NICE National Institute for Health and Care Excellence

NICE guidance

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces HST12.

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, 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's 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. The clinical trial evidence shows 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 for highly specialised technologies. 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.

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 years is 300 mg every other week, which has an 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. The company had an additional commercial agreement as part of the managed access agreement which did not apply during the appraisal because it was a time-limited agreement.

Sustainability

2.5 For information, see BioMarin's webpage on environmental stewardship.

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 have a diagnostic delay. They explained that currently there is no routine national 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 healthcare professionals, there is a general lack of awareness of CLN2. Also, the early symptoms of CLN2 are seen in numerous other conditions. They explained that this can result in delays to diagnosis, in which time the child's symptoms may get worse. But the clinical experts also explained how awareness of CLN2 is improving and is leading to children being diagnosed earlier than they once were. 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 affect a child's schooling, and ability to play with friends, 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. So, they 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 of 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. In response to consultation, the patient experts and a patient organisation reminded the committee of the devastating nature of untreated CLN2. The committee acknowledged the high unmet need and the devastating nature of untreated CLN2. It concluded that CLN2 has an overwhelming impact on the lives of children with CLN2 and their families.

Clinical management

Positioning and comparators

3.3 Cerliponase alfa is the only treatment available to treat the underlying cause of CLN2. Supportive care aims to relieve symptoms and maintain function and quality of life. It can include medicines 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 having cerliponase alfa has transformed how CLN2 is perceived. 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 CNL2, regardless of motor language (ML) score. But the clinical experts explained that people who are diagnosed earlier, so have less disease progression, and start treatment earlier 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 19-203 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 years and needed enrolment of at least 5 participants under 2 years. NICE's highly specialised technologies guidance 12 (from now, HST12) 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 people 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 getting medicines, meeting with healthcare professionals, and accessing specialist services and appointments. They suggested that 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 people with untreated CLN2. At the first committee meeting, the EAG said 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 had a slower rate of decline, people are likely to have 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 people having treatment. It added that they could depend on a person's age and how progressed their condition was when they started 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 showed 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 multistate Markov model that tracked the progression of people 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. It started in health state 1 with an ML score of 6 (the best health state; normal or near-normal motor and language function) and moved to health state 7 with an ML score of 0 (no motor or language function). Health state 8 was defined as people with an ML score of 0 with vision loss. Health state 9 was an additional need for palliative care. 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, musculoskeletal pain). It also assumed a relative treatment benefit for cerliponase alfa. This was 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 said that the estimates of the proportion of people assumed to have 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 whether using treatment-dependent estimates of the proportion of people assumed to have progressive symptoms introduced the possibility of double counting the treatment benefit from cerliponase alfa. But the EAG said 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 have fewer progressive symptoms when having cerliponase alfa compared with standard care. They explained that there was data that supported a reduction in seizures, but they had also seen reductions in myoclonus, pain and the need for a feeding tube. The committee concluded that the company's estimates of the proportion of people having 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 (an ML score of 6) and that all other people (12.5%) would start treatment in health state 2 (an ML score of 5). The company said that its choice of starting distribution was informed by the younger than 3 years subgroup from study 190-203. It thought that this subgroup reflected the people who would have cerliponase alfa in the

near future. It said that the baseline ML score at the start of treatment would be higher than in the study 190-203 full population and MAA cohort. This was 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. This is because of the impact of COVID-19, which caused delays to diagnosis and starting treatment 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 have been younger and have less progressed disease than people 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. It assumed half the people 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 (the Generation Study) is underway, but it is uncertain whether 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 provided by one 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 their centre: 28.5% of children starting with an ML score of 6, 28.5% with an ML score of 5, and 42% with an ML score of 4.

The company said 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 affected 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 said that the pandemic continues to affect 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 thought 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 (an ML score of 4) and 2.5% would start treatment in health state 4 (an ML score of 3). It said that it thought 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 said that, in the last 2 years, they had not seen anyone diagnosed with an ML score below 5. They agreed that the distribution the EAG's clinical experts thought 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 said 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 if 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. These were deemed confidential by the company and so cannot be presented here. The EAG explained that the proportion of people that started 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 people 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 will start treatment in health state 1. The committee thought 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.

