

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cerliponase alfa in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of cerliponase alfa in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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

After consultation:

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

For further details, see the [interim process and methods of the highly specialised technologies programme](#).

The key dates for this evaluation are:

Closing date for comments: 5th March 2018

Second evaluation committee meeting: 20th March 2018

Details of membership of the evaluation committee are given in section 6.

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

1 Recommendations

- 1.1 Cerliponase alfa is not recommended, within its marketing authorisation, for treating neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.
- 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. This decision should be made jointly by the clinician, and the child and the child'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.

Clinical evidence suggests that, in the short term, cerliponase alfa improves quality of life, and slows the deterioration of motor and language function. However, there is no long-term clinical evidence, so assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty.

The cost-effectiveness estimates for cerliponase alfa are all much higher than the range NICE normally considers acceptable for highly specialised technologies.

Therefore, cerliponase alfa does not appear to provide value for money within the context of a highly specialised service, and cannot be recommended for use in the NHS.

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 of 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 option available for CLN2. Clinical management focuses on symptom control, monitoring and preventing complications, and palliative care. The aim is to maintain function 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 (ERT), 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 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 (ICV) access device (reservoir and catheter). It must only be given in a healthcare setting by a trained healthcare professional knowledgeable in ICV 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, convulsions,

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 two 150 mg vials.

4 Consideration of the evidence

The evaluation committee (see section 6) 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 ceroid lipofuscinosis type 2 (CLN2) is a progressive and relentless condition, and that there are 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 starts between the ages of 2 years and 4 years, when children may show delayed language development, followed by seizures and some loss of motor function (for example, increase in falls). Progression is then very rapid, leading to: deterioration in and then loss of speech and walking ability; movement disorders (myoclonus, dystonia, and chorea); pain; progressive dementia; and loss of vision. Children also have progressive difficulties with swallowing, constipation, hydration, respiratory function

and sleep disturbance, and may need gastrostomy feeding. Current treatment options focus on symptomatic relief, and supportive and palliative care. Most children with CLN2 become completely immobile and blind, and die between 8 years of age 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

- 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 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 also stated that most children diagnosed with CLN2 have a history of developmental delays, but that about 10% of all children in England have some developmental delay, so this alone is not sufficient to trigger suspicion of CLN2. This makes diagnosis at the earliest stage of the disease difficult. The parents 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 experienced seizures and motor issues, can be long and uncertain. The clinical experts highlighted that an earlier diagnosis would be critical to stabilising the disease earlier in its course if an effective treatment becomes available. The patient experts stated that, in addition to providing earlier access to treatment, an earlier diagnosis could allow diagnosis in younger asymptomatic siblings, and enable parents to make informed reproductive choices and get earlier support. The committee recognised that diagnosing CLN2 is difficult and it considered that this

was a relevant issue for consideration. It was aware that the company intended to implement a campaign to improve awareness and initiate earlier testing (the details have been deemed commercial in confidence by the company). The committee concluded that measures to support earlier diagnosis are important.

Impact 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 disease at diagnosis has a huge emotional impact on families. As symptoms progress, children become increasingly reliant on their carers and are usually completely reliant by the age of 6 years. 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 one child in a family is affected and this increases the burden on their parents. The committee noted the findings of a study that suggested the quality of life for carers is lower when the disease is severe than when the child has died. 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 source of 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, grand mal seizures, myoclonus, and feeding and swallowing). 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, it 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 the company had presented secondary analyses using the Hamburg scale, which includes both vision and seizure domains. 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.

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. This was 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, where 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, with more sophisticated methods such as the repeated measures mixed effects model resulting 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 agreed 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. The data from the most recent (96 weeks) cut off is 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 of cerliponase alfa. The results from the 48-week analysis 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 exceeded the expected rate of 50% in the untreated population with statistical significance.
- 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 achieve 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 the progression of the disease 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 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 indicated a durable treatment effect and broad based stabilisation of the disease 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 parent 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, treated 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, which therefore affect quality of life significantly, but there is the possibility that other events may not be captured. The expert stated that children remain vulnerable to epilepsy when having cerliponase alfa and that children in the trial remained on medication for epilepsy. The committee concluded that the long-term effect of cerliponase alfa on seizures remained uncertain.
- Vision: the company stated that patients treated with cerliponase alfa had a slower decline in vision (as measured by the vision domain in the Hamburg rating scale) than untreated patients. The ERG noted that baseline vision scores were higher for the cerliponase alfa group, so the comparability of the groups 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 ERG also noted concerns relating to the lack of biological plausibility of cerliponase alfa slowing vision deterioration, because cerliponase alfa is administered by ICV and it may not reach therapeutic levels in the retina due to the blood-retinal barrier. The company however stated that central brain function also affects vision and therefore some improvement in vision was biologically plausible through the impact of treatment directly on the brain. In the EMA's clinical assessment of cerliponase alfa, it noted that an effect on retinal tissue could not be totally excluded with ICV administration, but suggested 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.

