CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

CERLIPONASE ALFA (BRINEURA — BIOMARIN PHARMACEUTICAL [CANADA] INC.)
Indication: For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that cerliponase alfa be reimbursed for the treatment of CLN2 disease, also known as TPP1 deficiency, if the following conditions are met:

Conditions for Reimbursement

Initiation Criteria

1. A confirmed diagnosis of CLN2 disease based on TPP1 enzyme activity and CLN2 genotype analysis.
2. Patient who meets all of the following:
   - 2.1 has a minimum score of ≥ 1 in each of the motor and the language domains of the CLN2 Clinical Rating Scale
   - 2.2 has an aggregate motor–language score of ≥ 3 on the CLN2 Clinical Rating Scale.

Discontinuation Criteria

1. Patients must be assessed every 24 weeks for changes in motor and language function using the CLN2 Clinical Rating Scale.
2. Treatment must be discontinued if:
   - 2.1 there is a reduction of ≥ 2 points in the aggregate motor–language score of the CLN2 Clinical Rating Scale that is maintained over any two consecutive 24-week assessments; or
   - 2.2 the aggregate motor–language score of the CLN2 Clinical Rating Scale reaches zero at two consecutive 24-week assessments.

Pricing Condition

1. Price reduction.

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    2.2 the aggregate motor–language score of the CLN2 Clinical Rating Scale reaches zero at two consecutive 24-week assessments.

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Reasons for the Recommendation

1. In studies 201 and 202, CLN2 disease was confirmed using TPP1 enzyme activity and CLN2 genotype analysis; enrolled patients had an aggregate CLN2 motor–language score on the Clinical Rating Scale of 3 (minimally) to 6, and a score of ≥ 1 (minimally) in each of the motor and language domains.
2. Given the pathophysiology and current understanding of CLN2 disease, cerliponase alfa is not expected to reverse accrued clinical deficits in patients with CLN2. Evidence is lacking for initiation of cerliponase alpha for patients in whom motor and language function has deteriorated to an aggregate motor–language score of less than 3 on the CLN2 Clinical Rating Scale.
3. The results of two studies (Study 201, a single-arm, open-label, uncontrolled study of 24 patients with CLN2 disease and Study 202, an ongoing extension of Study 201) reported an unadjusted mean (± standard deviation [SD]) decline in the motor–language score of 0.27 (± 0.35) per 48-week period for patients treated with cerliponase alfa (intention-to-treat population, N = 23). This compared with a decline of 2.12 (± 0.98) per 48-week period for unmatched historical controls (N = 42). The hazard ratio comparing the treated patients with the unmatched historical controls for the time to an unreversed ≥ 2-point decline in the motor–language score was 0.08 (95% confidence interval [CI], 0.02 to 0.23) favouring treated patients.
4. Based on the population considered by CDEC (which is aligned with the clinical trial population), the incremental cost-utility ratio (ICUR) for cerliponase alfa compared with best supportive care (BSC) was approximately $2 million per quality-adjusted life-year (QALY). A price reduction of more than 99% is required for cerliponase alfa to achieve an ICUR of $100,000 per QALY based on the CADTH best estimate.

Implementation Considerations

- Based on the CLN2 Clinical Rating Scale employed in studies 201 and 202, a score of zero on the motor and language domains is defined as “can no longer independently walk or crawl” and “no intelligible words or vocalizations,” respectively.

