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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

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.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

Tables

Figure

CADTH

Abbreviations

AE	adverse event
BSC	best supportive care
CLN2	neuronal ceroid lipofuscinosis type 2
ICUR	incremental cost-utility ratio
ICV	intracerebroventricular
PedsQL	Pediatric Quality of Life Inventory
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Cerliponase alfa (Brineura)
Study Question	What is the cost-effectiveness of cerliponase alfa relative to current symptomatic care (i.e., best supportive care) for patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients of any age with a confirmed diagnosis of CLN2 disease
Treatment	300 mg cerliponase alfa administered every other week by intracerebroventricular (ICV) infusion, adjusted doses for infants up until two years of age
Outcome	Quality-adjusted life-years (QALYs)
Comparator	Best supportive care (BSC)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (95 years)
Results for Base Case	ICUR: $1,811,059 per QALY gained for cerliponase alfa vs. BSC
Key Limitations	• There was no direct evidence comparing cerliponase alfa with BSC, and there is substantial uncertainty regarding the comparative clinical effectiveness of cerliponase alfa and BSC due to the limitations with using data from an historical cohort for BSC compared with treated patients, the limitations with the matching process, and the lack of long-term data available. • The manufacturer's model does not appropriately consider the clinical pathway of disease. Health states were based on a combined motor and language scale score from the CLN2 rating scale; assumptions for other symptoms applied to the base health states, but patient transitions in the first seven stages were based solely on combined motor and language scores. Clinical experts indicated the model structure does not appropriately consider important milestones such as developmental issues, seizure rates, vision loss, and palliative care. • 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. • There were issues identified with the methods used to derive the utility values, which were used by the manufacturer in its base case, which were associated with substantial uncertainty.
CDR Estimates	• CADTH could not address limitations regarding the model structure or comparative effectiveness. • CADTH conducted reanalyses that included removal of the probability of improvement, equal seizure rates for both cerliponase alfa and BSC, application of the utilities identified using the PedsQL tool, and removal of caregiver disutilities and productivity losses. • These revisions resulted in CADTH's best estimate ICUR of $1,718,976 per QALY gained for cerliponase alfa versus BSC, though whether this estimate reflects the true ICUR is uncertain. • The probability that cerliponase alfa was cost-effective assuming that the threshold value for a QALY was $500,000 was 0%. Several scenario analyses were also conducted to assess various alternate assumptions: • Changing the initial distribution of patients to reflect distribution of patients in cerliponase alfa trials instead of assuming future improvement in diagnoses will lead to earlier detection (ICUR, $2,069,907 per QALY gained for cerliponase alfa versus BSC). • If cerliponase alfa is stopped at a score of 1 or 2 on the motor and language scale instead of 0, the ICUR would be lower (score of 1 = $1,488,569; score of 2 = $1,449,359).

BSC = best supportive care; CLN2 = neuronal ceroid lipofuscinosis type 2; ICUR = incremental cost-utility ratio; PedsQL = Pediatric Quality of Life Inventory; QALY = quality-adjusted life-year; vs. = versus.

Drug	Cerliponase alfa (Brineura)
Indication	For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency
Reimbursement Request	As per indication
Dosage Form	150 mg/5 mL solution for administration by intracerebroventricular infusion
NOC Date	December 19, 2018
Manufacturer	BioMarin Pharmaceutical (Canada) Inc.

Executive Summary

Background

Cerliponase alfa (Brineura) is a solution for administration by intracerebroventricular (ICV) infusion that is currently under review by Health Canada with a proposed indication for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl-peptidase-1 deficiency. The manufacturer's reimbursement request was as per the indication.[1]

The recommended dosage for cerliponase alfa is 300 mg (10 mL solution) administered every other week by ICV infusion for people aged two years or older.[2] It 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). The annual cost per patient aged two years or older 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.[3]

