committee recognised that there were substantial benefits with cerliponase alfa during the trial. However, it noted that cerliponase alfa could be expected to be used for decades, and that the results could not show whether the disease would remain stabilised over that period

of time. The committee heard from 1 clinical expert that, if disease was stabilised at an early stage, then age appropriate development could be expected going forward. However, another clinical expert stated that meeting developmental milestones at younger ages, as seen in trials, may not necessarily reflect long-term development. The committee concluded that, although cerliponase alfa would likely provide long-term benefits, assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty.

4.12 The committee recalled that, after consultation, the company submitted further clinical data (see section 4.8). However, these data are deemed to be academic in confidence by the company, so cannot be presented. The company considered that this additional evidence supported a trend towards long-term disease stabilisation. The committee agreed that the evidence showed that the substantial benefits seen with cerliponase alfa continued. However, it concluded that the additional evidence submitted after consultation did not change its conclusion that the assumptions about disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty.

Asymptomatic and presymptomatic diagnosis

4.13 The committee noted that the decision problem included a subgroup of siblings with confirmed CLN2 who were asymptomatic and presymptomatic. It was aware that there was an ongoing trial (190-203) including younger siblings of patients in 190-201, but noted that no results are currently available. A parent stated that their child was taking part in this trial, and that they continued to meet age appropriate development milestones without any signs of CLN2. The expert explained that this was in contrast to the experience with their older child with CLN2 diagnosed at a later stage. The company acknowledged that no clinical evidence was currently available but stated that, by definition, disease progression would not have been seen in patients with CLN2 who were asymptomatic

or presymptomatic. This meant they would have a CLN2 clinical rating score of 6 at diagnosis and start of treatment, with the expectation that the disease would stabilise in this health state. In the EMA's clinical assessment of cerliponase alfa, it highlighted the importance of starting treatment in children as young as possible. However, it noted that there were no children under 3 years old in 190-201, and the youngest child in the sibling trial was 2 years old. The committee was aware of the current absence of any evidence, but recognised that children with disease diagnosed and treated earlier in the pathway will have better outcomes.

Mortality

4.14 The committee was aware that, by assuming long-term disease stabilisation (see section 4.11), the company's base case implicitly assumed that patients having cerliponase alfa would have the same life expectancy as the general population. The ERG stated that this was unrealistic and considered that mortality related to neurological progression, as well as extra-neurological mortality, was relevant. The committee agreed that, because it had concluded that the assumption around late stabilisation was very uncertain (see sections 4.11 and 4.12), it was plausible that patients would have further disease progression with an associated mortality risk. The ERG explained that, while death usually occurs because of complications from neurological degeneration, the expression of TPP1 is not limited to the central nervous system and untreated accumulation of ceroid lipofuscin could lead to pancreatic, intestinal, cardiac and hepatic impairment. The company emphasised that CLN2 is primarily a neurological degenerative disorder rather than a multifunctional disorder. It stated that there has been no experience of any cardiac adverse events for people having cerliponase alfa in the clinical development programme. The company also stated that patients with atypical CLN2 who survived longer than usual did not have high rates of cardiovascular disease. The committee considered that patients with atypical disease may not have the likely mortality outcomes seen in

patients with more typical disease treated with cerliponase alfa. It was also aware that the EMA had not dismissed concerns about cardiac impairment, although this related more to potential adverse effects of treatment. However, after consultation, the committee heard strong testimonies that there was no experience of extra-neurological progression in patients having cerliponase alfa. The clinical experts emphasised that there was no expectation of extra-neurological mortality. The committee acknowledged that, without longer-term data, the effect of CLN2 on mortality because of effects in other body systems was completely unknown. It agreed that extra-neurological mortality, although plausible, was not supported by the trial evidence nor the clinical experts. The committee concluded that, because of disease severity, collecting further data of continued neurological progression-related mortality was appropriate, but incorporating extra-neurological mortality risk was not.

