NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 (review of HST12)

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

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

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

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

Issue date: May 2025

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using cerliponase alfa in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 6 June 2025
- Fourth evaluation committee meeting: 10 July 2025
- Details of the evaluation committee are given in section 4

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 deficiency.

1.2 This recommendation is not intended to affect treatment with cerliponase alfa that was funded with managed access before final guidance was published. People already having cerliponase alfa for treating CLN2, or who start cerliponase alfa before the end of the managed access period (December 2025), can continue with treatment until they and their NHS healthcare professional consider it appropriate to stop. This decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

This evaluation reviews the evidence for cerliponase alfa for CLN2 (NICE highly specialised technologies guidance 12). It also reviews new data collected as part of the managed access agreement (MAA). CLN2 is a type of Batten disease, which is a group of rare genetic disorders. It progresses rapidly, causing seizures and dementia, and gradual loss of speech, mobility and vision. It leads to greatly reduced quality of life and a shortened life expectancy. Cerliponase alfa has been available through the MAA but is not routinely available in the NHS. Standard care without cerliponase alfa is supportive, aiming to relieve symptoms and maintain function and quality of life.

The new evidence includes data from clinical trials and from children having treatment in the NHS in England. Clinical trial evidence suggests that cerliponase alfa slows progression of CLN2. Patient experts and clinical experts have also explained that cerliponase alfa is a transformative treatment. But there is not much evidence about how well it works long term.

The committee took into account the condition's rarity, severity and the effect of cerliponase alfa on quality and length of life. But using the proposed price of the

medicine, the most likely cost-effectiveness estimate is not within what NICE considers an acceptable use of NHS resources. So, cerliponase alfa is not recommended.

2 Information about cerliponase alfa

Marketing authorisation indication

2.1 Cerliponase alfa (Brineura, BioMarin) is indicated for 'the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cerliponase alfa (PDF only).

Price

2.3 The list price of cerliponase alfa is £20,107 per 300-mg pack consisting of two 150-mg vials (excluding VAT, company submission). The recommended dosage for people over 2 is 300 mg every other week (annual cost of £522,782 per person).

2.4 The company has a commercial arrangement, which would have applied if cerliponase alfa had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

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

The condition

Details of condition

3.1 Neuronal ceroid lipofuscinosis type 2 (CLN2) is a rare genetic disease caused by deficiency of an enzyme called tripeptidyl peptidase 1 (TPP1). It is a 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 prevents the cells from functioning as they should. The clinical experts explained that time to diagnosis is variable, but children with CLN2 often experience a diagnostic delay. They explained that currently there is no screening programme for CLN2 so unless a child has an older sibling with CLN2 they will only be diagnosed after symptoms appear. The clinical experts explained that among clinicians there is a general lack of awareness of CLN2, although that is improving, and the early symptoms of CLN2 are observed in numerous other conditions. They explained that this can result in delays to diagnosis, in which time the child's symptoms may get worse. The exact prevalence and incidence of CLN2 is unknown. It is estimated that, in the UK, about 3 to 6 children are diagnosed each year and currently about 30 to 50 children are living with the condition.

Burden of the condition

3.2 A submission from a patient organisation explained that CLN2 has a devastating impact on every aspect of a child's development and everyday life. It described how CLN2 can impact a child's schooling, ability to play with friends, ability to manage their self-care and participate in family activities. It explained that CLN2 has a significant impact on parents and unaffected siblings, negatively affecting their physical and mental health. The patient organisation advised that most parents are full-time carers and need financial support, home adaptations, social care, mental health support and personal assistance to be able to cope with the daily tasks of caring for their child. A patient expert explained how it is shocking to learn that a child who was born healthy has a progressive

disease and will gradually lose all their skills. Several patient experts described feeling alone and isolated and experiencing anticipatory grief. The committee recognised that CLN2 is a rapidly progressive and devastating condition. It concluded that CLN2 has a substantial impact on the lives of children with CLN2 and their families.

Clinical management

Positioning and comparators

3.3 Cerliponase alfa is currently the only treatment available to treat the underlying cause of the condition. The clinical experts explained that there are no clinical guidelines for treating CLN2, and without cerliponase alfa treatment options are limited to supportive care. Supportive care aims to relieve symptoms and maintain function and quality of life. It can include medications to manage symptoms (such as seizures, dystonia and myoclonus) and interventions such as speech and language therapy and physiotherapy. The patient experts explained that the care children have can differ from area to area and carers often have to fight to access the support they need. The clinical experts explained that cerliponase alfa has transformed how CLN2 is perceived, and it is now considered a treatable condition. They advised that people having cerliponase alfa will live longer and remain in much better health than people who only have supportive care. The marketing authorisation allows for cerliponase alfa to be used at any stage of disease regardless of Motor-Language (ML) score. But the clinical experts explained that people who are diagnosed earlier and start treatment earlier with less disease progression benefit the most from cerliponase alfa.