The manufacturer submitted a cost-utility analysis comparing cerliponase alfa infusion once every other week with best supportive care (BSC; symptomatic treatment — i.e., accruing health state and symptom treatment costs only) in patients of any age with a confirmed diagnosis of CLN2 disease.[3] The model was conducted from the Canadian public health care payer perspective with a lifetime time horizon of approximately 95 years. The submitted model was in the form of a cohort-level state-transition (Markov) model with ten health states; higher health state numbers represented better health (Figure 1). The first seven health states (health state 1 through health state 7) were based on combined scores from the motor and language domains of the CLN2 Clinical Rating Scale (maximum score of 6, lowest score of 0; higher rating scale scores equate to greater health).[3] Once an individual achieved a combined score of 0 (the lowest motor and language score possible), they could move to a health state that incorporated loss of vision (health state 8), and a subsequent state that incorporated a score of 0, with loss of vision and requiring palliative care (health state 9). The final health state was death. Patients entered the model at an average age [redacted] years (based on data from the matched comparison), and were evenly distributed between health states 1, 2, and 3. 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.[3-5] 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 adverse events were identified from the literature.[3]

In the manufacturer's base case, over the lifetime time horizon, cerliponase alfa was associated with an incremental cost of $18,446,778, while accruing an incremental 10.19 quality-adjusted life-years (QALYs) that incorporated a predicted 17 incremental life-years. The resulting incremental cost per QALY was $1,811,059 for cerliponase alfa versus BSC. In approximately 25% of iterations, the incremental cost-utility ratio (ICUR) was below a willingness to pay of $1.9 million per QALY.[3]

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the manufacturer's economic evaluation.

There is substantial uncertainty regarding the comparative clinical effectiveness of cerliponase alfa with BSC. No direct comparative evidence for cerliponase alfa was available; therefore, the manufacturer undertook a matching exercise in which patients from two cerliponase alfa studies (201 and 202) were matched one-to-one with historical cohort patients. The historical cohort was based on a retrospective chart review. As noted in the CADTH clinical review, although there may have been challenges to implementing a prospective, untreated control group within study 201 and 202, there are several limitations with the use of a historical control: there are challenges with interpreting data from retrospective chart reviews, there were differences in the definitions in the motor and language scale scores between the retrospective review and clinical trials, and patients in the historical control may have been treated decades earlier than the cerliponase alfa trials, over which time clinical practice has changed. Additionally, there were concerns with the matching process, in that there may be imbalances between the groups due to known and unknown prognostic factors. Moreover, based on the information provided by the manufacturer regarding the population used in the model and the information provided to the clinical review team, there is uncertainty as to whether the matched patient cohort assessed in the clinical review (n = 21) aligns with the population the model transition probabilities were based on (n = 23). Furthermore, the manufacturer suggested that patients on both cerliponase alfa and BSC could improve motor and language scores, with greater improvements in patients on cerliponase alfa, which would suggest that there may be clinical improvement (or reversibility) in the condition. Feedback from the clinical experts was that this assumption was associated with a substantial amount of uncertainty. Finally, the long-term effectiveness of cerliponase alfa was extrapolated from 96 weeks of clinical trial data over a lifetime time horizon and assumed maintenance of effect. This assumption is highly uncertain and likely overestimates the benefit of cerliponase alfa compared with BSC. While the data suggest there is a benefit on the CLN2 motor and language scale scores for cerliponase alfa in patients with CLN2, the magnitude of benefit from the matched analysis is likely overestimated, and the impact on overall disease progression is uncertain.

The manufacturer's model structure was considered to be of questionable validity based on feedback received by the clinical experts consulted for this review. The manufacturer provided information to justify the choice of the motor and language scores as the most appropriate measure of disease progression; however, the clinical experts considered that developmental issues, seizure rates, requirement for a feeding tube, vision loss, and palliative care were key markers of disease progression. Although several of these components of the disease were incorporated into the manufacturer's model, the main health states focused on a combined motor and language score from the CLN2 Clinical Rating Scale to denote the major markers of disease progression. Vision loss and palliative

care were assumed to only occur once a patient reached a score of 0 on the combined motor and language scale. These assumptions were not considered appropriate. Feedback from the clinical experts indicated that palliative care could be discussed with the patient's family at any time over the pathway of care; additionally, as noted in the clinical review, there is no evidence that cerliponase alfa had any impact on delaying time to vision loss, which the model implicitly assumes with delayed progression to a combined motor and language scale score of 0. These issues relating to the model structure result in greater uncertainty of the comparative efficacy estimates in the model.

