cerliponase alfa 150mg solution for infusion (Brineura®)

BioMarin International Limited

04 September 2020

The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Key points:

- CLN2 disease is a severe, neurodegenerative condition, diagnosed in childhood with devastating symptoms affecting multiple aspects of the child's life. There are no other medicines licensed for this condition.

- A phase I/II study reported a clinically relevant treatment effect with cerliponase alfa, measured by the CLN2 motor/language (ML) scale at 48 weeks. This treatment effect was maintained through to week 96 in an extension study. Cerliponase alfa was also associated with significant treatment benefits when indirectly compared to standard of care from a historical control group.

- The quality of life data are potentially difficult to interpret but can be considered positive. The stabilisation observed may be beneficial considering the decline in quality of life typically observed with CLN2 disease.

- A model-based health economic evaluation suggests that cerliponase alfa is associated with a substantial gain in quality-adjusted life years compared to standard of care. However, the following issues add to the uncertainty of the results: assumptions regarding long term disease stabilisation; the distribution of patients in different starting health states; utility value estimates and the long time horizon.

- Despite a Patient Access Scheme (PAS) that improves the cost-effectiveness of cerliponase alfa, the treatment's cost in relation to its health benefits remains high.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.[1]

Dosing Information

The recommended dose is 300mg cerliponase alfa administered once every other week by intracerebroventricular infusion. In patients less than 2 years of age, lower doses are recommended (see Summary of Product Characteristics [SPC]).

Pre-treatment of patients with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion.

Continuation of long-term treatment should be subject to regular clinical evaluation whether the benefits are considered to outweigh the potential risks to individual patients.

Cerliponase alfa must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.

For advice on dose adjustments to manage adverse events see the SPC.[1]

Product availability date

September 2019

SMC ultra-orphan designation

Cerliponase alfa has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of CLN2 disease is estimated to be ≤1 in 50,000 (or less than around 100 people in Scotland).
- Cerliponase alfa has European Medicines Agency (EMA) orphan designation for the treatment of CLN2 disease and this was maintained at the time of Marketing Authorisation.
- CLN2 disease is chronic and severely disabling due to rapid decline in speech, seizures (often refractory), loss of mobility, cognitive decline, ataxia, myoclonus, spasticity, dystonia, and visual deterioration.

- CLN2 disease is a genetic, paediatric, neurodegenerative condition that requires highly specialised management.

Background

Cerliponase alfa is an enzyme replacement therapy, a recombinant form of human tripeptidyl peptidase 1 (TPP1). It reduces lysosomal toxin accumulation and is expected to restore deficient TPP1 activity in the brain which has been caused by the CLN2 gene mutation.

Cerliponase alfa is an inactive pro-drug that is administered into the cerebrospinal fluid (CSF) by infusion, via a surgically implanted intracerebroventricular access device. It must be given in a healthcare setting by a trained healthcare professional knowledgeable in intracerebroventricular infusion administration.

Cerliponase alfa is the first medicine to be approved for use in CLN2 disease.[2]

Nature of condition

CLN2 disease is a severe, neurodegenerative lysosomal storage disorder. Patients with CLN2 generally present with slowing of development and psychomotor regression, usually at age 2-3 years. The disease progresses rapidly over the course of 2 to 3 years and diagnosis is generally confirmed around 4 years of age. Epilepsy typically develops between 2 and 4 years of age. It usually presents with variable seizure types and is often refractory to treatment. Other symptoms include decline in speech, loss of mobility, cognitive decline, ataxia, myoclonus, spasticity, dystonia, and visual deterioration. Generally, by around 6 years of age, patients lose vision, are wheelchair-bound and require gastrostomy feeding with death occurring between 8 years and early adolescence. Atypical cases where onset is later and disease course more protracted have also been described in the literature.[2]

There are no other medicines licensed for this condition and patients are generally managed using palliative care principles involving symptomatic treatments. There is a high unmet need in these patients.

Clinical experts consulted by SMC considered that cerliponase alfa fills an unmet need in this therapeutic area with no other treatment options, as it reduces the decline in the patient's clinical condition.