Discussion Points

- The principal unmet need in patients with CLN2 disease is the paucity of disease-modifying treatments.
- The magnitude of the treatment effect of cerliponase alfa on the decline in the motor–language score was considered to be uncertain due to inherent methodologic limitations, primarily related to non-blinded assessment and comparison with historical control groups. It is unclear how the historical control groups compared with treated patients with respect to the methods used for diagnosis and key patient characteristics such as genotype, age of onset, time since symptom onset, disease severity, TPP1 activity, and co-interventions used. BSC is expected to change over time and thus differ between the study patients and the historical controls. Between-group differences in patient characteristics, co-interventions, and BSC confound results, rendering the treatment effect of cerliponase uncertain. However, the committee discussed that the reported effect size for the between-group comparison of the rate of decline in the motor–language score was sufficiently large to suggest some clinical benefit of cerliponase alfa on the rate of decline in motor–language function.
- Given the rarity of CLN2 disease, the relationship of genotype to phenotype, including age of onset, severity of disease, and rate of deterioration, has not been fully elucidated. Thus, it is unclear if all the patients in studies 201 and 202 and the historical control groups had the same likelihood for responding to cerliponase alfa.
- The committee considered the CLN2 Clinical Rating Scale employed in the trials to have uncertain clinical meaningfulness to patients and/or caregivers in terms of either independent or assisted activities of daily living and health-related quality of life (HRQoL). Further, the committee noted that the clinical meaning of a one- or two-point change using this ordinal scale may differ across the range of the scale, further complicating interpretation.
- There is no evidence that cerliponase alfa has a beneficial effect on many of the symptoms important to patients or clinical consequences of CLN2 disease, including pain, myoclonus, movement disorders, seizures, impaired cognition, ability to perform basic activities of daily living, and visual impairment.
- Despite reported correlations between the CLN2 motor–language score and the Pediatric Quality of Life Inventory (PedsQL) and other quality of life measures, the impact of cerliponase alfa on HRQoL for patients in the studies is uncertain given the mixed results for the different HRQoL instruments used, the considerable inter-patient variability in response, and the lack of HRQoL data for a comparison group.
- The committee discussed that although cerliponase alfa is the first Health Canada–approved treatment to directly target the underlying pathobiology of CLN2 disease, BSC should encompass both pharmacological and non-pharmacological management of symptoms and the condition by a multidisciplinary team. The committee noted that treatment with cerliponase alfa would not eliminate the need for such care.
- There are serious risks associated with intracerebroventricular (ICV) administration of cerliponase alfa through a surgically implanted reservoir and catheter (e.g., infections of the central nervous system, seizures, and cerebral hemorrhage) and adverse events (AEs) associated with treatment (e.g., hypersensitivity reactions) that could limit the potential benefits of therapy. The committee concluded that any potential therapeutic benefit of cerliponase alfa in patients who have reached an aggregate motor–language score of zero is likely to be outweighed by the potential harms inherent in the administration of the drug.
- The committee noted that the implantation of the reservoir, the biweekly infusions, and the management of any related complications would be done in tertiary care facilities, which may present a barrier to access to treatment, particularly for those not located in close proximity to such a facility.
- The committee discussed that conducting a randomized controlled trial would be challenging in this very rare condition. However, the committee noted that a randomized controlled trial that reported relevant symptom and functional outcomes would provide more convincing evidence of a clinically meaningful benefit of cerliponase alfa.

Background

Cerliponase alfa has a Health Canada indication for the treatment of CLN2 disease, also known as TPP1 deficiency. Cerliponase alfa is a recombinant human tripeptidyl peptidase 1. It is available as a 30 mg/mL solution for ICV infusion. The Health Canada–recommended dosage in patients two years of age and older is 300 mg (10 mL solution) administered once every other week by ICV infusion.

CLN2 disease is an autosomal recessive neurodegenerative lysosomal storage disorder caused by deficient activity of TPP1. Deficiency in TPP1 activity results in the accumulation of lysosomal storage materials in the central nervous system, which leads to a progressive decline in motor function. CLN2 is a pediatric-onset disease that is characterized by motor deterioration, language delay, seizures, ataxia, dementia, blindness, and early death.

Summary of Evidence Considered by the CADTH Canadian Drug Expert Committee

The committee considered the following information prepared by CADTH: a systematic review of randomized and non-randomized trials of cerliponase alfa and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with CLN2 disease, and input from one parent of a child with CLN2 disease.

Summary of Patient Input

No patient-group input was received. The following is a summary of input from the perspective of one parent of a child with CLN2 disease.