In response to consultation, the company maintained that the 'best achievable' estimate of ML score distribution at the time of diagnosis in 5 years' time from its advisory board should be used. It said that this distribution was supported by clinical expertise and accounted for the increasing likelihood that newborn screening will be implemented. The clinical experts reiterated that, in the last 2 years, they had not seen anyone diagnosed with an ML score below 5. They also reiterated that, without newborn screening, it is still possible that some people could be diagnosed with ML scores below 5. The clinical experts described the work that is ongoing to introduce a dried-blood spot testing method for newborn screening into the NHS. The committee noted that the 10-year health plan for England outlines the government's longer-term ambition to make genomic sequencing at birth universal. The committee recognised the work that is ongoing to improve early diagnosis. It also acknowledged comments from a clinical expert. These were that improvements in early diagnosis could continue without introducing newborn screening and that the 'best achievable' estimate from the company's advisory board was plausible. The committee concluded that the 'best achievable' estimate of ML score distribution at the time of diagnosis in 5 years' from the company's advisory board should be used in decision making. This was because of the aspirational plans announced by the government, and despite this estimate being associated with considerable uncertainty.

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 (an 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 reasonable 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 everyone who started treatment in health state 1 would be the same. There would be some people who were presymptomatic with normal motor and language function and some people with symptoms, and near-normal motor and language function. The clinical experts advised that only children who are presymptomatic would be likely not to progress to health state 2 (an ML score of 5) in 6 years. So, the committee decided that 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 started 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 started 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 started 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's and EAG's 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 that 'initial stabilisers' would have 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 have 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 thought 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 are not classified as 'initial stabilisers'.

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 said 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 have reflected 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 said that the pooled data had limitations because it included people who:

- were diagnosed before cerliponase alfa was available

- had delays to diagnosis and 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 have introduced bias against cerliponase alfa because it included people who had 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 have introduced 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 an analysis using the pooled data but excluding data from the MAA. The company provided that analysis for the second committee meeting but 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 had 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 had 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 that progression from the more progressed health states would be slower in people who started treatment with less progressed disease than in people who started treatment in the more progressed health states.

At the second committee meeting, the EAG maintained that study 190-203 may not have reflected the population who would have cerliponase alfa in NHS clinical practice and may have overestimated the effectiveness of cerliponase alfa. The EAG noted that, when the baseline distribution informed by its clinical experts' estimates of clinical practice in 5 years' time (see section 3.7) was used with the study 190-203 data, the average time in health state 1 for the modelled cohort was 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 seen 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 have reflected the population that would have cerliponase alfa in NHS clinical practice. It was also concerned 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 other health state. It decided this may mitigate some of the effect of delayed treatment initiation and difficulty accessing other interventions that people in study 190-201/202 and the MAA had. The committee concluded that the pooled data, including data from the MAA, was reasonable for decision making.

After the second committee meeting, the company said that its advisory board suggested there was a consensus among clinical experts that study 190-203 best reflected 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 thought 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 the 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 section 3.8 and section 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 thought that applying the 'initial stabiliser' assumptions to data from study 190-203 may have double-counted 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 states 6 and 7 because these transitions were not seen 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 with the 'most realistic' estimate of ML score distribution at the time of diagnosis in 5 years' time from the company's advisory board and the committee's other preferred assumptions, the model assumed that the average time in health state 1 for the modelled cohort was less than 20 years. The committee understood that, because of the relatively short follow-up periods in the studies, it was not known how long people would spend in health state 1. The clinical experts advised that it may be possible to be in health state 1 for up to 20 years, but that this was likely overly optimistic.

In response to consultation, the company and patient group maintained that the data from study 190-203 most closely reflected current diagnosis, referral and treatment. The company reiterated the limitations associated with the pooled data. The committee recalled that it had concluded that study 190-203 was more likely than the pooled data to reflect current NHS clinical practice. But it also recalled that both the data from study 190-203 and the pooled data had limitations. The EAG reiterated its concern that applying the 'initial stabiliser' assumptions to data from study 190-203 may have double counted the benefits of starting treatment earlier with less progressed disease. It provided estimates for the expected time spent in health state 1 for someone who starts treatment in health state 1, after applying the 'initial stabiliser' assumptions to the pooled data and data from study 190-203. When the pooled data was used, the expected time in health state 1 was 19.6 years. But when the study 190-203 data was used the expected time was 34.5 years.