- 4.9 The parents stated that cerliponase alfa has had great effect on the physical health of their children and an immeasurable impact 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, whereas other children who did not take part in the cerliponase alfa trials had deteriorated significantly, and many 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 the administration of cerliponase alfa via ICV posed any additional risks or burden for patients. The clinical experts stated that ICV administration 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 practice 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 cerliponase alfa was effective in the short term in treating the key neurological aspects of CLN2.

Long-term effectiveness

4.10 The committee discussed the long term effectiveness of cerliponase alfa, and was aware that the assumptions regarding the stabilisation of disease were a key driver of results from the economic model. The company used the results on the primary outcome to categorise patients having cerliponase alfa into 2 groups, early and late stabilisers. 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 due to 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 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 electroencephalogram, suggesting that disease progression had not halted completely.

The committee heard from the clinical experts that no long-term data were available, so long-term effects were uncertain. One clinical expert anticipated that, if disease was diagnosed and stabilised at an early stage, then age appropriate development would be expected going forward. However, another clinical expert stated that meeting developmental milestones at younger ages, as seen in trials, was not necessarily reflective of later-stage development. The committee agreed that, in the absence of any evidence, it was not possible to predict the long-term effects of cerliponase alfa. It concluded that the assumptions of disease stabilisation, and late stabilisation in particular, were associated with substantial uncertainty.

Asymptomatic and pre-symptomatic siblings subgroup

4.11 The committee noted that the decision problem included a subgroup of siblings with confirmed CLN2 who were asymptomatic and pre-symptomatic. It was aware that there was an ongoing trial (190-203) that included younger siblings of patients included in 190-201, but noted that no results are currently available. A parent stated that their child was taking part in this trial, and they continued to meet age appropriate development milestones without any signs of CLN2. The expert explained that this was a 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 pre-symptomatic. 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 below the age of 3 years 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 could have better outcomes (see section 4.2).

Mortality

4.12 The committee was aware that, by assuming long-term disease stabilisation (see section 4.10), the company implicitly assumed that patients treated with 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 section 4.10), it was plausible that patients would have further progression of disease 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 may 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 effect with cerliponase alfa in the clinical development programme. A clinical expert supported this, stating that no extra-neurological effect has been seen in patients currently being followed. The company also stated that patients with atypical CLN2 who survived longer than usual did not experience high rates of cardiovascular disease. The committee considered that patients with atypical disease may not have the likely mortality outcomes 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. The clinical experts agreed that there was very little information on longer-term causes of mortality in patients with CLN2. The committee acknowledged that, without longer-term data, the

effect of CLN2 on mortality due to affects in other body systems was completely unknown. It concluded that given the severity of the CLN2, it was unrealistic to assume that patients who had cerliponase alfa would have the same life expectancy as the general population.

Health-related quality of life

4.13 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. Changes in scores for the CLN2-disease-specific instrument, CLN2QL, reflected those in PedsQL. 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

4.14 The company presented a de novo 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, and moving to health state 7 with a CLN2 score of 0. 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.

- 4.15 The company, in its base case, incorporated a discount rate of 1.5% for costs and benefits. It justified this deviation from the reference case (3.5%), stating that the benefits of treatment are expected to be substantial and sustained over a lifetime. 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) states that a non-reference-case rate of 1.5% 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, and if the treatment does not commit the NHS to significant irrecoverable costs. The committee recalled its discussions around disease stabilisation (see section 4.10) and did not consider it likely that people with CLN2 treated with cerliponase alfa would be considered to have 'normal or near-normal health'. Moreover, the

committee noted that patients with CLN2 would need life-long treatment with cerliponase alfa, with costs incurred over a lifetime rather than at the outset. The committee concluded that there was no justification for deviating from the reference case discount rate of 3.5% for costs and benefits.