Impact of new technology

Comparative efficacy

Study 190-201 was a multi-centre, open-label, single-arm, phase I/II study which evaluated the efficacy and safety of cerliponase alfa in 24 children with CLN2 disease aged between 3 and 16 years old. Eligible patients had stable seizures and seizure medication (as judged by investigator), and had early to moderate disease progression (defined as a score of 3 to 6 on the combined motor and language domains of the CLN2 Clinical Rating Scale (CLN2 ML), with a score of at least 1 in each of the motor and language domains. Patients received cerliponase alfa 300mg via intracerebroventricular infusion every 2 weeks for 48 weeks. An antihistamine was administered approximately 30 minutes before each infusion. Antipyretics and sedative medications were also permitted as pre-treatments at the discretion of the investigator and in accordance with local standard practice. Patients who completed 48 weeks treatment in study 190-201 and did not have a decline of >3 points or a score of 0 on CLN2 ML scale could continue on the same dose of cerliponase alfa for up to 240 weeks in extension study 190-202. [2, 3]

The primary outcome was the change from baseline in CLN2 ML score at 48 weeks. The CLN2 ML scale was an ad hoc outcome measure that was adapted from two established CLN2 scales: the Hamburg Scale and the Weill Cornell Scale. Each domain is scored between 0 and 3 where a score of 3 signifies age-defined normal and a score of 0 minimal or no function. The primary outcome was evaluated using responder analyses (where a lack of either a 2-point or 1-point decline in CLN2 ML score was classed as a responder) and slope analysis (rate of mean decline in CLN2 ML scores). Efficacy analyses were performed in the intention-to-treat (ITT) population (n=23), which included all patients who received cerliponase alfa and reported any efficacy results, excluding one patient who withdrew from the study after a single infusion of study drug due to inability to continue with study procedures. Every patient that completed Study 190-201 (n= 23) continued into the long-term Study 190-202.[2]

Over a 48-week period where patients received cerliponase 300mg every 14 days, the mean CLN2 ML score declined from 3.5 to 3.1 points. When compared to the expected rate of decline based on the natural history study (2 points per 48 weeks), the study results were statistically significant (p <0.001).[3] Benefits were maintained in the extension study 190-202. See Table 1 for details.

Table 1. Rate of decline in score of CLN2 Clinical Rating Scale Movement and Language (CLN2 ML) score in studies 190—201 and 190-202.[3]

Rate of decline (Points per 48 weeks)	Study 190-201 (n=23)	Study 190-202 (n=23)
	End of study (primary outcome)	Interim analysis November 2017
Duration of treatment	48 weeks	96 weeks
Mean (SD)	0.40 (0.809)*	0.27 (0.350)
Median	0.00	0.34
Min, Max	-0.88, 2.02	-0.36, 1.00
95% CI	0.05, 0.75	0.12, 0.42
p vs fixed natural history**	<0.001	<0.001

* Positive estimates indicate clinical decline; negative estimates indicate clinical improvement; ** p-value based on 1-sample T-test comparing rate of decline to the value 2, which was taken from the natural history database; CI = confidence interval; SD = standard deviation.

Responder analysis of the primary outcome showed that 87% (20/23) of the ITT population had a response to treatment, defined as the absence of a 2-point decline on CLN2 ML scale. The other 13% (3/23) were non-responders (i.e. had a 2-point decline or greater). Almost two thirds of patients (65%) in the study either had no change or an improvement in CLN2 ML scale score. Responder rates (absence of 1-point decline) for the separate motor and language domain scores for the ITT population were 78% (18/23) and 70% (16/23) respectively.[3] See Table 2 for details.

Table 2. Primary outcome responder analysis of Study 190-201 and 190-202 (ITT population).[3]

Outcome	Study 190-201 (n= 23)	Study 190-202 (n=23)
Treatment duration	48 weeks	96 weeks
Response defined as the absence of two-point decline in CLN2 ML score		
Response	87% (20) (95% CI: 66% to 97%)	87% (20) (95% CI: 66% to 97%)
Non-response	13% (3)	13% (3)
Response defined as the absence of one-point decline in CLN2ML score *		
Response	65% (15) (95% CI: 43% to 84%)	52% (12) (95% CI: 31% to 73%)
Non-response	35% (8)	48% (11)

* The table considers CLN2 assessments through Day 340 (relative to first 300mg infusion)

Secondary outcomes of Study 190-201 included changes in 9-point (motor/language/vision) and 12-point (motor/language/vision/seizures) CLN2 Clinical Rating Scales.[3] See Table 3 for details.