The committee recalled earlier testimony from the clinical experts outlining that how long someone would spend in health state 1 was uncertain, and that up to 20 years may be possible but likely overly optimistic. The committee did

not hear any justification for the estimate of 34.5 years in health state 1 produced by applying the 'initial stabiliser' assumptions to the data from study 190-203. The committee recalled that the EAG explained that, when the study 190-203 data was used without applying the 'initial stabiliser' assumptions, the expected time spent in health state 1 for someone starting treatment in this health state was almost identical to when the 'initial stabiliser' assumptions were applied to the pooled data. It thought that applying the 'initial stabiliser' assumptions to data from study 190-203 likely double counted the benefits of starting treatment earlier with less progressed disease. The committee concluded that, when used with the 'initial stabiliser' assumptions, the pooled data (despite its limitations) produced more plausible estimates of time spent in health state 1. So, it concluded that this data should be used for decision making. The committee also concluded that it would take the uncertainty of using the pooled data in the long-term treatment effect of cerliponase alfa 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 said 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 said 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 said 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 thought that it was unlikely that cerliponase alfa would generate substantial improvements in motor and language function. The committee noted the company had submitted a Markov model that used a cohort-level modelling approach which 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 seen in the clinical data. The committee concluded that the company's estimation method was suitable for decision making.

Vision-loss progression

3.12 In the company's submission, it said that all clinical evidence pointed to continued deterioration of visual function in people having cerliponase alfa. It added that there was no significant indication that treatment could improve or stabilise vision. The company included vision-loss progression in its base case by assuming that:

- everyone in health states 7 to 9 had 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 years.

The company said 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 years and most people will have complete loss of vision by age 10 years. The clinical experts at the meeting explained that vision loss usually begins around age 5 years with most people having near-complete vision loss by around age 9 years. 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 were delivered into the eye by intravitreal injections. The company said that some improvement in vision is biologically plausible even when cerliponase alfa is

infused directly into the brain. This is because of the effect central brain function has on vision loss. The patient experts explained that, although most children have vision loss by age 10 years, some have been shown to have slower vision loss and retain their vision for longer, or show no vision loss at all.

The committee noted that it had not been presented with any clinical evidence to support the assumption that cerliponase alfa delays vision loss. It acknowledged comments from the clinical experts that most people will have vision loss by around age 9 years. The committee concluded that the EAG's approach to modelling vision loss should be used in decision making. In response to consultation, the clinical experts noted the benefits of delivering cerliponase alfa into the eye by intravitreal injections had not been accounted for in the model. The committee noted that intravitreal injections are not covered by the current marketing authorisation for cerliponase alfa. The committee noted that guidance can only be issued in accordance with the current marketing authorisation. The committee concluded that it had not been presented with any clinical evidence to change its preference for using the EAG's approach to modelling vision loss 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 (an ML score of 1). People were assumed to have standard care after stopping treatment. The company said 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 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 that 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 (an 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 that people would stop cerliponase alfa in health state 7. The clinical experts explained that they would expect treatment to stop when people reach health states 6 or 7, and after considering both the advantages and disadvantages of stopping, and 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 said 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 that 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 said 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 said that ML score would not be used alone to decide if treatment should be stopped. The clinical expert said that quality-of-life questionnaires were used as part of the stopping criteria in the MAA. They added 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 having 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. (2021) study used in the model assumed that the health-related quality of life of 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 (an 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 people 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 said that it did not support the inclusion of starting rules. It added 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 and clinical experts said 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, people who start 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 it would mean that someone who was diagnosed in that progressed health state would not be eligible for treatment. The committee concluded that, ideally, there would be no starting rules and that 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. It added that how this could be done would need to be proposed by stakeholders.