- 4.16 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 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.
- 4.17 The committee discussed the inclusion of progressive vision loss in the model. It noted that vision loss within the model is linked to a patient's progression through the health states which are defined by deterioration in motor and language function, with complete vision loss occurring in health state 8. However, for patients treated with cerliponase alfa, any stabilisation of motor and language function may not result in a similar stabilisation of visual function. Therefore the model does not adequately capture vision loss for patients having cerliponase alfa. The committee recalled its consideration (see section 4.8) that there was no evidence to suggest that cerliponase alfa would have an effect on stabilising vision in people with CLN2, and agreed with the ERG that the model should account for progressive vision loss. The committee noted that the ERG presented a scenario exploring incorporation of 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.

4.18 The ERG identified some cost items that were not included in the company's model. These included additional monitoring costs electrocardiograms (ECGs), provision of 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 (PSSRU) 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 the age of 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 it did not have a significant impact on the results.

Model assumptions

- 4.19 The company incorporated assumptions relating to the disease progression of early and late stabilisers in the model (see section 4.10). The committee understood this to imply that 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 and it reiterated the substantial uncertainty around assuming long-term stabilisation of disease 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, cerliponase alfa patients achieving stabilisation by week 16 would remain stable for the entire time horizon of the model but late stabilisers would continue experiencing 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.
- 4.20 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. For this, the company assumed that patients will be diagnosed in an earlier health state in the future, with most patients (about 80%) starting treatment in health states 1 and 2 (CLN2 score 6 and 5 respectively). The ERG highlighted that this differed substantially from the trial, which included 16% of patients with a CLN score of 5 or 6. The company explained that it intended to implement a campaign to support earlier diagnosis. The ERG highlighted that the assumption of earlier diagnosis had a considerable impact on the quality-adjusted life years (QALYs) gained in the model but that there was little evidence to show how this

could be achieved. The committee discussed the details of the company's programme (commercial in confidence). It supported any initiative to enable earlier diagnosis because it recognised that any gains from treatment would be larger if treatment was started in early stages of the disease. However, it considered that the company's assumptions around diagnosis in the model were too optimistic. In its exploratory analyses, the ERG reflected the distribution of patients from the natural history study 190-901, and the committee concluded that this was appropriate.

- 4.21 In its base case, the company assumed that disease-related mortality depends on time in that 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 4.12) 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 impact of incorporating neurological progression-related mortality and extra-neurological progression-related mortality, and the committee concluded that this was appropriate.

Utility values

- 4.22 The committee noted that the utility data collected in the clinical studies (190-201/202) were not included because utility values were not available for all health states and no utility values 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 experiencing 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 that had an unclear association with the motor and language scale that defined the health states. The committee discussed that it would generally prefer the inclusion of 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.

- 4.23 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 not determined only by the health state patients were in, but also by the treatment they had. The ERG highlighted that the vignettes imply significant additional benefits of treatment 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 improves seizure control, control of dystonia and myoclonus, and delays the need for a feeding tube. 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 was potentially a reasonable representation of the children's health-related quality of life, it would imply utility values that exceed those of the adult general population. The ERG applied a disutility for patients over the age of 18 to account for this. The committee concluded that applying differential utility values for patients who had or had not had treatment was inappropriate, and that adjusting utility values for those over the age of 18 was preferable.

4.24 The company included disutility values for carers and siblings in the economic model in all 10 health states and for the entire duration of treatment. The committee was satisfied with the principle of the inclusion of these disutility values but discussed the ERG's concern that they continue 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 have liked 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 the inclusion of disutility values for carers and siblings for 30 years was sufficiently robust for its decision-making.

Cost-effectiveness analysis results

4.25 The committee considered the results of the economic analysis. The incremental cost-effectiveness ratios (ICERs) have been deemed commercial in confidence by the company, so cannot be reported. The committee noted that the incremental QALYs gained for patients who had cerliponase alfa estimated in the company's base case was 30.42. However, the committee noted that this was based on an analysis incorporating assumptions that it did not consider to be realistic. The committee noted that the ERG presented results incorporating the committee's preferred assumptions, including:

- a starting population based on the 190-901 cohort (see section 4.20)
- ERG-calculated transition probabilities for patients who had cerliponase alfa (see section 4.16)

- partial stabilisation for patients who had cerliponase alfa (see section 4.19)
- including extra-neurological and neuro-disability-related mortality (see section 4.21)
- assuming all patients go blind over time, and incur related support costs and disutility (see section 4.17)
- assuming health state utilities are the same for both treatment arms using EQ-5D-3L data (see section 4.22)
- applying age-adjusted utilities (see section 4.23)
- removing carer and sibling disutility after 30 years (see section 4.24);
- including additional resource use items (ECG, psychiatric support, residential care) (see section 4.18)
- applying discount rate of 3.5% for costs and benefits (see section 4.15).