Clinical effectiveness

Data sources

3.4 Clinical effectiveness evidence for cerliponase alfa came from study 190-201/202, study 190-203 and the managed access agreement (MAA). Study 190-201 was a single-arm open-label study. After completing study

190-201 people were enrolled in study 190-202. This was an open-label extension study that aimed to provide continued access to cerliponase alfa and assess long-term safety and efficacy. Study 190-203 was a post-authorisation efficacy study that primarily enrolled children under 3 and required enrolment of at least 5 participants under 2. NICE's highly specialised technology (HST) guidance 12 recommended cerliponase alfa only if the conditions in the MAA were followed. The MAA included a data collection agreement that aimed to address areas of clinical uncertainty. The MAA cohort represented all people eligible to have cerliponase alfa in England. This included people who started treatment as part of a trial or extended-access programme and those who started treatment under the terms of the MAA. The patient experts explained that during the COVID-19 pandemic children could not go to school, and families faced difficulties obtaining medicines, meeting with clinicians and accessing specialist services and appointments. They suggested this could have resulted in data collected during the MAA failing to accurately capture the benefits of cerliponase alfa.

The primary efficacy outcome in the studies and the MAA was changes in the ML subscale of the CLN2 clinical rating scale, assessed using several analysis methods. To provide comparative evidence, people in each of the studies and the MAA cohort were matched to people from study 190-901. Study 190-901 was a natural history study that retrospectively evaluated disease progression in patients with untreated CLN2. At the first committee meeting, the EAG stated that the evidence from the studies and the MAA showed conclusively that cerliponase alfa slowed disease progression. But it advised that there were areas of outstanding uncertainty in the data from the clinical studies and the MAA. It explained that, although the clinical evidence suggested people having cerliponase alfa experienced a slower rate of decline, people are likely to experience varying rates of decline over time. Also, long-term effectiveness was uncertain because data was not available beyond 6 years of follow up.

The EAG advised that the rate of decline and benefits of cerliponase alfa could vary between patients and could depend on their age and how progressed their condition was when they started having treatment. The EAG noted that evidence on the impact of cerliponase alfa on non-neurological outcomes was limited. It explained that if cerliponase alfa extended life, non-neurological outcomes would have a greater impact on health-related quality of life. It also advised that, although there was some evidence to suggest cerliponase alfa may help prevent seizures and reduce their severity, the impact of seizure prevention on quality of life was uncertain. This outstanding uncertainty could only be resolved with additional data collection and longer follow up. The committee concluded that the results from the studies and the MAA suggested that cerliponase alfa is effective at slowing disease progression. But it noted the EAG's concerns about outstanding uncertainty in the data. The committee understood that additional data would not become available during this evaluation.

Economic model

Company's modelling approach

3.5 The company submitted the same model that was used in HST12. This was a multi-state Markov model, which tracked the progression of patients through 10 distinct health states defined by ML scores and other clinical factors. It used the CLN2 clinical rating scale and ML subscale to define health states 1 to 7, starting in health state 1 with an ML score of 6 (the best health state; normal or near-normal motor and language function) and moving to health state 7 with an ML score of 0 (no motor or language function). Health state 8 was defined as patients with an ML score of 0 with vision loss. An additional need for palliative care progressed patients from health state 8 to health state 9, and health state 10 was death. The committee concluded that the model structure was appropriate for decision making.

Progressive symptoms

3.6 The company's model assumed that moving to a worse health state was associated with an increase in the proportion of people with progressive symptoms (distress, dystonia, myoclonus, need for a feeding tube and musculoskeletal pain). It also assumed a relative treatment benefit for cerliponase alfa, because the proportion of people assumed to have each progressive symptom in a specific health state was treatment dependent and lower for cerliponase alfa. The company stated that the estimates of the proportion of people assumed to experience progressive symptoms were elicited from clinical experts. At the first committee meeting, the EAG noted that the company had chosen not to use available data to inform or validate these estimates. The EAG questioned if using treatment-dependent estimates of the proportion of people assumed to experience progressive symptoms introduced the possibility of double counting the treatment benefit from cerliponase alfa. But the EAG stated that its clinical experts agreed that the company's estimates of these proportions in each health state and between treatment arms were clinically plausible. At the first committee meeting, the clinical experts agreed that people in a given health state would be expected to experience fewer progressive symptoms when having cerliponase alfa compared with standard care. They explained there was data that supported a reduction in seizures, but they had also observed reductions in myoclonus, pain and the need for a feeding tube. The committee concluded that the company's estimates of the proportion of people that experience progressive symptoms were suitable for decision making.

Baseline distribution

3.7 The starting baseline distribution in the company's original base case assumed that most people (87.5%) would start treatment in health state 1 (ML score of 6) and that all other people (12.5%) would start treatment in health state 2 (ML score of 5). The company stated that its choice of starting distribution was informed by the younger than 3 years subgroup