In response to consultation, comments were received stating that, if it meant some children could have cerliponase alfa, perhaps a starting rule should be considered. But a patient expert expressed strong opposition to introducing starting criteria. They explained how their 2 daughters had started treatment with different ML scores, but both benefited hugely from having cerliponase alfa. At the fourth committee meeting, the representative for the patient organisation also strongly opposed a starting rule. They thought that cerliponase alfa should be available to everyone who would benefit from it. They explained that introducing a starting rule would mean people who had a delayed diagnosis would be unable to access cerliponase alfa. The committee acknowledged the strong opposition for a starting rule and concluded that it would consider all people newly diagnosed with CLN2 regardless of their ML score when evaluating cerliponase alfa.

Non-reference-case analysis

3.15 The committee noted that section 4.4.16 of NICE's technology appraisal and highly specialised technologies guidance 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. In considering a non-reference-case analysis

alongside the reference case, the committee will consider the extent to which the cost effectiveness of the technology is driven by factors outside its direct cost and benefits. After the first meeting, the committee asked for a non-reference-case analysis with background care costs removed to be explored. It said that the rationale for removing specific background care costs, and any structural assumptions used in the analysis, should be clearly documented. In response, 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 said that treatment with cerliponase alfa is associated with longer-term survival, which results in increased background care costs that do not represent direct, intrinsic consequences of treatment. The committee noted that this was not unique to this evaluation and that many technologies have effects on costs and outcomes over a patient's lifetime.

The committee noted that the NICE technology appraisal and highly specialised technologies guidance 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. Nevertheless, the committee considered the non-reference case analysis alongside the company base-case analysis without the background costs removed. The committee noted that it had not been provided with compelling evidence or a clear rationale for removing the background care costs. It also noted that the main driver of cost effectiveness was the acquisition cost of cerliponase alfa and not the background costs. So, it concluded at the second meeting that only the reference-case analyses should be used for decision making. Before the third committee meeting, the company provided additional scenarios that included background care costs in line with the committees preferred modelling assumption. In response to consultation, the company said that its submission before the second committee meeting clearly documented the rationale and justification for removing background care costs. The EAG explained that it had considered the justification provided by the company. It decided that it did not warrant the removal of background care costs from the base-case analysis. The committee concluded that it had not seen any evidence to change its preference that only the reference-case analyses should be used for decision making.

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 whether a person was having cerliponase alfa or standard care. Utility values were taken from Gissen et al. (2021), which 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 Gissen et al., which were:

- 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.
- The vignettes assumed different progressive symptom burdens between treatment arms. But it was not clear how this aligned with the assumed proportion of people having progressive symptoms used to inform the resource-use assumptions in the model (see section 3.6).
- 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 Gissen et al., which were:

- The differences in utility values between cerliponase alfa and standard care was substantial after health state 5.
- 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 have been 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 get utilities for the standard care arm, data from Gissen et al. had to be used. So, the issues of robustness of the data from the study remained. The committee recalled what it heard from the clinical experts about differences in the progressive symptoms between treatment arms (see section 3.6). It also recalled what it heard from patient experts about the benefits of cerliponase alfa extending beyond its impact on motor and language function. So, based on what it had heard, the committee accepted that 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 Gissen et al. But, based on the scenarios and evidence presented, it concluded that utilities from Gissen et al. 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
- 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 everyone. 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. This was 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 so 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 they thought that once a year would probably be useful so that 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. This 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. It preferred including neurodisability mortality in all health states because it 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 have. 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 only had a minor impact on the cost-effectiveness results. At the third meeting, the committee noted the additional scenarios presented by the company. These included neurodisability