The assumption of delayed progression prior to reaching vision loss and palliative care resulted in a large survival benefit for cerliponase alfa due to the way mortality was applied in the model. This resulted in an estimated 17.6 additional life-years (and 10.2 additional QALYs) for cerliponase alfa. This survival benefit was considered to be overestimated by the clinical experts consulted by CADTH based on the available data. Additionally, the clinical review conducted by CADTH indicated the data provided do not allow for any conclusions to be drawn regarding survival, nor is it known whether maintenance of motor and language functions correlates with improved survival in patients with CLN2 disease. Feedback from the clinical experts suggested that though a survival benefit for cerliponase alfa was theoretically plausible, it had yet to be proven. Feedback from the experts suggested that an incremental life expectancy of five years may be reasonable. This is also more closely aligned with the published estimates of other review groups.

The model submitted by the manufacturer also indicated additional benefit was obtained from cerliponase alfa in the form of fewer seizures and a greater probability of improvement in combined motor and language score. The CADTH clinical review and feedback from the clinical experts consulted by CADTH indicated the benefits of cerliponase alfa on seizure control are uncertain.

The manufacturer's approach to deriving utility values from a vignette study in which eight clinical experts acted as proxies for patients with CLN2 was associated with substantial uncertainty. Although there are concerns with the other approaches taken by the manufacturer in scenario analyses, CADTH considered that there were less methodological issues with the mapping of Pediatric Quality of Life questionnaire data to EuroQol 5-Dimensions, and determined the values were more likely to reflect of the quality of life of patients with CLN2.

Several other limitations were identified, including the assumptions regarding the population in each health state at baseline, inappropriate application of caregiver utilities and productivity losses, the lack of consideration of relevant and impactful adverse events, and uncertain cost and resource use assumptions.

CADTH undertook reanalyses of the manufacturer's model to address some of the previously mentioned limitations. In the revised analysis the probability of improvement was removed and these proportions were shifted to maintaining a health state, the seizure rates for BSC were applied to cerliponase alfa, the utilities identified using the Pediatric Quality of Life tool were applied, and caregiver disutilities and productivity losses were removed. Additional scenario analyses were conducted assessing the impact of a different starting population disease severity distribution based on study 201, stopping treatment with cerliponase alfa in patients with combined motor and language scores of either 2 or 1 (as opposed to 0), and re-incorporating caregiver disutility.

CADTH's best estimate found that cerliponase alfa is more costly and more effective than BSC, with an ICUR of 1,718,976 per QALY. However, as several important considerations

could not be adequately addressed, it is uncertain whether this estimate reflects the true cost-effectiveness of cerliponase alfa. Incorporating earlier stopping rules reduced the ICUR (approximately $1.4 million per QALY), while using the baseline distribution from study 201 (the population on which efficacy data is based) resulted in a higher ICUR (approximately $2.1 million per QALY). CADTH also undertook exploratory analyses to test alternate assumptions given the lack of long-term comparative effectiveness that resulted in an increased ICUR.

Conclusions

CADTH identified several important limitations with the model structure and comparative effectiveness that could not be adequately addressed in CADTH reanalyses.

CADTH's best estimate was that cerliponase alfa was associated with an ICUR of $1,718,976 per QALY compared with BSC, which is similar to the ICUR estimated by the manufacturer; however, given the limitations that could not be addressed, there is substantial uncertainty whether CADTHs estimate reflects the true ICUR for cerliponase alfa compared with BSC.