from study 190-203. It believed that this subgroup reflected the people who would have cerliponase alfa in the near future. It stated that the baseline ML score at the start of treatment would be higher than in the study 190-203 full population and MAA cohort, because of earlier diagnosis and a shorter time between diagnosis and starting treatment. It noted that the ML score at the start of treatment in the study 190-203 full population and MAA cohort may have been lower than would be expected in clinical practice because of the impact of COVID-19 on delays to diagnosis and treatment initiation in these cohorts. At the first committee meeting, the EAG agreed with the limitations associated with data from the MAA cohort identified by the company. But the EAG advised that the full cohort in study 190-203 and the younger than 3 years subgroup may be younger and have less progressed disease than those being diagnosed in clinical practice. It also advised that a limitation of the data from both the full population and the younger than 3 years subgroup was the small sample size. The EAG's original base case used the committee's preferred starting distribution from HST12 and assumed half would start treatment in health state 1 and half would start treatment in health state 2. The clinical experts advised that people are being diagnosed earlier, with less disease progression because of improved training and education. But the clinical experts explained that some people are diagnosed with ML scores below 5. They advised that this will continue without newborn genetic screening being routinely available. NHS England stated that a research project is underway, but it is uncertain if it will result in newborn genetic screening for CLN2 becoming routinely available. So, at the first committee meeting, the committee thought the distributions used in both the company's and EAG's original base cases were optimistic. It requested further analysis using data taken from current clinical practice excluding people who had delayed diagnosis or treatment because of COVID-19. The committee also noted the baseline distributions stated by 1 of the clinical experts at the first committee meeting were plausible and should be considered in a scenario

analysis. These were based on data from his centre: 28.5% starting with a ML score of 6, 28.5% with a ML score of 5, and 42% with an ML score of 4.

The company stated that analysis using data from current clinical practice excluding the impact of COVID-19 was not possible because all data from the clinical trials and MAA cohort was impacted by COVID-19. It noted that data from before the COVID-19 pandemic was unsuitable because people were diagnosed before cerliponase alfa was available. The company stated that the pandemic continues to impact diagnosis with some children potentially having not been diagnosed yet because of pandemic-related delays. Before the second committee meeting, the company updated its base case to use the starting distribution that the EAG's clinical experts believed described clinical practice in 5 years' time. This distribution assumed that 50% of people would start treatment in health state 1, 35% would start treatment in health state 2, 12.5% would start treatment in health state 3 (ML score of 4) and 2.5% would start treatment in health state 4 (ML score of 3). It stated that it believed this distribution provided the best estimate of a starting distribution unaffected by COVID-19. In the absence of any other data presented by the company, the EAG updated its base case to use the starting distribution suggested by the clinical expert at the first meeting. At the second committee meeting, a clinical expert stated that in the last 2 years they had not seen a patient diagnosed with an ML score below 5. They agreed that the distribution the EAG's clinical experts believed described clinical practice in 5 years' time best reflected what they would expect to see in NHS clinical practice. Before the third committee meeting, the company convened an advisory board comprised of the clinical experts that had attended the previous committee meetings and 2 clinical experts from outside of England. The company stated that the advisory board had reached a consensus on the best achievable estimate of ML score distribution at the time of diagnosis in 5 years' time when assuming that newborn screening is not available. The committee noted that a 'most

conservative' scenario and a 'realistic' scenario were also obtained from the advisory board, which were deemed confidential and so cannot be presented here. The EAG explained that the proportion of patients that start treatment in health state 1 was a particularly influential parameter. At the third committee meeting, the clinical experts explained that although ML score at diagnosis has improved it is difficult to know if that improvement will continue. So, it is difficult to predict what proportion of patients will start treatment in health state 1 in 5 years' time. One of the clinical experts estimated that it could be between 50% and 70% of people. The committee noted that the best achievable distribution from the company's advisory board assumed 70% of people start treatment in health state 1. The committee considered that it had not been presented with evidence to suggest that this was plausible. The committee decided that the starting population was highly uncertain and, given the uncertainty, clinical expert opinion was the most robust source of data. The committee concluded that the 'most realistic' estimate of ML score distribution at the time of diagnosis in 5 years' time from the company's advisory board should be used in decision making.

Disease stabilisation proportion of 'initial stabilisers'

3.8 At the first committee meeting, the company's base case assumed that everyone who started having cerliponase alfa in health state 1 (ML score of 6) was classified as an 'initial stabiliser' and would remain in health state 1 for the next 6 years. After 6 years, transitions to worse health states for this group were assumed to occur at half the rate of the transitions for people having cerliponase alfa who were not classified as an 'initial stabiliser'. The company justified this approach based on an observation that none of the children in the younger than 3 years subgroup from study 190-203 with a baseline ML score of 6 had a change in ML score after 6 years of follow up. The EAG advised that there was not enough data to support this assumption. The EAG's clinical experts suggested that, based on the evidence presented, it was not unreasonable to assume that people who started having cerliponase alfa

in health state 1 would remain in that health state for 6 years. But the EAG's clinical experts also suggested that it may be too optimistic to assume that 100% of people who started having cerliponase alfa in health state 1 would be initial stabilisers. The EAG's base case assumed that 80% of people who started having cerliponase alfa in health state 1 were initial stabilisers. At the first committee meeting, the clinical experts explained that not every person who started treatment in health state 1 would be the same. There would be some who were pre-symptomatic with normal motor and language function and some with symptoms and near-normal motor and language function. The clinical experts advised that only children who are pre-symptomatic would be likely not to progress to health state 2 (ML score of 5) in 6 years. So, the committee decided the company's assumption that 100% of children who started having cerliponase alfa in health state 1 would be initial stabilisers was unlikely. At the first meeting, the committee concluded that the EAG's assumption that 80% of people who start having cerliponase alfa in health state 1 would be initial stabilisers was more plausible and should be used for decision making. Before the second committee meeting, the company updated its base case in line with this. For the third committee meeting, the company provided additional scenarios assuming that 100% of people who started having cerliponase alfa in health state 1 would be initial stabilisers. The EAG noted that no new empirical evidence was provided to support this assumption. The clinical experts reiterated that some people who start treatment in health state 1 would be symptomatic and some of these people would be expected to progress to health state 2 within 6 years. So, the clinical experts agreed that assuming 80% of people who start having cerliponase alfa in health state 1 would be initial stabilisers was more plausible. The committee concluded that it had not seen any evidence to change its preference for assuming that 80% of people who start having cerliponase alfa in health state 1 would be initial stabilisers.