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 technology appraisal and highly specialised technologies guidance 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. The committee understood that section 6.2.34 of NICE's technology appraisal and highly specialised technologies guidance manual specifies circumstances when the committee should be aware that evidence generation is particularly difficult for certain technologies or populations. This is because they are rare diseases, for use in a population that is mainly children, or the technology is innovative and complex. The committee thought that, for this evaluation, all 3 circumstances applied. So, the committee concluded that it was appropriate to accept a higher degree of uncertainty. 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). The committee considered the circumstances of the evaluation, the uncertainty and the evidence as a whole. It concluded that the QALY weight associated with its preferred assumptions should be applied because it is likely that cerliponase alfa offers significant QALY gains. The amount of QALY weighting to be applied is less than the maximum QALY weighting possible but is commercial in confidence and cannot be reported here. 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 the circumstances of the evaluation contributed to the uncertainty. But the committee decided that the inclusion of the 'initial stabiliser' assumptions (see section 3.8 and section 3.9) mitigated much of the uncertainty associated with the choice of data used to inform the transition probabilities. To account for any outstanding uncertainty, the committee concluded that the QALY weighting should be increased by 0.2 on top of the QALY weighting associated with the committee's preferred assumptions.

The committee noted 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 technology appraisal and highly specialised technologies guidance 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 it had accepted the company's approach to incorporating carer and sibling disutility into the model. So, it thought that the QALY gains of carers and siblings were accounted for elsewhere in the cost-effectiveness estimates.

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 have progressive symptoms (see section 3.6)
- baseline distribution informed by the clinician estimate of the best achievable ML score distribution at the time of diagnosis in 5 years' time when assuming that newborn screening is not available (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, and, 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 Gissen et al. (2021) (see section 3.16)
- using the EAG's estimates of ECG monitoring costs (see section 3.17)
- including neurodisability 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. The company had an additional commercial agreement as part of the managed access agreement which did not apply during the appraisal because it was a time-limited agreement. However, had this commercial arrangement applied, the ICERs were still 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 this results in an issue of equality of access to treatment. The committee noted that the patient and 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. In response to consultation, clinical experts, consultees and stakeholders suggested that the recommendation in the draft guidance constituted indirect disability and age discrimination. They explained that people with CLN2 would be considered disabled under the Equality Act 2010. They further explained that not recommending cerliponase alfa for children diagnosed after the end of the MAA extension will disproportionately impact younger children. This is because they are unlikely to be diagnosed before age 3 years because of a lack of clinical symptoms. A stakeholder also stated that any potential disparities in diagnosis or referral patterns should be addressed to ensure treatments are equally available to all racial groups. Age, disability and race are protected characteristics under the Equality Act 2010. Access to cerliponase alfa started during the access agreement period is not considered routine commissioning (see section 3.24). The recommendation represents the committee's final decision on whether cerliponase alfa should be routinely commissioned by the NHS. Also, it does not restrict access to treatment for some people over others. So, the committee agreed these were not potential equality issues. The committee concluded that no additional considerations were needed about equality 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, and the clinical and patient experts, the committee concluded that

cerliponase alfa is an innovative treatment.

Uncaptured benefits

3.23 The company said 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 it 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 considered.

Managed access arrangements

3.24 In response to consultation, a patient organisation commented that not recommending cerliponase alfa for children who have not started treatment before the end of the managed access period creates a discriminatory distinction based on diagnosis timing. The patient organisation explained that children diagnosed before the end of the managed access period will have cerliponase alfa and have slower progression and enhanced quality of life. But, without cerliponase alfa, children diagnosed after the end of the managed access period will likely die by early adolescence. The patient group and stakeholders suggested that there were other ethical concerns. They suggested that families could be in a situation in which 1 sibling would be able to access cerliponase alfa while another would not. They also suggested that it would be unethical to expect healthcare professionals to withhold cerliponase alfa from children diagnosed after the end of the managed access period, while continuing to offer it to people who started treatment before the end of the managed access period. The committee noted the concerns from stakeholders that there would be inequity in access with people being offered different treatments depending on time of diagnosis. The committee noted that treatments available through managed access are not commissioned routinely by the NHS but are made

available to patients for a time-limited period. The committee noted that all managed access agreements are reviewed at the end of the managed access period and, if the treatment is not recommended, it will then not be available in the NHS for people who have not yet started treatment.

Conclusion

Recommendation

3.25 The committee recognised that 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 NHS resources for highly specialised technologies. So, cerliponase alfa is not recommended for treating CLN2.

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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Joanna Richardson
Technical adviser

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