Neither the CADTH or manufacturer-estimated ICUR are considered cost-effective at a conventional willingness-to-pay threshold, and both are highly uncertain given the limitations identified with the model, particularly the lack of comparative clinical effectiveness information and uncertainty regarding the historical cohort, as well as the modelling of disease progression. The probability that cerliponase alfa was cost-effective assuming that the threshold value for a QALY was $500,000 was 0%. Price reductions of 75% and more than 99% are required to achieve willingness-to-pay thresholds of $500,000 and $100,000 per QALY, respectively. Based on the manufacturer's submitted price, the annual cost of treatment with cerliponase alfa is $844,202 in persons aged two years or older.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE submission

The manufacturer submitted a cost-utility analysis of cerliponase alfa versus best supportive care (BSC) in patients of any age with a confirmed diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2) disease. The analysis was conducted over a lifetime time horizon (approximately 95 years) from the Canadian public health care payer perspective with a cohort-level state-transition model programmed in Microsoft Excel. The model health states were primarily based on the combined motor and language scores on the CLN2 Clinical Rating Scale, with lower scores indicating increased disease severity, as well as other key clinical characteristics.[3] Health states 1 to 7 were defined as a score of 6 to 0, respectively, on the CLN2 scale. Health states 8 and 9 corresponded to a score of 0 on the CLN2 scale with vision loss, and with vision loss and requiring palliative care, respectively. Health state 10 corresponded to death (Figure 1).[3]

The cohort entered the model with an average age of [redacted] years, derived from a matched one-to-one cohort[1] of cerliponase alfa patients from two trials (studies 201 and 202)[4,5] and a historical cohort.[6] Patients entered the model distributed in thirds: 34% with a score of 6, 33% with a score of 5, and 33% with a score of 4. This initial distribution was based on clinical expert opinion of the expected distribution of CLN2 scores at which patients would be expected to begin cerliponase alfa or BSC. Every two week cycle, patients could then experience a one-point change in severity of their disease (improve or worsen), or remain in the same health state. Once patients reached health state 7, time to event (52 weeks) was used to determine when they moved to the subsequent states of vision loss and palliative care. Once patients experienced vision loss, they could only remain in that state or go into palliative care, while patients in palliative care could only remain in that state or transition to the death state.[3]

Transition probabilities for these states were obtained from the pivotal cerliponase alfa study for the treatment group,[4,5] and the one-to-one matched cohort study for the BSC group.[6] In its submitted report, the manufacturer indicated patients on cerliponase alfa would stabilize and no longer experience any decline in health state within the base case after a certain period, but when the model was reviewed, the results used to obtain the base case indicated this setting was not activated within the model. Death from the disease was only assumed to occur to patients in the palliative care health state and the length of time spent in the palliative care health state was based on an assumption. Age-related mortality based on life tables from Statistics Canada were applied to all health states as well. Adverse event (AE) risks from cerliponase alfa were also obtained from the pivotal studies.[4,5]

The manufacturer undertook an unpublished utility study to obtain treatment-specific utility values for both cerliponase alfa and BSC for all nine non-death health states (submitted to CADTH as an accompanying report).[7] Through this study, the manufacturer created 18 vignettes for each possible health state and sent them to eight expert clinicians and asked them to complete the EuroQol 5-Dimension 5-Levels questionnaire as a proxy for patients experiencing the description in the vignettes. The values elicited from the questionnaire were mapped to the EuroQol 5-Dimension 3-Levels values. The manufacturer also included caregiver disutilities in the reference case obtained from a mix of clinical expert opinion, literature, and interpolation. AE disutilities were obtained from a variety of sources in the literature.[3]

Resource use for each health state was obtained from a mix of clinical expert opinion and a global Delphi panel,[8] while the costs were obtained from the Ontario Ministry of Health Schedule of Benefits[9] and a website for non-covered benefits.[10] Costs were also applied for seizures and other progressive symptoms, with the resulting medication costs obtained from the Ontario Drug Benefit e-Formulary,[11] while the number of annual seizures was obtained from a utility study report,[7] and proportion of patients experiencing such progressive symptoms was obtained from a mix of trial data and a Delphi expert panel.[8]