Disease stabilisation risk reduction for 'initial stabilisers'

3.9 At the first and second committee meetings both the company and EAG base cases assumed that after 6 years, transitions to worse health states for 'initial stabilisers' occurred at half the rate of the transitions for people who were not classified as initial stabilisers. For the third committee meeting, the company provided additional scenarios assuming initial stabilisers would experience a 75% risk reduction relative to non-initial stabilisers. The EAG noted that no empirical evidence was provided to support this assumption. The clinical experts explained that they would expect initial stabilisers to experience a reduction in the rate of progression relative to people who started treatment in more progressed health states, but that the extent of the reduction is uncertain. The clinical experts considered that a 50% risk reduction for initial stabilisers was likely more plausible than a 75% reduction. The committee concluded that it preferred the assumption that transitions to worse health states for initial stabilisers occur at half the rate of people having treatment who were not classified as an initial stabiliser.

Evidence informing transition probabilities

3.10 The company's original base case used data from study 190-203 to derive transition probabilities in health states 1 to 7 for people having cerliponase alfa. The company stated that the population in study 190-203 most closely reflected the population that would have cerliponase alfa in the near future. It also noted that using this data meant that in its original base case the transition probabilities and characteristics of the starting population (see section 3.7) were informed by the same study. But it advised that the transition probabilities were informed by the full study 190-203 population because there was insufficient data available from the younger than 3 years subgroup. The EAG noted that study 190-203 had a small sample size. It also advised that study 190-203 may not reflect the population currently having cerliponase alfa in clinical practice or the population likely to have cerliponase alfa in the near future. The EAG used pooled data from study 190-201/202, study 190-203 and the MAA cohort to derive transition probabilities in health states 1 to 7 for people

having cerliponase alfa in its original base case. The company stated that the pooled data had limitations because it included people who were diagnosed before cerliponase alfa was available and people who experienced delays to diagnosis, delayed treatment initiation and difficulty accessing other interventions, such as physiotherapy, because of the COVID-19 pandemic. The EAG acknowledged that using the pooled data may introduce bias against cerliponase alfa because it included people who experienced delays and interruptions to their treatment.

The committee considered the company's justification for using data from study 190-203. At the first committee meeting, it decided that the population in study 190-203 likely reflected a population that starts treatment at a younger age and with less progressed disease than is currently seen in the NHS without newborn genetic screening, which may introduce bias in favour of cerliponase alfa. The committee acknowledged that the COVID-19 pandemic may have meant that data collected during the MAA period underestimated the benefits of cerliponase alfa (see section 3.4). At the first meeting, the committee requested analysis using the pooled data but excluding data from the MAA. The company provided the analysis using the pooled data but excluding data from the MAA for the second committee meeting. It maintained its preference for using data from study 190-203. The company reiterated that data from study 190-201 and 190-202 included people who experienced a delay to starting treatment because cerliponase alfa was not available when they were first diagnosed. The company noted that data from study 190-201 included data from people who experienced disease progression during the study's dose-escalation phase. The clinical experts explained that delays to having cerliponase alfa would lead to worse outcomes. They would expect progression from the more progressed health states would be slower in people who started treatment with less progressed disease than those who started treatment in the more progressed health states. At the second committee meeting, the EAG maintained that study 190-203 may not

reflect the population who would have cerliponase alfa in NHS clinical practice and may overestimate the effectiveness of cerliponase alfa. The EAG noted that when the baseline distribution informed by the clinical experts' estimates of clinical practice in 5 years' time (see section 3.7) was used, alongside the study 190-203 data, the model assumed people starting treatment with an ML score of 6 would not experience a worsening in ML score for 22 years. This was compared with 11 years when the pooled data was used, including data from the MAA. The clinical expert explained that although children who start treatment with an ML score of 6 have been observed to maintain that score for several years, it is unlikely their condition would not progress for 22 years. The EAG explained that the pooled data, including data from the MAA, reflected most of the existing evidence based on sample size and length of follow up.

The committee remained concerned that the population in study 190-203 may not reflect the population that would have cerliponase alfa in NHS clinical practice, and that study 190-203 was based on a small sample size and had limited follow up. It agreed that using study 190-203 data generated estimates of the time spent with an ML score of 6 that appeared implausible. The committee discussed the assumption that after 6 years, 'initial stabilisers' would transition to worse health states at half the rate of people who entered the model in any health state other than health state 1. It decided this may mitigate some of the impact of delayed treatment initiation and difficulty accessing other interventions experienced by people in study 190-201/202 and the MAA. The committee concluded that the pooled data, including data from the MAA, was reasonable for decision making.