Based on this analysis, the committee noted that the incremental QALYs gained with cerliponase alfa decreased from 30.42 estimated by the company to 4.34 QALYs gained. The committee was mindful 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.

4.26 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 resource. 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. The undiscounted incremental QALYs in the in the committee's preferred analysis was 5.89. The committee concluded cerliponase alfa does not meet the criteria for applying a QALY weight

(that is, a lifetime undiscounted incremental QALY gain of at least 10). The committee noted that the ICER based on their analysis was substantially higher than £100,000 per QALY gained. The committee noted that, even if QALY weighting was applied, the ICERs were substantially higher than what could be considered cost effective.

- 4.27 The committee discussed the subgroup including asymptomatic and pre-symptomatic siblings. It recalled (see section 4.11) that the company expected that these patients, at diagnosis, would have a CLN2 clinical rating score of 6, with the assumption that the disease would stabilise in this health state. On this basis, the company presented a subgroup analysis in the economic model assuming 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 disease progressed. As a result, the ICERs are lower for this subgroup. The committee considered that this was plausible but remained aware that there was no clinical evidence available in this population. Moreover, the committee noted that ICERs still remained higher than what could be considered cost effective.

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

- 4.28 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 significant impact of CLN2 on families, including the emotional impact on carers, family relationships and siblings with the disease. It noted that there is a significant 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 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 that, 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, such as productivity losses and disutilities, were included in the economic analysis. However, it recognised that the full impact of the extent of benefits beyond direct health benefits had not been quantified. The committee also agreed that consideration of these in a qualitative manner would not be sufficient to impact on their recommendation given the difference between their estimate of a most plausible ICER and the threshold level considered to be cost effective.

Managed access agreement

4.29 The committee heard from the company that it acknowledged the uncertainties in the evidence base and that it intended to engage with NHS England, stakeholders and NICE to develop a managed access agreement for cerliponase alfa. The company stated that it expected this to include clinical as well as financial criteria. The committee had not been presented with the details of the agreement, so could not take it into account in its decision-making. However, the committee discussed whether a managed access agreement would be welcomed. It agreed that real world evidence to show that the outcomes and assumptions presented are plausible would be useful. It also acknowledged the need to manage the financial risk to the NHS given the high cost of cerliponase alfa. The committee broadly discussed the key elements that it would like to see included in a managed access agreement. Most crucially, the committee noted that it would be key to identify the relevant population and establish appropriate start and stop criteria. It noted that earlier treatment was likely to be most beneficial, but considered there would be important ethical considerations in specifying eligibility criteria. It also

recalled that there were a number of areas of clinical uncertainty that could benefit from further data, including: CLN2 clinical rating scores over time; seizures; visual acuity; extra-neurological symptoms; cause of mortality; and, if possible, measures of quality of life. The committee concluded it would welcome consideration of a managed access agreement including clinical criteria and commercial agreements.

Conclusion

4.30 The committee recognised that CLN2 is a devastating condition, with a debilitating and life-limiting impact on the children affected, and it has a significant emotional and financial impact on their families. It was convinced that cerliponase alfa offers an effective treatment option in the short term. However, in the absence of long-term evidence, the committee considered that company's assumptions around disease stabilisation, mortality and earlier diagnosis were unrealistic. Incorporating assumptions it considered to be more plausible resulted in undiscounted QALY gains of 5.89, so the criteria for QALY weighting could not be applied. The committee was aware that the ICERs were substantially above the range normally considered a cost-effective use of NHS resources, even if QALY weighting could be applied. It agreed that cerliponase alfa is innovative and has non-health-related benefits, and that these should be taken into account in its decision-making. The committee considered that it did not have adequate quantitative or qualitative data. However, it considered that that cerliponase alfa was unlikely to be considered a cost-effective use of NHS resources, even taking such factors into account. The committee acknowledged the company's intention to engage with NHS England to develop a managed access agreement to address clinical and financial uncertainties, but concluded that it could not recommend cerliponase alfa for use in the NHS in England based on the current submission.

5 Proposed date for review of guidance

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether 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

February 2018

6 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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