- The parent described a healthy, bright, and active child, who at the age of eight began to have difficulties with walking, running, and falling, in addition to impairment in cognitive ability. Over a two-year period, symptoms worsened to requiring the use of a walker and wheelchair at school, and "significant intellectual disability."
- The parent indicated that once started on treatment (approximately two years after the first symptoms had manifested at age eight) his rapid decline ceased and plateaued. The child first began treatment with cerliponase alfa by travelling to a centre in the US and the family needed to sell their house to make this possible. The child now receives treatment with cerliponase alfa through a hospital in Canada. Currently, at 12 years of age, the child uses a walker with additional assistance, has difficulty speaking, and struggles with intellectual disability. The parent indicated that she understood that cerliponase alfa would not repair the damage the disease had caused. She further described the experience of some other families with children with CLN2, describing the "heart wrenching decisions" made not to begin treatment for their children because the disease had done too much damage, with children being fed via g-tube, suctioned daily, and unable to see, speak, or move.
- The child's mother quit her full-time job to become a caregiver, noting that her child absolutely requires a caregiver with him to help with transfers, bathing, food preparation, and safety measures. Arrangements for transportation to and from school were needed as was an individualized educational plan and attendance in school in a special needs class.
- The cerliponase alfa infusion process takes approximately 4.5 hours and is preceded and followed by clinical assessments; the hospital visit takes a full day. The parent reported that the medication is very well tolerated, other than fatigue caused by the diphenhydramine and ondansetron. Overall, she described this treatment as being effective, stating that she has witnessed the halting of the decline of her child's condition since treatment began.

Clinical Trials

The systematic review included three open-label, non-randomized trials without control groups in patients with CLN2 disease (studies 201, 202, and 203).

Study 201 and its extension, Study 202, were phase I/II, multi-centre, open-label, single-arm studies of cerliponase alfa in 24 patients with a confirmed diagnosis of CLN2 disease by TPP1 enzyme activity and CLN2 genotype analysis with a motor–language score of 3 to 6 on the CLN2 Clinical Rating Scale. However, there were few patients in Study 201 with a high motor–language score at screening; 8% of patients had a motor–language score of 6 and 8% of patients had a motor–language score of 5. The majority of patients had motor–language scores in the middle range at screening, 29% with a score of 4 and 54% with a score of 3; no patients had a score of less than 3 at screening. The age range at study entry was between three and eight years old. Doses were escalated

during Study 201 until a stable dose of 300 mg of cerliponase alfa via ICV infusion every two weeks was reached. CLN2 Clinical Rating Scale assessments occurred every four weeks during the dose escalation period and then every eight weeks during the stable dose period. Study 202 (N = 23) is ongoing; the most recently available efficacy data are from November 2016. Post-hoc comparisons were made between the treated patients in studies 201 and 202 and historical controls. Study 203 administered a stable dose of 300 mg cerliponase alfa every two weeks to siblings of the children enrolled in studies 201 and 202 who were also diagnosed with CLN2 disease. This trial is currently ongoing with [redacted] enrolled; however, only a report (which was based on [redacted]) with a data cut-off of November 2016 was available. Thus, the committee's discussion was focused primarily on studies 201 and 202.

There was no concurrent control group in studies 201, 202, or 203. Rather, the manufacturer conducted statistical comparisons of the results from studies 201 and 202 with those from a natural history cohort (Study 901). There are several reports that described historical patients and compared these historical controls with treated patients from studies 201 and 202.

Key limitations of the trials included the small sample sizes, lack of concurrent control groups, uncertain validity, and inconsistencies in the scales used to compare treated patients with historical controls.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following:

- survival; however, survival data were not provided for the historical control groups
- functional outcomes with respect to motor, language, vision, and seizure frequency, as measured by the CLN2 Clinical Rating Scale, which scores each of the four components from 0 to 3, with higher scores indicating better function. The change in the combined motor–language score (range of 0 to 6) was the primary outcome. The CLN2 Clinical Rating Scale used in studies 201 and 202 was an adaptation of the Hamburg and Weill Cornell scales for late infantile neuronal ceroid lipofuscinosis. Definitions for the motor and language scores used in studies 201 and 202 are described in Table 1.
- components of vision (0 to 3 points) and seizure (0 to 3 points) were also assessed individually and as a composite score of motor–language–vision–seizure (0 to 12 points)
- HRQoL, assessed using the PedsQL (including both a Parent Report for Toddlers and a Family Impact Module), both of which have scores ranging from 0 to 100, with higher scores indicating better function. In addition, the EuroQol 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L) instrument was assessed in Study 202. It consists of an EQ-5D descriptive system and the EQ visual analogue scale (VAS). The descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five levels. The EQ VAS records the respondent's self-rated health on a vertical VAS where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). Finally, HRQoL was also assessed with a CLN2 disease-based HRQoL instrument, the CLN2 Quality of Life Questionnaire, which includes 28 items related to seizures, feeding, sleep, behaviour, and daily activities
- brain MRI changes (whole brain volume, cortical grey matter volume, white matter volume, cerebrospinal fluid volume).