Manufacturer's Base Case

In the manufacturer's base case, over the lifetime time horizon, those receiving BSC accrued total costs of $225,268, while accruing negative quality-adjusted life-years (QALYs; –0.56 over an estimated five life-years). Consequently, those receiving cerliponase alfa accrued total costs of $18,672,046 and total QALYs of 9.62 over an estimated 22 life-years. This resulted in an incremental cost per QALY of $1,811,059 for cerliponase alfa versus BSC (Table 2).

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs	Incremental Cost of Cerliponase Alfa	Total QALYs	Incremental QALYs of Cerliponase Alfa	Incremental Cost per QALY
Best supportive care	$225,268	–	–0.56	–	–
Cerliponase alfa	$18,672,046	$18,446,778	9.62	10.19	$1,811,059

BSC = best supportive care; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic submission.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a number of one-way sensitivity analyses and scenario analyses to determine what the model drivers were and to test alternative assumptions.[3] In the sensitivity analyses, the model was most sensitive to the utility values for certain health states, while the scenario analyses using alternative utility values, population starting points when entering the model, and treatment stopping rules resulted in the greatest change in incremental cost-utility ratio (ICUR) (Table 14). Notably, the ICUR rose to $2,013,762 per QALY when the starting population matched that of the clinical study at baseline; when Pediatric Quality of Life (PedsQL) utility values were used, the ICUR decreased to $1,314,834 per QALY; when patients stopped receiving cerliponase alfa upon reaching a score of 1 instead of 0, the ICUR decreased to $1,619,151 per QALY.[3]

Limitations of Manufacturer's Submission

- **The comparative effectiveness estimates are uncertain:** There is substantial uncertainty regarding the comparative effectiveness of cerliponase alfa with BSC.
  - Clinical data were derived from two clinical trials of cerliponase alfa and a historical cohort of patients with CLN2 (which was used as a proxy for BSC) who were matched one-to-one with [redacted] patients from studies 201 and 202.[1,3] As highlighted in the clinical review, although there may have been challenges to implementing a prospective, untreated control group within studies 201 and 202, there are several limitations with comparing trial data with a historical control. Although the

manufacturer attempted to match patients using known prognostic factors, the amount of residual confounding is unknown, and there may still be imbalances between the groups in known or unknown prognostic factors. Additionally, given that some of the data for patients in the historical cohort was from a much earlier time point than the cerliponase alfa trials, there were likely differences in standard of care, nutritional support, and seizure treatment, all of which could substantially impact disease progression. Furthermore, attempting to ascertain relevant information retrospectively from patient records is challenging; differences in the definitions of the motor and language scores may impact the interpretation of comparative analyses. These limitations lead to uncertainty in the resulting transition probabilities derived from the historical cohort. One of the clinical experts consulted by CADTH for this review also noted concern with regards to the training, expertise, and lack of identification of the clinician conducting the assessment in the historical cohort.