Health-related quality of life

4.15 The committee noted that, to measure quality of life, the studies included the Paediatric Quality of Life Inventory (PedsQL) Parent Report for Toddlers, the PedsQL family impact module (PedsQL-FIM) instruments and a CLN2-based quality-of-life instrument. Additionally, EQ-5D-5L data were collected in the 190-202 extension study. Variations in EQ-5D-5L scores were compared with a baseline point when patients transitioned from 190-201. Analysis of EQ-5D-5L scores found no change or a favourable change when comparing baseline scores with week 97 follow up. There was a mean improvement in PedsQL score from baseline to week 49, but a mean decline from week 49 to 97, resulting in an overall reduction in quality of life from baseline to week 97. Consistent findings were seen in the family impact module of the instrument, with an improvement from baseline to week 49, but an overall decline by week 97. However, changes in scores for the CLN2-disease-specific instrument, CLN2QL, indicated overall improvement in quality of life from baseline to week 97. The committee was aware of the experiences reported by

parents of children with CLN2 about the severity and burden of untreated disease, and the quality-of-life benefits with cerliponase alfa. It concluded that treatment with cerliponase alfa was associated with at least an initial improvement in quality of life.

Cost to the NHS and value for money

Economic model

4.16 The company presented a cost-effectiveness analysis comparing cerliponase alfa with standard of care. The cost-effectiveness results were estimated using a multi-state Markov model, which tracked the progression of patients through 10 unique health states based on CLN2 clinical rating scores and other clinical factors. The committee heard from the company that the model structure was based on natural history data and clinical expert opinion. The CLN2 clinical rating scale was used to define health states 1 to 7, starting in health state 1 with a CLN2 score of 6 (the best health state; normal or near-normal motor and language function), and moving to health state 7 with a CLN2 score of 0 (no motor or language function). Health state 8 was defined as patients with a CLN2 clinical rating score of 0 with complete vision loss (defined by clinical experts as the point where no further loss of vision would be expected to affect the patient's quality of life). An additional need for palliative care progressed patients from health state 8 to health state 9, and health state 10 was death. To capture aspects of disease progression beyond motor and language domains, the company used a Delphi panel to validate other progressive symptoms included in each health-state definition (such as, chronic seizures, disease-related distress, dystonia, myoclonus, vision and the use of a feeding tube). The committee was satisfied that the model structure reflected the course of CLN2.

Transition through the model

4.17 To model the progression of CLN2 through the economic model the company estimated transitional probabilities from data collected in the natural history study (190-901) for the comparator arm, and from 190-201/202 at week 24 for the cerliponase alfa arm. Transitions in the more progressed states (7 to 9) were informed by clinical expert opinion in both arms. The ERG stated that, although transition probabilities were not a key driver in the model, it preferred to estimate cerliponase alfa transition probabilities using individual patient data available in the clinical study report. The committee concluded that using individual patient data was a more robust approach.

4.18 The committee discussed including progressive vision loss in the model, which was linked to a patient's progression through the health states. These states were defined by deterioration in motor and language function, with complete vision loss occurring in health state 8. However, for patients having cerliponase alfa, any stabilisation of motor and language function may not have resulted in a similar stabilisation of visual function. Therefore, the model did not adequately capture vision loss for patients having cerliponase alfa. The committee recalled its consideration (see section 4.9) that there was no evidence to suggest that cerliponase alfa would have an effect on stabilising vision in people with CLN2. It also agreed with the ERG that the model should have accounted for progressive vision loss. The committee noted that the ERG presented a scenario exploring incorporating a disutility and additional costs associated with blindness. These were applied to the proportion of patients having cerliponase alfa in health states 1 to 6 who were estimated to have complete vision loss. The committee concluded that this was appropriate.