Table 3. Changes in 9-point and 12-point CLN2 Clinical Rating Scales at Week 49. Study 190-201 (ITT population).[3]

Domains included	Motor Language	Motor Language Vision	Motor Language Vision Seizures
Possible score range	0-6	0-9	0-12
Baseline mean (SD)	3.5 (1.20)	6.3 (1.34)	8.0 (1.83)
Endpoint mean (SD)	3.0 (1.33)	5.7 (1.56)	7.9 (2.07)
Change mean (SD)	-0.4 (0.79)	-0.6 (1.03)	-0.1 (1.93)

SD = standard deviation

Health Related Quality of Life (HRQoL) was assessed using three questionnaires: PedsQL Parent Report for Toddlers, PedsQL Parent Family Impact, and CLN2 disease-based Quality of Life. The PedsQL Parent Report for Toddlers instrument measures physical, emotional, social and school functioning. The Parent Family Impact instrument comprises the following dimensions: physical functioning, emotional functioning, social functioning, cognitive functioning, communication, worry, daily activities, and family relationships. These instruments were used at baseline and week 49.[3] Overall, the results appeared to suggest stabilisation in quality of life.

The outcomes of patients treated with cerliponase alfa in Study 190-201/202 were also indirectly compared with untreated patients from the natural history study (Study 190-901) using a matching process. When patients were matched 1:1 based on age (age difference ≤3 months), baseline CLN2 score and genotype, this resulted in 17 matched pairs of patients. There was a relevant and statistically significantly higher proportion of responders (with a decrease in the rate of disease progression measured by the ML scale score) in the cerliponase alfa group compared with matched untreated patients; mean decrease from baseline in CLN2 ML score of 0.20±0.67 points versus 1.90±1.23 points over 48 weeks in cerliponase alfa treated patients and historical controls respectively. After 96 weeks, the mean decrease in the CLN2 ML score was 0.50±0.71 points among the treated patients and 2.80±1.10 points among the historical patients from 190-901. Additionally, rates of decline in the total CLN2 score (motor, language, vision, and seizure domains) were evaluated. After 48 weeks, the cerliponase alfa treatment group had a mean improvement of 0.30±1.70 points in total CLN2 score compared with a decline of 2.80±2.04 points in the historical control group. After 96 weeks, the mean increase in the total score among treated patients was 0.40±2.08 points; a decrease of 4.30±2.26 points among the historical controls was reported.[2, 3]

Comparative safety

All patients in Study 190-201/202 had at least one treatment-emergent adverse event (AE), 96% (23/24) experienced at least one drug-related AE, and 79% (18/24) had at least one serious AE. Most patients (58%) had an adverse drug reaction (ADR) with moderate severity as highest severity level, one quarter (25%) had ADRs with only mild severity, and at least 1 severe ADR occurred in 13% of patients. Drug related serious AE occurred in 33% of patients. No AEs led to study discontinuation or permanent discontinuation of study drug.[3]

The most common AEs related to cerliponase alfa treatment as assessed by investigator included pyrexia (46%), hypersensitivity (38%), seizure (38%), epilepsy (17%), vomiting (13%), headache (13%), feeling jittery (8%) and myoclonus (8%).[3] The large majority of seizures (>90%) reported were grade 1 or 2 in severity, and 94% were considered unrelated to treatment; no clear pattern between seizures and treatment with cerliponase alfa was observed. Almost half (46%) of patients in Study 190-201/202 experienced a total of 30 device-related AEs over the total treatment period. Needle issue (5 events in 4 patients), device leakage (5 events in 1 patient), and pleocytosis (3 events in 3 patients), device malfunction (2 events in 2 patients), and propionibacterium infection (2 events in 1 patient) are the only device-related AEs to have occurred more than once. Two patients had 3 incidences of intracerebroventricular access device infections which were considered serious. All device-related infections resolved after treatment with antibiotics and removal/replacement of the device; 4 devices were replaced during the studies.[3]

The EMA stated that characterising the safety profile of cerliponase alfa was difficult given the limitations of the study design and the very limited pre-clinical safety data package. They concluded that although there have been potentially serious ADRs and device related issues, to date they have been manageable. Given the rarity of the condition and the lack of treatment options, cerliponase alfa was approved for use under exceptional circumstances. The submitting company have been asked by the EMA to conduct and submit the results of a phase 2 study (Study 190-203) in order to further evaluate the efficacy and safety of cerliponase alfa.[3]

Clinical effectiveness issues

Key strengths:

- Cerliponase alfa provided a clinically relevant treatment effect; almost two thirds of patients (65%) in the study either had no change or an improvement in CLN2 ML score at week 48, in a condition where rapid progression is typical. A large proportion of patients (87%) responded to treatment, defined as not having a 2-point decline on the ML scale at week 48 of treatment.[3]

- The ad hoc primary outcome measure was appropriate. Patient representatives approached by the EMA emphasised that motor and language skills were the most

important domains to consider in the day to day life of patients and their families.[3]

- Longer-term data from the extension Study 190-202 showed a maintenance of treatment effect, and seemed to be independent of baseline ML score.[3]

- The primary results were supported by additional matched indirect comparisons with patient level data from a historical study.