After the second committee meeting, the company stated that its advisory board suggested there was a consensus among clinical experts that study 190-203 best reflects people who would have cerliponase alfa in the NHS. At the third meeting, the committee recalled its discussion on the

appropriate baseline distribution (see section 3.7). It considered that, given its updated preferred baseline distribution based on updated clinical opinion, study 190-203 was more likely than the pooled data to reflect current NHS clinical practice. But the committee also recalled the limitations of the data from study 190-203. The committee asked the company and EAG if any alternative data sources were available, given the limitations of both the pooled data and the data from study 190-203. The EAG and company responded that no alternative data sources were available. The EAG explained that the uncertainties and potential bias of each data source needed to be considered. The EAG advised that the initial stabiliser assumptions (see sections 3.8 and 3.9) amplified the impact of using data from study 190-203. The EAG explained that this was because study 190-203 had a much higher proportion of people in health state 1. It considered that applying the initial stabiliser assumptions to data from study 190-203 may double-count the benefits of starting treatment earlier with less progressed disease. The EAG also noted that the pooled data had to be used to inform transitions from health state 6 and 7 because these transitions were not observed in study 190-203. The committee acknowledged the limitations of the pooled data. It concluded that after considering the advantages and disadvantages of both the data from study 190-203 and the pooled data, it still preferred using the pooled data including data from the MAA for decision making. The committee noted that when the pooled data was used, alongside the committee's preferred updated baseline distribution and other preferred assumptions, the model assumed the average time in health state 1 was less than 20 years. The committee understood that because of the relatively short follow-up periods in the studies, it is not known how long people would spend in health state 1. The clinical experts advised that up to 20 years in health state 1 was possible, but likely overly optimistic. So, the committee decided that using the pooled data may potentially result in a conservative estimate of the efficacy of cerliponase alfa. The committee concluded that it would take this into account in its decision making.

Estimation method informing transition probabilities

3.11 At the first committee meeting, the EAG noted that for this evaluation the company used a different method to estimate transition probabilities than the method it used in HST12. The EAG stated that it was uncertain how robust the company's transition probabilities were compared with alternative estimation methods. It was concerned with the company's estimation method. First, the transition probabilities were informed by a small number of events. Second, the company used an arbitrary initial value for all transition intensities. Third, the transition probabilities in the cerliponase alfa arm allowed backward transitions to healthier health states. The EAG's clinical experts had suggested that some backwards transitions were temporary improvements or random variation. The EAG stated that including backward transitions meant that in the model some people could transition to increasingly healthier health states, which it found clinically implausible. The company stated that its clinical experts had suggested that transitions to healthier health states are possible when a person is having cerliponase alfa. The clinical experts at the meeting agreed that people can transition to healthier health states. But they explained this would only occur when a person is close to the threshold between health states and perhaps had an illness that temporarily moved them to a lower ML state. The person regains skills when they recover from the illness. The clinical experts considered it unlikely that cerliponase alfa would generate substantial improvements in motor and language function. The committee noted the company had submitted a Markov model, which used a cohort-level modelling approach that did not consider the outcomes of individuals. So, the committee decided it was not accurate to make references to individuals transitioning to increasingly healthier health states. It decided it was appropriate to include backwards transitions because these were observed in the clinical data. The committee concluded that the company's estimation method was suitable for decision making.

Vision loss progression

3.12 The company included vision-loss progression in its base case by assuming that everyone in health states 7 to 9 experienced vision loss and, for people in health states 1 to 6, the proportion of people with vision loss increased linearly from 0% at age 6 to 100% at age 20. The company stated that the linear loss of vision assumption was informed by clinical experts. At the first committee meeting, the EAG explained that the company's assumptions implied a delay to vision loss in the cerliponase alfa arm compared with the standard care arm. The EAG's base case assumed that cerliponase alfa had no impact on vision loss. The EAG's clinical experts had suggested that vision loss starts around age 5 and most people will have complete loss of vision by age 10. The clinical experts at the meeting explained that vision loss usually begins around age 5 with most people experiencing near-complete vision loss by around age 9. They noted that cerliponase alfa is currently infused directly into the brain. The clinical experts advised that it would only improve vision loss if it was delivered into the eye by intravitreal injections. The company stated that some improvement in vision was biologically plausible even when cerliponase alfa is infused directly into the brain. This was because of the effect central brain function has on vision loss. The patient experts explained that although most children experience vision loss by age 10, some have been shown to experience slower vision loss and retain their vision for longer or show no vision loss at all. The committee noted that it had not seen evidence to support the assumption that cerliponase alfa delays vision loss. It acknowledged comments from the clinical experts that most people will experience vision loss by around age 9. The committee concluded that the EAG's approach to modelling vision loss should be used in decision making.

Stopping treatment

3.13 In the MAA, stopping treatment depended on a number of criteria including:

- age at start of treatment
- time on treatment
- decline in ML score persisting for 3 or more infusions
- reduction in proxy-reported patient quality of life.