Table 1: Scoring Definitions for the Motor and Language Components of the Ceroid Lipofuscinosis Type 2 Clinical Rating Scale Used in Studies 201 and 202

	Motor Score	Language Score
3	Grossly normal gait. No prominent ataxia, instability, shortened stride, or pathologic falls.	Apparently normal language. Intelligible and grossly age-appropriate.
2	Independent gait, as defined by ability to walk without support for 10 autonomous steps. May have obvious instability, and may have intermittent falls.	Language has become recognizably abnormal: some intelligible words, but does not form sentences to convey concepts, requests, or needs.
1	Requires external assistance to walk, and without support can only take fewer than 10 steps or crawl.	Hardly understandable. Few intelligible words in the context of unintelligible vocalizations.
0	Can no longer independently walk or crawl.	No intelligible words or vocalizations.

The review protocol pre-specified a number of additional outcomes of interest, such as improvement of swallowing function to allow removal of feeding tube, return of ability to walk, and reduction of seizure incidence to null; however, the trials were not designed to specifically evaluate these outcomes.

The primary efficacy outcome of studies 201 and 202 was the CLN2 Clinical Rating Scale motor–language score, and response was defined as the absence of an unreversed two-point decline or score of 0 in the motor–language score by week 96 in Study 202. In Study 203, the manufacturer stated that the "efficacy endpoint of primary interest" is the motor–language scale, but the study follow-up was not long enough to assess this outcome.