Key uncertainties:

- Study 190-201 was a small, single-arm, open-label study, and so prone to various forms of bias. The EMA accepted this approach despite its limitations given the rarity of CLN2 disease, the rapid progression of disease, and the lack of treatment options. Further evidence from Study 190-203 will be reported.[3]

- No dose-finding studies have been carried out for cerliponase alfa, and consequently 300mg every 14 days, as used in Study 190-201/202, may not be optimal for all patients. However, this dose has demonstrated a notable treatment effect in the overall study population.[3]

- Long-term efficacy and safety data are limited for cerliponase alfa and a survival benefit has not been demonstrated.

- The population of Study 190-201/202 was largely representative of the licensed indication however did not include patients aged less than 3 years old or patients with severe disease.

Clinical experts consulted by SMC considered that cerliponase alfa is a therapeutic advancement due to the apparent halt in disease progression observed in a majority of patients and due to the lack of any treatment options.

Overall the clinical case was considered sufficiently robust. The limitations in study design have been adequately addressed through indirect comparison with historical data within the context of an ultra-rare, rapidly progressive condition without treatments.

Impact beyond direct health benefits and on specialist services

Cerliponase alfa may delay patients from progressing to later health states, which could be associated with greater numbers of appointments with specialist clinicians and therapists.

Additionally, by halting the progression of CLN2 disease, cerliponase alfa may also have a positive impact on the emotional and psychological wellbeing of family members/carers, family and social relationships, the education and social interaction of the affected child, and family finances. Cerliponase alfa must be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. This would likely be a centralised setting, which would impact on the service, the patients and their families.

Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The Batten Disease Family Association, which is a registered charity.

- The Batten Disease Family Association has received 18% pharmaceutical company funding in the past two years, including from the submitting company.

- CLN2 disease has a devastating impact on the lives of affected children. The disease is rapidly progressing and children lose their ability to walk, talk, swallow and see. They also develop complex, drug resistant epilepsy and childhood dementia. Quality of life for the whole family is dramatically reduced and parents have to rapidly learn to care for a profoundly disabled child.

- There is currently no treatment available in Scotland that slows down the progression of the disease. Children with CLN2 disease will be on a range of medication to manage the symptoms of the condition including complex epilepsy, constipation and reflux. They will require support for swallowing difficulties, oral secretions and respiratory function. In later stages children may need ventilation. The children are fully dependent on their parents/family for every aspect of their day to day care. The condition is always terminal.

- Cerliponase alfa is the only treatment that has been shown to slow the progression of the disease, by replacing the missing enzyme. Children who have accessed treatment have been able to maintain their ability to walk and talk, have fewer seizures and have been able to live a more 'normal' life. For their families, the burden of care is less overwhelming. This is particularly apparent in children who have been able to access the treatment younger, at an earlier stage of the disease. A reduction in seizures, the ability to maintain skills and improvements in sleep, all impact positively on the whole family.

- Treatment involves a commitment by families as it is frequent and intrusive. Cerliponase alfa is administered via an infusion directly into the fluid around the brain. It requires an initial operation to place a 'port' in the brain and then twice monthly visits to hospital for administration.

- Whilst not a cure, this is potentially a life changing therapy for children with CLN2 disease. Access to cerliponase alfa gives affected families hope for the future and families welcome this opportunity.

Value for money

The economic model presented by the submitting company was a multi-state Markov model to assess the cost-effectiveness of cerliponase alfa versus standard of care for the treatment of CLN2 disease. Current standard of care includes symptomatic treatments for managing

seizures, motor control loss and feeding/control of aspiration risk. It also includes disease management such as physical and speech therapy, different medications for myoclonus, spasticity, dystonia and pain as well as end-of-life care when disease is at an advanced stage.