The company's original and updated base cases assumed that people stopped cerliponase alfa after they entered health state 6 (ML score of 1). People were assumed to have standard care after stopping treatment. The company stated that after a person entered health state 6, continued treatment with cerliponase alfa would be unlikely to improve motor and language capabilities. At the first committee meeting the EAG noted that in the company's base case people who previously had cerliponase alfa remained in health state 6 for 3.2 years on average, but the costs and utilities were the same as the standard care arm. The EAG's clinical experts and the clinical experts at the meeting agreed it was possible that some treatment effect would remain after stopping cerliponase alfa. But it was unlikely that a person who stopped having cerliponase alfa would remain in health state 6 for more than 3 years. The EAG noted that in HST12 people were assumed to stop cerliponase alfa in health state 7 (ML score of 0). The EAG advised that the company had not provided strong evidence to support stopping treatment in health state 6. So, in its base cases the EAG assumed people would stop cerliponase alfa in health state 7. The clinical experts explained that they would expect treatment to stop when people reach health state 6 or 7 and after considering both the advantages and disadvantages of stopping alongside the family's perception of quality of life. The patient experts advised that carers would be best positioned to make informed decisions about stopping treatment and would be willing to do so. A patient expert stated that the decision to stop treatment should not be based only on loss of

speech and walking ability (that is, ML score). They explained that continuing treatment could potentially benefit characteristics other than mobility and language that could have a positive impact on health-related quality of life. The committee decided it was likely some people would continue to have treatment in health state 6, so assuming treatment stopped in health state 7 was appropriate for decision making.

At the first meeting, the committee asked for additional analysis that included stopping rules to identify subgroups of people for whom the evidence suggests cerliponase alfa is particularly clinically or cost effective. In response, the company stated that it did not support the inclusion of a stopping rule and that no evidence existed supporting one. It advised that patient groups and carers would strongly oppose the introduction of a stopping rule. The company's clinical experts and the clinical expert at the second meeting stated that ML score would not be used alone to decide if treatment should be stopped. The clinical expert stated that quality-of-life questionnaires were used as part of the stopping criteria in the MAA and that if cerliponase alfa were recommended for routine use then these questionnaires could continue to be used. Also, the clinical expert at the second meeting reiterated that treatment may continue to provide benefits even after loss of motor and language function. At the second meeting, a patient expert explained that they thought the decision to stop treatment would be made when the person was experiencing very low health-related quality of life. But they emphasised that deciding when to stop treatment was a highly personal decision and should be considered on an individual basis.

The committee noted that the utilities from the Gissen et al. 2012 study used in the model assumed that the health-related quality of life experienced by people having cerliponase alfa in health state 7 was considered worse than death (negative utilities). But the model still predicted quality-adjusted life year (QALY) gains in health state 7. So, the

committee concluded that assuming treatment stopped when people reached health state 7 was the best approximation of what would happen in clinical practice and should be used for decision making. But it agreed that in clinical practice treatment should not be stopped just because a person has reached health state 7 (ML score of 0). Instead, treatment should continue until the person's family, carers and NHS healthcare professional decide it is appropriate to stop. The committee noted that possibly for some patients in health state 7, cerliponase alfa may be used as a palliative care option. It agreed that other options should be used instead of cerliponase alfa, if this is the case. The additional scenarios provided by the company before the third committee meeting assumed treatment stopped when people reached health state 7, in line with the committee's preferred modelling assumption.

Starting treatment

3.14 After the first meeting, the committee asked for analyses that included starting rules to identify subgroups of people for whom the evidence suggested cerliponase alfa is particularly clinically effective or cost effective. The company stated that it did not support the inclusion of starting rules and that it was possible to improve the ML score people start treatment at without introducing a starting rule; that is, by introducing newborn genetic screening (see section 3.7). It advised that patient groups and carers would strongly oppose the introduction of starting rules. But the company did provide additional scenario analyses assuming starting populations with ML scores of 5 or 6. At the second committee meeting, the patient experts and clinical expert stated that they did not support the inclusion of a starting rule. They explained that although there was evidence to suggest people benefit more from having cerliponase alfa earlier, those who started treatment with more progressed disease would also benefit. The committee was concerned that including a starting rule would mean that someone who started treatment earlier would be eligible to have treatment once they reached a more progressed health state, but someone who was diagnosed in that progressed health state would not be

eligible. It concluded that ideally there would be no starting rules and it would prefer to consider the whole population when evaluating cerliponase alfa. But it agreed that it was open to exploring starting rules if that was a way to make cerliponase alfa available for some people, but how this could be done would need to be proposed by stakeholders.

Non-reference case analysis

3.15 The committee noted that section 4.4.16 of NICE's health technology evaluations manual states that the committee may consider a non-reference case analysis with the background care costs removed if the NHS is providing care that is expensive or would not be considered cost effective at NICE's normal levels. After the first meeting, the committee asked for a non-reference case analysis with background care costs removed. It stated that the rationale for removing specific background care costs, and any structural assumptions used in the analysis, should be clearly documented. The company removed costs related to health state, vision loss, psychiatric and behavioural support and residential care from both arms in its updated base case. It only included the costs associated with drug acquisition, administration, monitoring and managing adverse treatment effects of cerliponase alfa. The company stated that treatment with cerliponase alfa is associated with longer-term survival that results in increased background care costs that do not represent direct, intrinsic consequences of treatment. The committee noted the NICE health technology evaluations manual states that the analysis excluding background care costs should be considered alongside the reference-case analysis, so the company should not have removed them from its updated base case. The committee noted that it had not been provided with any evidence or a clear rationale for the removal of the background care costs. So, it concluded at the second meeting that only the reference-case analyses should be used for decision making. It noted that the additional scenarios presented by the company before the third committee meeting included background care costs in line with the committees preferred modelling assumption.