  - The model submitted by the manufacturer also indicated additional benefit was obtained from cerliponase alfa in the form of fewer seizures and a greater probability of improvement in combined motor and language score. The clinical experts consulted by CADTH indicated that there was limited data to support a reduction in all seizures (given the limited scope of the seizures assessed).
  - The manufacturer also reported that patients on cerliponase alfa or BSC could improve motor and language scores, which, given the manufacturer's model structure, suggests there is clinical improvement or reversibility with cerliponase alfa. Feedback from the clinical experts was that an assumption of clinical improvement was associated with a substantial amount of uncertainty given the model structure and limited clinical evidence to support such an assumption. The cost-effectiveness and estimate of survival benefit for cerliponase alfa compared with BSC varies considerably depending on whether this assumption is appropriate.
  - CADTH's best estimate attempted to address the limitations with the clinical assumptions by applying the same seizure rates to cerliponase alfa and BSC, as well as by removing the probability of improvement to a higher combined motor and language score (assuming this probability moved to maintaining the health state).
- **Model structure:** The clinical experts consulted by CADTH considered that developmental issues, seizure rates, requirement for a feeding tube, vision loss, and palliative care were key markers of disease progression. Although several of these components of the disease were incorporated into the manufacturer's model, the main health states focused on a combined motor and language score from the CLN2 Clinical Rating Scale to denote the major markers of disease progression which was the basis for patients transitioning through the model.
  - The manufacturer attempted to justify the use of the motor and language scores as the appropriate measure of disease progression to align with the clinical trial of cerliponase alfa (primary end points were the motor and language domains of the CLN2 Clinical Rating Scale), highlighting the limitations with the availability of data to compare cerliponase alfa with natural history data (historical cohort), and noting potential confounders associated with the impact of treatment on the seizure domain; indicating the incorporation of these components would make the model overly complex.[12] However, although complexity is an important consideration, the model could have incorporated important milestones in the disease progression without becoming too structurally or computationally complex. Further, the manufacturer's responses do not adequately address important milestones in disease progression (such as vision loss) and how they are incorporated within the submitted "memoryless" model.

- The manufacturer assumed vision loss and palliative care could only occur once a patient reached a combined score of 0 on the CLN2 Clinical Rating sub-scales for motor and language. This was used as a simplifying assumption by the manufacturer; however, feedback from the clinical experts consulted by CADTH indicated that although cerliponase alfa may slow progression on the motor and language scales, there is no evidence to suggest cerliponase alfa is able to cross the blood-brain barrier and impact vision loss. Thus, patients may progress to vision loss despite having a combined motor and language scale score higher than 0, which cannot be considered in the model and likely overestimates the effect of cerliponase alfa.
- The health states incorporated based on the motor and language function did not appear to denote the individual score values. For example, one patient may have a score of 3 on the motor scale and 1 on the language scale, whereas another patient might have a score of 1 on the motor scale and 3 on the language scale. While both patients have combined scores of 4 and are treated the same within the model with regards to utility and resource use, these patients would actually be quite different in such regards according to feedback from the clinical experts consulted by CADTH. This issue is of importance with regards to assigning utilities to health states. CADTH noted that the vignettes specify that scores of 5, 3, and 1 on the motor and language scale are based on higher language scores (e.g., for combined score of 5, language equals 3, motor equals 2, and so forth).[7]
- The clinical experts consulted by CADTH also indicated that patients may require palliative care at an earlier time point (higher combined scores), but that this was highly dependent upon discussions between the treating physician and the patient's family.
- Due to the small number of patients in the matched analysis used to inform the manufacturer's model (n = 23), the manufacturer grouped together health states to calculate transition probabilities to increase the sample size and prevent clinically implausible values. While likely necessary given the potential for implausible values, the health states are clinically distinct, and the transition probabilities obtained from these groupings may not be representative of the actual transition probabilities for the grouped states if they had been calculated on their own. As a result, these groupings increase uncertainty within the model. The parameter uncertainty with regards to transition probabilities could also not be considered as there were no probability distributions used for these inputs. Moreover, based on the information provided by the manufacturer regarding the population used in the model and the information provided to the clinical review team, there is uncertainty as to whether the matched patient cohort assessed in the clinical review ([redacted]) aligns with the population the model transition probabilities were based on (n = 23). Neither of these limitations could be addressed within the CADTH reanalyses.

- **Uncertain long-term effectiveness:** The long-term effectiveness of cerliponase alfa remains uncertain as there is no data to inform transition probabilities beyond 96 weeks, which is important given this is expected to be a lifetime treatment. The manufacturer's assumptions result in a large extended benefit beyond the two years of data available that introduces a substantial amount of uncertainty and likely biases the results in favour of cerliponase alfa. This limitation could not be appropriately tested in the CADTH reanalyses. However, CADTH considered an exploratory analysis with a two-year time horizon, and an exploratory analysis that assumed the same efficacy as BSC for cerliponase alfa from 96 weeks onward. These analyses resulted in increased ICURs, though they may underestimate the benefit of cerliponase alfa.