The model used a 95-year lifetime horizon, and tracked disease progression through 10 unique health states. Patients could transition between health states after each 2-week cycle. Health states 1-7 were based on CLN2 clinical rating scale scores. The scale consisted of two domains (motor and language) and scores ranged from 6 (least severe; score of 3 in each domain) to zero (most severe). Health state 8 signified complete vision loss; health state 9 signified palliative care and health state 10 was death. In the base case provided by the company, a health and social care perspective for costs was used, but a wider (patient, sibling and carer) perspective on benefits was adopted. Sensitivity analysis was provided where only a patient perspective was used for health benefits in the model, and also where a wider societal perspective on costs was used to capture productivity losses for family members.

Clinical evidence informing the economic analysis was obtained from the 190-201/202 single arm studies and the 190-901 natural history study. Transitions for patients on cerliponase alfa were based on 96-week patient level data from the 190-201/202 study and from the 190-901 study for the comparator arm. Transitions in more progressed states (7-9) were based on clinical expert opinion as long term data were unavailable.

The model categorised patients on cerliponase alfa as being either early stabilisers or late stabilisers depending on response status by week 16. For early stabilisers with a positive response by week 16, patients maintained their health state for the remainder of the time horizon. In the base case, approximately 74% of patients were early stabilisers. For late stabilisers, patients would decline at a constant rate of 1 point (ie move up 1 health state) every 80 weeks for the remainder of the time horizon. The health of late stabilisers was therefore akin to a situation of partial stabilisation. For the comparator arm, no stabilisation was assumed and there would be a decline in health status, informed by the natural history study. Transition rates between health states 7 to 10 were the same for both cerliponase alfa and standard of care arms in the model. The proportion of patients in each health state experiencing progressive symptoms (epilepsy, reported distress, dystonia, myoclonus and the requirement of a feeding tube) was the same in the cerliponase alfa arm as the standard of care arm. Four types of mortality were modelled – disease-related mortality, neuro-disability related mortality, infection-related mortality and age-related mortality.

Quality of life data were collected during study 190-201/202 but were not used in the model as they did not cover the full range of CLN2 disease stages. Health state utility values were obtained through a separately conducted utility study in July 2017 and subsequently applied in the base case of the model (with age-adjustment). This allowed for health states to incorporate all relevant aspects of the disease that impact quality of life, including progressive symptoms that are not captured by the CLN2 Clinical Rating Scale score.

Utility values were elicited indirectly using proxy responses of clinicians rather than patients themselves or their parents, with vignettes developed specific for each treatment across the 10 health states. Responses were based on the EQ5D-5L questionnaire, which were then mapped to the EQ5D-3L. Utility ranged from 0.99 (health state 1) to -0.211 (health state 9) for cerliponase alfa, and 1.0 (health state 1) to -0.39 (health state 9) for standard care. A vision-loss related utility decrement was applied to the proportion of cerliponase alfa patients in health states 1 to 6 to account for the absence of this domain in the CLN2 rating scale. Additional disutility was added to the model to represent the impact on quality of life felt by unaffected siblings that do not themselves have CLN2 disease, as well as caregivers.

The analysis included acquisition and administration costs for cerliponase alfa, anti-epileptic medicines, distress, dystonia and myoclonus medicines. Cerliponase alfa treatment duration was ongoing until health state 7. Different health state costs were also provided where costs such as specialist carers, language therapists, other health workers and educational support were included. A residential care cost was applied to 50% of the patients aged 18 and over and replaced the costs of specialist nursing and professional caregivers.

The annual cost of cerliponase alfa at list price is £522,782. A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

SMC is unable to present the with-PAS cost-effectiveness estimates that were considered due to the company's requirement for commercial confidentiality. Treatment cost of cerliponase alfa was the biggest contributor to incremental costs and the large QALY gains arose from the majority of patients being held in the least severe health states for an extended period of time.

The company provided scenario analyses, deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis. In the DSA, each variable was increased and decreased by 15% whilst all other variables were held constant. Medicines cost were the biggest driver in the DSA followed by health state utility values (for cerliponase arm). The relatively low range of variation was because the key model drivers were assumptions regarding the starting health state distribution of patients and transition probabilities (i.e. long term disease stabilisation) which could not be investigated via DSA.

The company also provided scenario analyses to explore uncertainty around key assumptions which could not be sufficiently explored in the DSA. These highlighted particular sensitivity to the starting distribution within the model, as well as the influence of more conservative utility estimates.

The key strengths and uncertainties of the economic evidence are summarised below:

Key strengths:

- The company used an appropriate model structure based on a disease progression scale that adequately reflects the course of CLN2.