Resource use in the model

4.19 The ERG identified some cost items that were not included in the company's model. These included additional monitoring costs, electrocardiograms (ECGs), providing psychiatric and psychological support, and residential care costs:

- The ERG stated that the EMA recommends an ECG during infusion every 6 months. Additionally, some patients may develop conduction disorders or heart disease, and ECG monitoring during each infusion is recommended in patients with present or past bradycardia, conduction disorders or structural heart disease. The ERG therefore applied an additional cost of an ECG to patients on treatment every 6 months and to the proportion of patients with heart disorders needing an ECG every infusion.
- On clinical expert advice, the cost of psychiatric support for patients was included in the model. This was based on behavioural symptoms associated with the disease.
- Patients entering adulthood with CLN2 may no longer have care at home, and are expected to receive a care package that might include stay in a care home with nursing. The ERG estimated the cost of this based on Personal Social Services Research Unit annual costs for a young adult with a severe acquired brain injury. This was used as a proxy because it was assumed that the level of care for these patients would be similar. It was applied in the model for 50% of patients over 18 years and replaced the costs of specialist nursing and NHS caregivers.

The committee considered these additional costs to be reflective of clinical practice in England, also noting that they did not have a substantial effect on the results.

Long-term stabilisation incorporated in the model

4.20 The company incorporated assumptions relating to the disease progression of early and late stabilisers in the model (see section 4.11). The committee understood that, in the company's base case, a patient's disease progression was modelled until week 96, after which they remained in the same health state for the remainder of the time horizon. The committee recalled its discussions around disease stabilisation. It reiterated the substantial uncertainty around assuming long-term disease stabilisation for all patients having treatment with cerliponase alfa. It noted that the ERG presented exploratory analyses including scenarios assuming no long-term disease stabilisation and partial stabilisation (for early stabilisers only). In the scenario assuming partial stabilisation, in patients having cerliponase alfa whose condition stabilised by week 16, the condition remained stable for the entire time horizon of the model, but late stabilisers continued to have disease progression after week 96. The rate of progression after week 96 was defined by the transition probabilities used to model progression between 17 weeks and 96 weeks. In the absence of any long-term evidence and the positive short-term experience with cerliponase alfa, the committee considered that assuming partial stabilisation may be reasonable and concluded that it would consider this scenario in its decision making.

4.21 The committee recalled that, after consultation, the company presented longer-term clinical data which it considered suggested a trend towards disease stabilisation (see section 4.8). The ERG illustrated that assumptions about any disease stabilisation are a key driver of the incremental cost-effectiveness ratio (ICER). The committee considered that the most it could conclude on the evidence presented was that the evidence supporting long-term stabilisation was no worse than that assumed previously. It therefore concluded that there was no change to its preferred approach to decision making, that is, the scenario incorporating partial stabilisation. However, it agreed that the clinical

uncertainty in long-term stabilisation remained a key uncertainty in the modelling.

4.22 In its base case, the company assumed that disease-related mortality depends on time in the palliative health state, which implies that patients cannot die of disease-related causes in earlier health states. No extra-neurological progression mortality risk was included. The committee recalled its discussion (see section 4.15) about how it was unrealistic to assume that patients having cerliponase alfa would have the same life expectancy as the general population. The ERG presented analyses exploring the effect of incorporating neurological progression-related mortality and extra-neurological progression-related mortality. The committee agreed that, because it did not expect disease to stabilise in 100% of patients, incorporating continued neurological progression-related mortality for some patients was appropriate. However, it recalled its conclusions that extra-neurological mortality, although plausible, was not supported by the trial evidence nor by the clinical experts (see section 4.15). The committee concluded that neurological progression-related mortality should be modelled, but extra-neurological related mortality should not.