- **Survival benefit from cerliponase alfa is uncertain:** The manufacturer's model predicts there is a survival benefit for cerliponase alfa. There is no evidence from the clinical studies to support a survival benefit for cerliponase alfa based on the clinical review conducted by CADTH. The clinical review conducted by CADTH indicated that the data provided does not allow for any conclusions to be drawn regarding survival, nor is it known whether maintenance of motor and language functions correlates with improved survival in patients with CLN2 disease. Despite this, the manufacturer's model assumed patients on cerliponase alfa did not experience any disease-related mortality unless they progressed to a score of 0 with vision loss and palliative care. Thus, while a patient's disease progression according to their combined motor and language score on the CLN2 Clinical Rating Scale might have slowed due to cerliponase alfa relative to BSC, other disease-related mortality is possibly still applicable given the potential for neurological and extra-neurological progression. According to the clinical experts consulted by CADTH, some survival benefit is likely possible; one expert suggested that five years may be reasonable, though not to the extent of nearly 18 years observed in the manufacturer's (deterministic) base case. This assumption increases uncertainty within the model. This limitation could not be addressed within the CADTH reanalyses, though by incorporating alternative assumptions, CADTH's best estimate reduced the estimated survival benefit to 5.7 years, which is similar to the potential benefit suggested by one of the clinical experts consulted by CADTH.
- **The utility values used to inform the base case were associated with methodological concerns:** Several methodological issues with the derivation of utilities were identified and, as a result, the utilities used in the manufacturer's base case are associated with substantial uncertainty. The manufacturer conducted a study to determine utility values for each health state using different vignettes for BSC and cerliponase alfa created by the manufacturer. These vignettes were then provided to a small sample of clinical experts (n = 8), at least one of whom was involved in the development of the study to derive the utilities. The clinical experts completed the EuroQol 5-Dimension 5-Levels, with these results transformed to the EuroQol 5-Dimension 3-Levels. The use of patient proxies is not ideal and may not accurately reflect the quality of life of the patient, especially in this case, which used clinicians as opposed to family members or caregivers. To address these issues, utility values obtained using the PedsQL mapped to utility values were applied in CADTH reanalyses. While these values are not ideal, they were considered more appropriate.
- **Caregiver impacts incorporated into base case not appropriate for the public payer perspective:** The manufacturer included costs and disutilities that are not applicable within the public payer perspective and are only suitable for the societal perspective. A caregiver disutility was applied within the manufacturer's base case to each health state, and caregiver productivity losses were included in health state costs. Both of these inputs were removed in CADTH reanalyses.
- **Potentially important AEs not incorporated:** The manufacturer's model incorporated several of the most common AEs from the cerliponase alfa trials, but omitted several other AEs that had been identified in the clinical data (or that had not been reported on altogether) that had been identified as important to include by the clinical experts consulted by CADTH. For example, one of the clinical experts consulted by CADTH for this review noted that the manufacturer did not report on shunt malfunctions, which may be costly and have a large clinical impact. The exclusion of relevant AEs (upper respiratory tract infections, nasopharyngitis, rhinitis, and constipation) is likely to underestimate the costs and overestimate the QALYs associated with cerliponase alfa.

CADTH was unable to include any additional AEs within the reanalyses due to limitations with the manufacturer's model.