Efficacy

- In studies 201 and 202, 20 out of 23 (87%) patients taking cerliponase alfa had an absence of an unreversed two-point decline or score of 0 in the motor–language score at 96 weeks (response). Patients had a mean decline (worsening) of 0.7 (SD: 0.8) points in the motor–language score after more than 97 weeks of treatment with the 300 mg dose, relative to baseline, while the motor–language–vision score (range: 0 to 9) decreased by a mean of 1.0 point (SD: 1.2) and the total CLN2 scale score (motor, language, vision, seizure; range: 0 to 12) decreased by a mean of 0.2 points (SD: 2.4). The mean rate of decline of motor–language score per 48-week period was 0.27 (SD: 0.35) for the intention-to-treat population (N = 23) and was 0.42 for the safety population (N = 24). In studies 201 and 202, 13 patients (56%) showed worsening of the motor–language score, nine patients (39%) showed no change, and one patient improved by one point, relative to baseline.
- Very few efficacy data were available from Study 203 because of the small sample size and the short duration of drug exposure at the time the interim report was written.
- HRQoL scores decreased (worsened) from baseline to week 97 in studies 201 and 202, as measured by the means of the PedsQL Parent Report for Toddlers (–5.7; SD: 18.9) and EQ-5D-5L EQ VAS (–9.9; SD: 24.0), and increased (improved) based on the CLN2 Disease-Based Quality of Life Instrument (+3.1; SD: 14.4). Scores for the PedsQL Family Impact Module increased slightly (measures impact on caregivers and family; –1.1; SD: 19.6). The variability in response for these HRQoL life scores, as can be seen by SDs larger than mean changes, lends uncertainty to any interpretation of these data.
- There were decreases in whole brain volume (–4.3%), cortical grey matter (–12.4%), and white matter (–2.7%) over the course of studies 201 and 202. There was a corresponding increase of 6.4% in cerebrospinal fluid volume. The clinical significance of these changes is unclear.
- Post-hoc comparisons were made between the treated population from studies 201 and 202 and the historical control populations. There were several historical control cohorts referenced in the study reports and publications with sample sizes of 42 (unmatched comparison), 17, and 21 (matched comparisons). The unadjusted mean rate of decline in the motor–language score per 48-week period was 0.27 ± 0.35 points among the 23 treated patients as compared with 2.12 ± 0.98 among the 42 unmatched historical controls, a difference of 1.85 ± 0.21 points (95% CI, 1.51 to 2.18; $P < 0.001$). The hazard ratio comparing the treated population in studies 201 and 202 with the unmatched historical control (N = 42) was 0.08 (95% CI, 0.02 to 0.23), favouring treated patients for the time to unreversed ≥ 2-point decline in the motor–language score. The hazard ratio comparing the treated population in studies 201 and 202 with the matched historical control (N = 21) for the same outcome was 0.05 (95% CI, 0.01 to 0.18), favouring treated patients.
- Compared with the historical control data, patients receiving cerliponase alfa appear to experience a two-point or greater decline in the CLN2 motor–language scale score at a slower rate. However, comparison to a historical control group cannot produce results that are as reliable as those within a randomized study. The investigators attempted to overcome this limitation by matching the treated patients to historical control patients using several known prognostic factors (e.g., age, genotype, baseline motor–language score). These methods would be expected to create populations that are more similar than unmatched populations, but the amount of residual confounding and the degree to which the treated and untreated patients differ remains unknown. After matching, there may be other known and unknown prognostic factors that remain unbalanced. A comprehensive understanding of genomic variants that increase (or decrease) disease severity present in both the treated population and the historical control group were not reported. Further, methods used in diagnosis may have differed between treated patients and historical controls. Additional limitations of using historical controls include the difficulty in assessing motor, language, seizure, or vision symptoms retrospectively from patient records and the lack of information regarding HRQoL for the historical controls.
- Another significant limitation is that while the scales used to assess symptom severity (motor, language, seizure, vision) applied the same numerical gradations in the treated patients and the historical control groups, the definitions corresponding to the severity levels (0, 1, 2, 3) were not the same. This creates uncertainty in the interpretation of comparative analyses of the motor–language scores in treated patients versus historical controls.

- Studies 201 and 202 are currently ongoing and no efficacy data are available beyond a follow-up period of approximately three years (the most recent report was provided from November 2016). Thus, it is unclear if the suggested benefits of treatment with cerliponase alfa versus no treatment, in terms of language and motor deterioration, would be maintained beyond this time period. In addition, the comparative efficacy of cerliponase alfa versus no treatment, in terms of mortality and HRQoL over the available study period, was not reported.

Harms (Safety)

- There were no reported deaths in patients treated with cerliponase alfa in studies 201 and 202 or Study 203.
- AEs thought to be related to cerliponase alfa and/or its administration were evident in the clinical trials and included hypersensitivity, pyrexia, pleocytosis, device malfunction, and device-related infection. In studies 201 and 202, hypersensitivity events were reported 37 times in 15 patients (63%). In studies 201 and 202, device-related AEs were reported 34 times in 12 patients (50%). Two ICV access devices were removed from two patients in Study 202 due to infection after more than four years of device use.
- An updated safety report with data as of April 2018 indicated that there have been [redacted].
- The assessment of harms was limited because there were no comparative AE data for the historical control group. CLN2 disease itself is associated with many symptoms and events that would be classified as AEs or SAEs, making it difficult to assess the relationship with cerliponase alfa for some AEs in the studies (e.g., seizures). The risks related to implantation, maintenance, and eventual removal of the ICV system are a significant consideration when deciding whether to initiate therapy with cerliponase alfa.

Cost and Cost-Effectiveness

Cerliponase alfa (Brineura) is available in 150 mg/5 mL vials at a price of $32,380.33 for a package of two vials ($16,190.17 per vial). At the recommended dosage of 300 mg administered every other week by ICV infusion, the annual cost per patient is $844,202. Additional treatment costs related to the insertion of the ICV delivery tube and administration of each infusion in hospital were reported to be incurred by the health care system.