Utility values

Source of utility values

3.16 Health-state utility values in the company's and EAG's base cases were assumed to depend on if a person was having cerliponase alfa or standard care. Utility values were taken from a study (Gissen et al. 2021) that asked 8 clinical experts to complete EQ-5D-5L questionnaires using vignettes that described the health states used in the model. The EQ-5D-5L scores were then mapped on to EQ-5D-3L scores. At the first committee meeting, the EAG explained that it had 3 concerns about the quality of the Gissen et al. (2021) study. First, there may have been bias in the validation of the vignettes because it was done by a single clinical expert who was also involved in the study. Second, the vignettes assumed different progressive symptom burdens between treatment arms. But it was not clear how this aligned with the assumed proportion of people experiencing progressive symptoms used to inform the resource-use assumptions in the model (see section 3.6). Third, NICE's reference case states that when it is not possible to measure health-related quality of life directly, the measure should come from a person's carer rather than clinical experts.

The EAG also identified 2 inconsistencies in the utility values taken from the Gissen et al. (2021) study. First, the difference in utility values between cerliponase alfa and standard care was substantial after health state 5. Second, there was a substantial decrease in utility between health states 4 and 5 in the standard care arm, but no corresponding decrease in the cerliponase alfa arm. The company and the EAG also considered scenarios using utilities derived from the MAA data. But the EAG explained that this data may be biased because treatment continuation in the MAA was conditional on maintenance of a health-related quality of life benefit. The EAG noted that the MAA data only provided utilities for cerliponase alfa. It explained that to obtain utilities for the standard care arm, data from the Gissen et al. (2021) study had to be used, so the

issues of robustness of the data from the study remained. Based on what it heard from the clinical experts about differences in the progressive symptoms experienced between treatment arms (see section 3.6), the committee accepted treatment-dependent utilities were plausible. It agreed with the EAG that utilities from the MAA were potentially biased and introduced additional uncertainty. The committee acknowledged the concerns and inconsistencies associated with the utility values from the Gissen et al. (2021) study. But based on the scenarios and evidence presented, it concluded that utilities from the Gissen et al. (2021) study were the least-worst for decision making.

Costs and resource use

Electrocardiogram monitoring

3.17 The company's original base case did not include costs associated with electrocardiogram (ECG) monitoring during cerliponase alfa administration. At the first committee meeting, the EAG noted that this was not in line with the summary of product characteristics. This states that ECG monitoring should be done during each infusion for people with a history of bradycardia, conduction disorder or with structural heart disease, and every 6 months for people with normal cardiac function. The EAG's original base case included the cost of an ECG every 6 months for all people. It explained that it used data from the MAA cohort to inform its assumptions about the proportion of people needing ECG monitoring during each infusion. It assumed that 3% had clinically significant cardiac abnormalities at baseline rising to 27% at 3.5 years. The committee concluded that ECG monitoring costs should be included in line with the summary of product characteristics.

After the first committee meeting, the company updated its base case to include the cost of ECG monitoring in line with the EAG's assumptions. But it did not include the cost of ECG monitoring every 6 months for people with normal cardiac function. This was because its clinical advisers

had commented that these people would not have ECG monitoring in clinical practice. The EAG explained that it did not find including ECG monitoring costs every 6 months to be excessively conservative because it also assumed the proportion of people with cardiac abnormalities would remain constant after 3.5 years. It explained that this assumption may have underestimated the proportion of people with cardiac abnormalities over time and therefore the costs associated with ECG monitoring. At the second committee meeting, a clinical expert explained that in the past an ECG was done for every infusion, but once a year would probably be useful so problems could be reviewed by a cardiologist. They added that there is not enough data yet to really know. The committee considered the arguments put forward but retained its preference for including ECG monitoring costs in line with the summary of product characteristics. At the third meeting the committee noted that the additional scenarios presented by the company included ECG monitoring costs in line with the summary of product characteristics, which was in line with the committee's preferred modelling assumption.

Other minor impacts on the cost-effectiveness results

3.18 In addition to the key issues discussed in sections 3.4 to 3.17, the EAG made 2 additional changes to its base case. The committee considered these changes and agreed with the EAG's approach. Including neuro-disability mortality in all health states was preferred because the committee decided it had not been provided with evidence to change its conclusion from HST12. The committee acknowledged advice from the clinical and patient experts about the behavioural symptoms people with CLN2 experience. It concluded that the cost of psychiatric and behavioural support should be included in the model. The committee concluded that the EAG's additional changes were appropriate and that these only had a minor impact on the cost-effectiveness results. At the third meeting, the committee noted that the additional scenarios presented by the company included neuro-disability mortality in all health states and

the cost of psychiatric and behavioural support in line with the committee's preferred modelling assumption.