Starting distribution of patients

4.23 The distribution of patients across health states at the start of the model was based on the population expected to have treatment for CLN2 in the UK. In the company's base case, it assumed that there is earlier diagnosis in clinical practice compared with the trial data. This was because clinical practice has improved since the trials were conducted and there may have been a delay between diagnosis and when people were recruited to the trial. The ERG highlighted that assuming earlier diagnosis had a considerable effect on the quality-adjusted life years (QALYs) gained in the model. However, it stated that there was little evidence to show the most plausible starting distribution. The starting distribution in the

company's base case assumed that most patients (about 80%) would start treatment in heath states 1 and 2 (CLN2 score 6 and 5 respectively), the least severe health states in the model. The ERG highlighted that this differed substantially from the trial, in which only 16% of patients were in these least severe health states. In a further analyses, the company presented an alternative scenario in which a smaller proportion (60%) were assumed to start treatment in health states 1 and 2. The distribution was: CLN2 score 6 – 20%; CLN2 score 5 – 40%; CLN2 score 4 – 25%; CLN2 score 3 – 10%; CLN2 score 2 – 5%.

4.24 Following consultation, the committee heard from NHS England that, since the NHS Genomics Medicines Service was established in 2018, much work has been done around standardisation of testing, including testing for CLN2. The company, clinical experts and NHS England considered that the work being done to improve access to genomic testing will change the current diagnostic pathway and will ensure children with CLN2 are identified earlier. They stated that this would mean children would more likely be identified while in the best health states. They considered that it would be reasonable to assume a starting distribution of CLN2 score 6 – 50% and CLN2 score 5 – 50% could rapidly be achieved in the near future. The committee acknowledged that gene panel testing had the potential to reduce time to diagnosis, and so lead to earlier treatment, over time. However, it was concerned that implementation was a complex and challenging task that needs national coordinated scientific and clinical expertise, and substantial project management and audit arrangements. It heard from the company, NHS England and the patient groups that they were all committed to working with stakeholders to increase awareness and support the earlier diagnosis of CLN2. The committee accepted the reassurance, particularly from NHS England, which is responsible for the roll out of gene panel testing. It concluded that it would assume a starting distribution of CLN2 score 6 – 50% and CLN2 score 5 – 50% in its decision making. However, it noted that this

assumption is currently aspirational and an improvement in CLN2 starting distribution needs to be rapidly achieved.

Utility values

4.25 The committee noted that the utility data collected in the clinical studies (190-201/202) were not included in the model. This was because utility values were not available for all health states, and none were available for patients having standard care. Instead, the utility values for the base case were derived from a utility study commissioned by the company, in which vignettes describing the health states for both cerliponase alfa and standard care were developed. The vignettes were validated by a clinical expert, and sent to 8 clinical experts who completed the EQ-5D-5L questionnaire as a proxy for patients in the health states. These were mapped to the EQ-5D-3L before being applied in the model. The committee was concerned about the robustness of the vignettes used to elicit these utility values. It noted that they contained additional disease elements, such as control of dystonia and myoclonus, disease-related pain, frequency of tonic-clonic seizures and the need for a feeding tube. The committee agreed that these additional disease elements had an unclear association with the motor and language scale that defined the health states. The committee discussed that it would generally prefer to include values directly collected in trials. It acknowledged, however, that the PedsQL measure excludes the possibility of negative values, so may not be realistic given the severity of disability with CLN2. The committee considered that neither source of data was sufficiently robust. However, it concluded that, in the absence of further evidence, it would consider analyses based on EQ-5D-3L values estimated from the utility study using vignettes.

4.26 The committee understood that the clinicians provided separate utility estimates for patients who did or did not have cerliponase alfa in each health state. These estimates were then accrued by patients as they