The manufacturer submitted a cost-utility analysis comparing 300 mg cerliponase alfa infusion once every other week with BSC and symptomatic treatment in patients with a confirmed diagnosis of CLN2 disease from the Canadian public health care payer perspective over a lifetime time horizon. The submitted Markov model included 10 health states. The first seven health states were based on combined scores from the motor and language domains of the manufacturer-derived CLN2 Clinical Rating Scale (maximum score of 6, low score of 0; higher Clinical Rating Scale scores equate to greater health). Once an individual progressed to a combined score of 0 (the lowest motor–language score possible), they could subsequently move to a health state that incorporated loss of vision (health state 8), and a subsequent state that also incorporated palliative care (health state 9). The final health state was death. Patients entered the model at an average age of 4.8 years (based on a matched cohort of patients from Study 201 and natural history data), and were evenly distributed among the three least severe health states based on clinical expert opinion. Patients could subsequently progress or improve based on transition probabilities derived from natural history (proxy for BSC) and efficacy data (cerliponase alfa) from patients who were matched one-to-one. Treatment was discontinued once patients reached a combined motor and language score of 0. Patients could only die of disease-related mortality once in the lowest health state (score of 0, vision loss, requiring palliative care); otherwise, age-related mortality was applied. The health state utilities were derived from a study conducted by the manufacturer, while disutilities for AEs were identified from the literature. In the manufacturer's base case, cerliponase alfa was associated with an incremental cost of $18,446,778 while accruing an incremental 10.19 QALYs, which incorporated a predicted 17.6 incremental life-years. The resulting incremental cost per QALY was $1,811,059 for cerliponase alfa versus BSC.

CADTH identified the following key limitations with the manufacturer's submitted economic analysis:

- There was no direct evidence comparing cerliponase alfa with BSC, and the manufacturer's matched comparison assessing the comparative clinical effectiveness of cerliponase alfa and BSC is highly uncertain due to concerns with the similarity in the patient populations between the historical cohort and treated patients, the matching process, and the lack of long-term data.
- The manufacturer's model does not appropriately consider the clinical pathway of disease. Clinical experts indicated that the model structure does not appropriately consider important milestones such as developmental issues, seizure rates, vision loss, and palliative care. There are also limitations with the use of a combined motor and language scale score from the CLN2 Clinical Rating Scale.
- Based on the assumptions considered by the manufacturer, the model predicted a large survival benefit (nearly 18 years), which is not supported by clinical evidence at this time.
- CADTH considered the utility values presented by the manufacturer to be associated with substantial uncertainty.

CADTH undertook reanalyses considering revised transition probabilities, equal seizure rates for cerliponase alfa and BSC, alternate utility values, and removal of caregiver disutilities and productivity losses. This resulted in a best estimate ICUR of $1,718,976 per QALY for cerliponase alfa compared with BSC, which is similar to the ICUR estimated by the manufacturer. The probability that cerliponase alfa was cost-effective, even if a decision-maker is willing to pay $500,000 per QALY, was 0%. CADTH undertook several relevant scenario analyses based on alternate initial patient distribution and stopping rules. Testing alternate patient distribution based on clinical trial data resulted in an ICUR of $2,069,907 per QALY for cerliponase alfa compared with BSC. If cerliponase alfa was assumed to be discontinued when patients reached higher combined motor and language scores (1 and 2 were tested), the ICURs decreased to approximately $1.5 million per QALY (from the CADTH best estimate ICUR).

Neither the CADTH or manufacturer-estimated ICURs are considered cost-effective at conventional willingness-to-pay thresholds, and both are highly uncertain given the limitations identified with the model that could not be addressed by CADTH, particularly the lack of direct, comparative clinical effectiveness information, as well as the modelling of disease progression in patients with CLN2. Price reductions of at least 75% and 99% are required to achieve willingness-to-pay thresholds of $500,000 and $100,000 per QALY, respectively, based on the CADTH best estimate analysis.

Request for Clarification

The CDR-participating drug plans filed a request for clarification during the embargo period for the CDEC recommendation of cerliponase alfa. The questions posed by the drug plans and responses from CDEC are summarized below.

Are there any considerations related to age for treatment initiation?