- The uncertainty regarding long-term disease stabilisation in the late-stabiliser patient subgroup was mitigated by assuming a partial stabilisation rate of 1 point decline per 80 weeks.

- To model the impact of neurological disability on mortality, a multiplier was applied to the general population mortality already included in the model.

- Carer and sibling disutility values were limited to a maximum of 30 years rather than being applied for the entirety of the time horizon.

Key weaknesses:

- The model makes an assumption of long term disease stabilisation on cerliponse alfa around which there is substantial uncertainty. Study 190-202 has a follow up period of 240 weeks, but only data up to 96 weeks were available for this analysis. While the short-term data are positive, there remain empirical questions on whether this trend would be supported in the longer-term. Data were not available on the proportion of patients experiencing progressive symptoms when receiving cerliponase alfa. Hence, for early stabilisers (around 75% of patients in the base case), effectiveness of cerliponase alfa was assumed to be absolute with no possibility of a waning effect or a drop-off in disease stabilisation as patients get older. This implies that early stabilisers would have the same life expectancy as the general population, despite the life threatening nature of this disease. In the base case analysis, this leads to rather unrealistic predictions of as many as 10% of patients being in health state 1 after 90 years. The company adjusted utility values downwards for patients over 18 years on cerliponase alfa as a way of keeping long term QALY gains in check, but this does not address the substantial survival benefit experienced by patients. A more conservative scenario with a small transition probability of declining health state in the long term may have been more realistic.

- The base case analysis assumed that about 80% of patients would start treatment in the least severe health states 1 and 2. In contrast, only 16% of patients were in the least severe states in the study. The company argued that this could be plausible in the future because of greater awareness of CLN2 and earlier diagnosis using epileptic gene panels programme. However, this may reflect aspirational expectations, and it may be more realistic to have a wider distribution of starting health states. An alternate scenario was requested, wherein the starting distribution of patients was adjusted to 20% (state 1), 40% (state 2), 25% (state 3), 15% (state 4). This had a significant upward impact on the ICER as a later starting health state substantially reduces the number of

QALYs gained.

- Utility values applied in the base case were elicited indirectly using a vignette approach, but these could potentially be overestimates for the cerliponase alfa arm. This is because separate vignettes were developed for each health state contingent on the type of treatment. This differs from the conventional approach of having a single vignette describing a specific health state. The vignettes for health states in the cerliponase alfa arm included additional treatment benefits in addition to cerliponase's primary effect on stabilising motor and language deterioration. This included improvements in seizure control, dystonia control and myoclonus which implied lower pain levels and delayed need for a feeding tube. While such broad based stabilisation is quite plausible, some of these improvements were not reported for patients in the clinical study.

- The time horizon of 95 years is arguably too long for a severe life threatening illness considering that the standard care median age of death for patients is 10.7 years of age. A shorter time horizon (eg 75 years) is probably more realistic and would still sufficiently acknowledge the assumption of long-term disease stabilisation conferred by cerliponase alfa.

- The method used to estimate mean rate of decline in CLN2 scores for the standard of care group could bias results. Mixed models repeated measures (MMRM) is the gold standard for analysing repeated measures as it uses all the available data. The company has clarified that they are unable to apply MMRM post hoc and it could lead to a higher degree of variation from the observed data. Hence, the impact of using an alternative to MMRM remains unknown.

The cost of cerliponase alfa in relation to its health benefits remains high and there are outstanding uncertainties relating to the clinical data and utility values used in the model.

Costs to NHS and Personal Social Services

The company estimated there would be no treated patients in the first two years and 1 treated patient in years 3 to 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

No relevant guidelines were identified.

Additional information: comparators

There are no relevant comparators.

Additional information: List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Cerliponase alfa	**300mg by intracerebroventricular infusion every 14 days**	**£522,782**

Costs taken from company submission on 2 March 2020. Costs do not take any patient access schemes into consideration.

References

1.   BioMarin Pharmaceutical Limited. Cerliponase alfa 150mg solution for infusion (Brineura®). Summary of Product Characteristics. .
2.   European Medicines Agency. (EMA) European Public Assessment Report. Cerliponase alfa (Brineura®). 21/04/2017, EMEA/H/C/004065/0000. www.ema.europa.eu.
3.   Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, *et al.* Study of intraventricular cerliponase alfa for CLN2 disease. New England Journal of Medicine. 2018;378(20):1898-907.

This assessment is based on data submitted by the applicant company up to and including 13 August 2020.

Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.