progressed through the health states of the economic model. Therefore, utility values were determined not only by the health state patients were in, but also by the treatment they had. The ERG highlighted that the vignettes implied substantial additional treatment benefits with cerliponase alfa over and above its primary effect on stabilising motor and language deterioration, some of which were not reported for patients in the clinical trials. Specifically, the vignettes implied that cerliponase alfa improved seizure control, and control of dystonia and myoclonus, so reducing associated pain and delaying the need for a feeding tube. The committee heard anecdotal evidence from the clinical experts that suggested cerliponase alfa was effective in controlling other aspects of CLN2 not captured by the model structure. In response to the consultation, the company presented an alternative scenario in which on-treatment utility values incorporated fewer additional disease elements (that is, it did not incorporate utility benefits from improved dystonia control and delaying the need for a feeding tube). In this scenario, it applied standard-of-care utility values in all health states, but patients on cerliponase alfa had a utility increment of 0.1 in health states 2 to 4 and 0.2 in health states 5 to 6. The ERG highlighted that on-treatment utility benefits in health states 2 to 7 were higher in the company's alternative scenario than in their original base case. This was contradictory to the claim that fewer additional treatment benefits were incorporated. It also noted that the utility increments incorporated by the company were chosen arbitrarily, and the supporting evidence was not consistent with the increments applied. The ERG acknowledged that there could be an improvement in tonic-clonic seizure control for patients having treatment, but including utility benefits associated with pain and myoclonus was too uncertain. To account for this, it applied a utility increment of 0.045 in health states 2 to 6. The committee also heard from the ERG that the utility values applied in the less severe health states (health states 1 and 2) were very high. The ERG stated that, while this potentially reasonably represented the children's health-related quality of life, it implied that the utility values

exceeded those of the adult general population. The ERG applied a disutility for patients over 18 years to account for this. The committee concluded that treatment with cerliponase alfa could result in some additional utility benefit beyond that achieved through delaying disease progression, and agreed that it would take the company's approach to modelling health-state utilities into consideration. It further concluded that adjusting utility values for people over 18 years old was preferable.

4.27 The company included disutility values for carers and siblings in the economic model in all 10 health states and for the entire treatment duration. The committee was satisfied with the principle of including these disutility values but discussed the ERG's concern that they continued for too long in the model. It agreed with the ERG that applying the disutilities for carers and siblings for the whole 95-year time horizon was unrealistic given life expectancy of parents, and also because disutility may change as siblings grow up and move on. Instead, the committee considered the ERG's exploration of applying the disutility values for 30 years to be more reflective of real life. The committee noted that it would like to have seen a scenario exploring different changes in disutility values for carers and siblings over time, but acknowledged that there was no evidence to suggest how these might vary with time. It concluded that the ERG scenario exploring including disutility values for carers and siblings for 30 years was sufficiently robust for its decision making.

Discount rate

4.28 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) specify that the discount rate that should be used in the reference case is 3.5% for costs and health effects. However, it also states that a non-reference-case rate of 1.5% for costs and health effects may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely

impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to substantial irrecoverable costs. The company, in its base case, incorporated a discount rate of 1.5% for costs and health effects. It justified this change from the reference case, stating that the benefits of treatment were expected to be substantial and sustained over a lifetime. The committee recalled its discussions around disease stabilisation (see sections 4.21 and 4.22) and did not consider it likely that people with CLN2 treated with cerliponase alfa would be considered to have 'normal or near-normal health'. The committee concluded that there was no justification for deviating from the reference case discount rate of 3.5% for costs and benefits.

Applying QALY weighting

4.29 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with cerliponase alfa, and highlighted that these were above 30 in the scenario that was considered most plausible by committee (see section 4.31; the exact QALY gains are considered commercial in confidence by the company, so cannot be reported here). Taking into account the incremental QALY gains associated with cerliponase alfa, the committee concluded that cerliponase alfa met the criteria for a QALY weight of 3.0.

Cost-effectiveness analysis results

4.30 The company and NHS England have agreed a confidential commercial arrangement as part of a proposed managed access agreement. The company considers all results of the economic analysis incorporating this arrangement commercial in confidence, so ICERs cannot be reported.

4.31 The committee considered that the ERG's analysis formed a reasonable basis for decision making. However, it agreed that several assumptions incorporated in the ERG analysis were overly conservative. The committee noted that the following ERG assumptions were plausible:

- ERG-calculated transition probabilities for patients who had cerliponase alfa (see section 4.18)
- assuming all patients go blind over time, and incur related support costs and disutility (see section 4.19)
- including additional resource use items (ECG, psychiatric support, residential care; see section 4.19)
- applying age-adjusted utilities (see section 4.26)
- removing carer and sibling disutility after 30 years (see section 4.27)
- applying a discount rate of 3.5% for costs and benefits (see section 4.28).