QALY weighting

Criteria for applying a QALY weighting

3.19 NICE's health technology evaluations manual specifies that a most plausible incremental cost-effectiveness ratio (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 size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. The committee understood that a weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. It considered the QALY gains associated with cerliponase alfa. It acknowledged the outstanding uncertainty in the data from the clinical studies and the MAA (see section 3.4) and the concerns and inconsistencies associated with the utility values used in the model (see section 3.15). But, after taking the uncertainty into account and considering the evidence as a whole, the committee concluded that the full QALY weight associated with its preferred assumptions should be applied because it is likely that cerliponase alfa offers significant QALY gains. The committee noted that the choice of data used to inform the transition probabilities had a substantial impact on the number of QALY gains. It acknowledged that using the pooled data may be conservative (see section 3.10). To account for this, the committee concluded that the QALY weighting should be increased by 0.2.

The committee noted that the company had presented QALY weightings that included the QALY gains associated with carers and siblings. The committee noted that section 6.2.24 of NICE's health technology evaluation manual states that the QALY weighting should be based on the

QALYs gained over the lifetime of the patient. So, only the QALYs gained by the person having cerliponase alfa should be used to inform the QALY weighting. The committee noted that QALY gains experienced by carers and siblings continued to be accounted for elsewhere in the ICER.

Cost-effectiveness estimates

Cost-effectiveness analysis results

3.20 Because of the confidential discount for cerliponase alfa, all cost-effectiveness results are commercial in confidence and cannot be reported here. But the committee noted that using the commercial discount both the company's and EAG's cost-effectiveness estimates were substantially higher than the threshold normally considered cost effective for highly specialised technologies. The committee preferred the following assumptions for decision making:

- using the company's estimates of the proportion of people that experience progressive symptoms (see section 3.6)
- baseline distribution informed by the clinician estimate of the baseline distribution in 5 years' time (see section 3.7)
- assuming 80% of people who start having cerliponase alfa in health state 1 are 'initial stabilisers' (see section 3.8)
- assuming an 'initial stabiliser' remains in health state 1 for 6 years. After 6 years, transitions to worse health states occur at half the rate of people who entered the model in any health state other than health state 1 (see section 3.9)
- transition probabilities informed by the pooled dataset, including data from the MAA (matched to study 190-901) (see section 3.10)
- using the company's method to estimate transition probabilities (see section 3.11)
- assuming cerliponase alfa has no impact on vision loss (see section 3.12)

- assuming treatment is stopped when people reach health state 7 (see section 3.13)
- including background care costs (see section 3.15)
- using utilities from the Gissen et al. (2021) study (see section 3.16)
- using the EAG's estimates of ECG monitoring costs (see section 3.17)
- including neuro-disability mortality in all health states (see section 3.18)
- including the cost of psychiatric and behavioural support (see section 3.18).

Using the committee's preferred assumptions and including the commercial discount, the most likely cost-effectiveness estimates for cerliponase alfa were substantially above the range that NICE considers an acceptable use of NHS resources for highly specialised technologies.

Other factors

Equality

3.21 A clinical expert explained that people who live in remote areas are not able to easily get to a treatment centre, and that this resulted in an issue of equality of access to treatment. The committee noted that patient experts, clinical experts and the company had explained that several additional specialist centres have opened across England since HST12 was published. This has made it easier for people to have treatment. The committee also noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE evaluation recommendation. The committee concluded that no additional considerations were needed regarding equalities concerns.

Innovation

3.22 HST12 concluded that cerliponase alfa is an innovative treatment that represents an important development in treating CLN2. After considering

the comments from the company, clinical experts and patient experts, the committee concluded that cerliponase alfa is an innovative treatment.

Uncaptured benefits

3.23 The company stated that cerliponase alfa provides benefits that were not captured in the cost-effectiveness estimates. These benefits included the impact of cerliponase alfa on productivity loss of parents and other carers and out of pocket expenses for things such as travel, accommodation and home modifications. The company also emphasised the lifelong emotional impact of bereavement on parents, siblings and the wider family. The committee considered the benefits identified by the company but decided these were outside the reference case, so should not be considered as part of its decision making. The committee concluded that all relevant benefits associated with cerliponase alfa had been taken into account.

Conclusion

Recommendation

3.24 The committee recognised cerliponase alfa is a transformative treatment. The new evidence included data from clinical trials and from people having treatment in the NHS in England. This evidence suggested that cerliponase alfa slows disease progression. But although it is an effective treatment, there is uncertainty about how effective it will be after long-term use. Based on the proposed price of the medicine the preferred cost-effectiveness estimates were substantially above the range NICE considers an acceptable use of resources for a highly specialised technology. So, cerliponase alfa is not recommended for treating CLN2.

3.25 As stated in section 3.14, the committee preferred to consider the whole population and have no starting rules when evaluating cerliponase alfa. But because cerliponase alfa is not recommended, the committee would be open to exploring starting rules if that was a way to make cerliponase alfa available for some people.

4 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

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

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Technical lead

Joanna Richardson
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Project managers

Jasdeep Hayre, Richard Diaz
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