CDEC noted that the Health Canada–approved indication for cerliponase alfa contains no age restriction, although the dosage and administration section of the Health Canada–approved product monograph states that safety and efficacy have not yet been established in children less than three years; children enrolled in Study 201 were three to eight years of age. CDEC discussed that a natural history study of CLN2 disease reported that the median age of diagnosis was 54.0 months (range: 47.5 to 60 months), and the age at first clinical symptom was 35.0 months (range: 24.0 to 38.5 months), consistent with the patient population enrolled in Study 201. The committee discussed that due to the increasing availability and application of genetic testing, diagnosis may occur at younger ages in the future, especially in families already having an affected child. There is little clinical trial data available to support the use of cerliponase alfa in children less than three years of age and/or who have not experienced clinical symptoms. However, the committee discussed that, given the nature of the condition, cerliponase alfa is not expected to reverse accrued clinical deficits and that earlier treatment may be the best chance to preserve motor and language functions. With the potential benefit of early treatment being a major consideration, and the absence of evidence to suggest that there is no benefit in children younger than three years of age diagnosed with this rare condition, the committee did not consider it appropriate to impose an age-based criterion for treatment initiation.

Are there any other clinical domains that should be considered other than motor and language to assess a patient's response to the drug?

The CLN2 Clinical Rating Scale used in studies 201 and 202 contains four domains: motor and language function, vision, and seizures. However, CDEC noted that the combination of motor and language function was the primary outcome and focus of the reviewed trials, with little data reported for the other domains. It is not known if the rate of decline for vision and seizures will be similar to the rate of decline in motor and language function, nor whether the decline is linear given the heterogeneity of clinical phenotype.

Thus, the attributable benefit (or harm) of cerliponase alfa on domains other than motor and language function is unknown. As such, any observed improvement in these domains cannot be attributed solely to cerliponase alfa with sufficient certainty to defend or warrant continuation in the context of the motor–language function decline described in the discontinuation criteria.

CDEC considered that the treating clinician along with a multidisciplinary team should consider the totality of the effect of treatment in relation to these four domains and the patient's clinical status to determine whether the benefit of cerliponase alfa continuation outweighs the harms. Given the lack of data related to the effect of cerliponase alfa in relation to the vision and seizure domains, CDEC is unable to specify renewal or discontinuation criteria that include these domains. However, this does not preclude the clinical team and the patient's substitute decision-maker(s) from considering domains beyond motor and language function when discussing whether and when treatment should be discontinued, as described in the following question.

Is a 24-week time period the preferred period to assess clinical outcomes or should there be some flexibility?

The definition of clinical response within studies 201 and 202 was based on the assumption from natural history that untreated patients would have an average decline of two points in their motor–language score per 48 weeks. However, CDEC considered that it would be advantageous to have more frequent assessments of patients with CLN2 (at least every 24 weeks as stated in the discontinuation criteria) given the disorder's heterogeneity and the need to assess complications with the administration reservoir. CDEC members believe that more frequent assessments might be appropriate for monitoring patients, but that requiring assessments at intervals of less than 24 weeks to determine whether reimbursement should continue would be impractical and unnecessarily burdensome given the slowly progressive nature of the disease.

CDEC further noted that it may be impractical to conduct assessments at intervals of exactly 24 weeks and that a variation of one to two weeks earlier or later is appropriate, such that assessments might be characterized as occurring every six months.

CDEC noted that, despite its recommendation for motor and language function to be assessed every 24 weeks, clinicians would be expected to conduct earlier and/or more frequent assessments if the patient's status warranted such action, and to consider discontinuation of cerliponase earlier than the 24-week assessment time points if:

- the totality of the patient's clinical status suggests that cerliponase alfa harm(s) outweigh any meaningful benefit(s) and/or
- the patient's capacity to respond meaningfully is lost.

CDEC considered that such assessments would be done as warranted, in consult with the patient's substitute decision-maker(s) and the multidisciplinary team managing the patient's total plan of care. The committee did not consider it necessary to state this formally in the discontinuation criteria.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 16, 2019 Meeting

Regrets

None

Conflicts of Interest

None

April 10, 2019 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None

May 15, 2019 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None