The committee recalled its conclusions about the starting population, disease stabilisation, mortality and utility values, and it agreed that the following assumptions should be incorporated into its preferred analysis:

- including continued neuro-disability-related mortality (see section 4.15)
- disease stabilisation for 74% of late stabilisers who had cerliponase alfa (see sections 4.21)
- a starting population in which patients start in health states 1 and 2 (CLN2 scores of 6 – 50% and 5 – 50; see section 4.24)

- assuming that there is a health-state utility increment for people having cerliponase alfa, as estimated by the company (see section 4.26).

The committee was aware of the uncertainty surrounding all the analyses in the absence of long-term evidence, including its preferred analysis, but concluded that this was more plausible than the company's base case.

4.32 Cerliponase alfa met the criteria for a QALY weighting of 3.0 (see section 4.29). The committee concluded that, while highly uncertain, the ICERs, with the QALY weighting applied, could plausibly be within the range NICE normally considers an effective use of NHS resources for highly specialised technologies.

4.33 The committee discussed the subgroup including asymptomatic and presymptomatic siblings. It recalled (see section 4.13) that the company expected that these patients, at diagnosis, would have a CLN2 clinical rating score of 6 (assuming that the disease would stabilise in this health state). On this basis, the company presented a subgroup analysis in the economic model. This assumed that these patients would start treatment in health state 1. In this, compared with the company's base case, more QALYs were accrued because patients entered the model in a less severe health state, so their disease stabilised before progression had occurred. This meant the ICERs were substantially lower for this subgroup. The committee considered that this was plausible but remained aware that there was no clinical evidence available in this population.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.34 The committee discussed the impact of cerliponase alfa beyond its direct health benefits and the testimony of the patient experts. It was aware of the very large impact of CLN2 on families, including the emotional effect

on carers, family relationships and siblings with the disease. It noted that there is a substantial financial impact on families from parents having to give up work to provide full-time care and because of the costs of home adaptation. The committee heard from parents that treatment with cerliponase alfa has completely changed their experience of having children with CLN2. This was because children remained healthy, able to live a normal life and attend mainstream school and activities. This, in turn, allowed parents to work and provide a normal childhood for siblings without the disease. The committee also noted comments that treatment with cerliponase alfa would reduce the expenditure incurred by non-NHS government departments that provide support for families affected by CLN2. The committee considered that some of these aspects were included in the economic analysis. However, it recognised that the full effect of benefits beyond direct health benefits had not been quantified. The committee considered the uncaptured benefits qualitatively in its decision making.

Managed access agreement

4.35 The company proposed a managed access agreement because it acknowledged that there were substantial uncertainties in the clinical evidence. It considered that this would: provide access to cerliponase alfa for people who would benefit most from treatment; and address key uncertainties by collecting longer-term clinical, health-related quality-of-life and neurodevelopmental data. The committee agreed that it would be useful to collect real world evidence to show that the outcomes and assumptions presented in the analysis were plausible. In particular, it noted that assumptions on long-term disease stabilisation (see section 4.21) and improvements in CLN2 starting distribution (see section 4.24) are currently very uncertain and have a substantial impact on the cost-effectiveness estimates. It also acknowledged the need to manage the financial risk to the NHS, given the high cost of cerliponase alfa and the substantial remaining clinical uncertainties. The committee

concluded that a managed access agreement would be appropriate to collect data to address some of the clinical uncertainties and the risk to the NHS.

4.36 The committee considered the criteria for starting and stopping treatment, as outlined in the proposed managed access agreement. The committee was aware that the company had developed the criteria with input from clinicians and patient groups. It heard from patient and clinical experts that the criteria would be acceptable to clinicians and patients because it would not be in the child's best interests to be on treatment if they did not meet the eligibility criteria or were not benefitting from treatment. With the expected improvements in access to genomic testing, this starting criterion is substantially worse than what is anticipated in clinical practice, so the committee expects all patients will be able to access treatment. (see section 4.24). The committee concluded that the starting and stopping criteria presented were relevant, and could be incorporated in the proposed managed access agreement.

4.37 The committee considered the data collection arrangements. It noted that there were several areas of clinical uncertainty that could benefit from further data, including: CLN2 clinical rating scores over time; the frequency and severity of tonic-clonic seizures; myoclonus and dystonia control; visual acuity; extra-neurological symptoms; cause of mortality; improvements in CLN2 score at diagnosis because of earlier diagnosis; and, if possible, measures of quality of life. The committee was satisfied that the company's proposed data collection could address the key clinical uncertainties that it had identified.

Equalities

4.38 There were no relevant equality issues raised in the company submission, ERG report, or patient and professional statements. During scoping, stakeholders highlighted that, if the indication was limited to people with early stages of the disease, people with more advanced disease may be

excluded. The committee noted that the population considered covers the full marketing authorisation for the drug but thought that earlier treatment was likely to be most beneficial. It concluded that there are important ethical and equality considerations in specifying eligibility criteria in the context of a managed access agreement, and that criteria should be developed with input from clinicians, patient representatives and patient groups, as was the case here. The committee heard from patient and clinical experts that the criteria were acceptable to clinicians and patients (see section 4.36). It concluded that it was satisfied that the criteria complies with NICE's obligations under the equalities legislation.

Conclusion

4.39 The committee recalled its earlier decisions and discussed the recommendation it could make for cerliponase alfa for treating CLN2. It considered that CLN2 is a rare, devastating condition, with a debilitating and life-limiting effect on children with the condition, and that it has a substantial emotional and financial impact on their families (see section 4.3). The committee understood that there was an unmet need for an effective treatment. After considering all available evidence, and the opinions of the clinical and patient experts, the committee agreed that cerliponase alfa is innovative and represents an important development in treating the condition (see section 4.1). It recognised that substantial benefits with cerliponase alfa in the short term have been shown, and that there are likely to be important longer-term effects, although these are associated with substantial uncertainty (see sections 4.11 and 4.21).

4.40 The committee considered the economic analyses. In the absence of persuasive long-term evidence, it considered that the company's original assumptions around disease stabilisation, mortality and starting distribution were unrealistic (see sections 4.14, 4.21 and 4.25). Taking into account its preferred assumptions, the committee agreed that cerliponase alfa was associated with substantial incremental QALY gains

and met the criteria for a QALY weight of 3.0 (see section 4.29). When applying a QALY weight of 3.0, the committee noted that, while highly uncertain, it was plausible that the ICER was within the range normally considered an effective use of NHS resources for highly specialised technologies (see section 4.32). Also, the committee noted that some benefits associated with cerliponase alfa had not been captured in the economic analysis (see section 4.34).

4.41 Taking all these factors into account, the committee agreed that cerliponase alfa could provide value for money within the context of a highly specialised service. It agreed that a managed access agreement is needed to manage the financial risk to the NHS, given the high cost of cerliponase alfa and the substantial remaining clinical uncertainties. Therefore, the committee recommended cerliponase alfa as an option for treating CLN2, only if the conditions in the managed access agreement are followed.

5 Implementation

5.1 When NICE recommends a treatment as an option for use within a managed access agreement, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a person has neuronal ceroid lipofuscinosis type 2 and the doctor responsible for their care thinks that cerliponase alfa is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within a managed access agreement. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within a managed access agreement, the NHS in Wales must usually provide funding and

resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

6 Review of guidance

6.1 The guidance on this technology will be reviewed and published in line with the criteria in the managed access agreement. The technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

October 2019

7 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

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

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.

NICE project team

Each highly specialised 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.

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