- **Assumed patient population is incongruent with the patient population on whom treatment efficacy is based:** The manufacturer assumed patients would be evenly split between health states corresponding to scores of 4, 5, and 6 on the CLN2 motor and language scales based on feedback from clinicians regarding future improvements in time to diagnosis leading to earlier treatment. While this distribution was supported by the clinical experts consulted by CADTH, as there were few patients with higher baseline scores on the combined motor and language scale (16% of the 24 patients in the cerliponase alfa trial had a score of 5 or 6), and the manufacturer assumed a substantial proportion of patients would be identified in these earlier states (approximately 67%), the application of the results of a very small subset of the population to the majority of the population on model entry may overestimate or underestimate the benefit of cerliponase alfa due to the small number of patients upon which the model transitions is based. The initial patient distribution is an important driver of patient transitions in the model and the distribution used in the model biases health state costs and QALYs in favour of cerliponase alfa. Given that the clinical experts consulted by CADTH indicated this is likely to be the case in the near future, this starting distribution was used in CADTH's best estimate. To address the uncertainty with this assumption, the distribution of patients at baseline of study 201 was used in a CADTH scenario analysis.
- Costs and resource use: Limitations relating to costs and resource use applied within the model were identified.
  - One of the clinical experts consulted by CADTH noted that the infusion costs incurred every other week were likely to be underestimated by the proxy source used by the manufacturer. The infusions would typically require highly specialized clinicians who are not accounted for within the infusion cost proxy used in the model. CADTH did not conduct reanalyses on this input, as reasonable increases in infusion administration costs do not have a notable impact on results and no suitable information for these costs could be identified.
  - Uncertainty regarding the funding of the intracerebroventricular (ICV) device was noted. The cost of the ICV device is not included in the manufacturer's model, and it indicated that these costs are typically covered by the intuition where the device is implanted. This cost to the health care system should have been considered, which would increase the costs associated with cerliponase alfa, though these additional device costs are unlikely to impact the results given their magnitude relative to the costs of cerliponase alfa.

CADTH Common Drug Review Reanalyses

CADTH conducted reanalyses to obtain a best estimate of the ICUR. A CADTH base case could not be identified due to the substantial uncertainty from a lack of comparative clinical effectiveness information, use of a historical cohort as a control group, and questionable model structure validity. The CADTH best estimate addressed some of the previously identified limitations that could be modified within the manufacturer's model by:

1. removing the probability of improvement, and shifting this probability to maintaining progression to the health state in question
2. applying similar seizure rates in both treatment groups, using the values for BSC
3. removing the caregiver disutility
4. removing caregiver productivity losses from the analysis

5. applying utilities obtained using the PedsQL tool mapped to utility values.

Results of the reanalyses are presented in Table 3. The single parameter changes relating to removing restorative transition probabilities, applying similar seizure rates in both the BSC and cerliponase alfa groups, and removing the caregiver disutility increased the ICUR relative to the manufacturer's base-case results, though to varying degrees. The change that most heavily impacted the model results was the removal of transition probabilities for improvement of disease severity (ICUR: $2,415,954 per QALY), which reduced the total QALYs for both interventions and the incremental QALYs. Using an alternate source of utility values (derived from PedsQL) increased the incremental QALYs in favour of cerliponase alfa, which resulted in an ICUR of $1,316,605 per QALY.

CADTHs best estimate combined each of the one-way analyses and resulted in a reduction in total costs ($7,687,465) and QALYs (6.25) for cerliponase alfa, and a reduction in total costs ($223,835) and an increase in total QALYs (1.90) for BSC, resulting in an ICUR of $1,718,976 per QALY. In this scenario, the model predicted that treatment with cerliponase alfa resulted in an additional 5.7 life-years over BSC (estimated based on the results from the deterministic analysis).

Table 3: CADTH Reanalyses

	Scenario	Treatment	QALYs	Cost	ICUR (per QALY)
	Base case, submitted by manufacturer	BSC	–0.56	$225,268	NA
		Cerliponase alfa	9.62	$18,672,046	$1,811,059
1	**Removal of probability of improvement, shifting this probability to maintaining progression to the health state in question**	BSC	–0.59	$223,153	NA
		Cerliponase alfa	2.47	$7,618,463	$2,415,954
2	**Applying similar seizure rates in both treatment groups, using the values for BSC**	BSC	–0.57	$225,278	NA
		Cerliponase alfa	9.68	$18,832,857	$1,817,075
3	**Removal of caregiver disutility**	BSC	–0.08	$225,197	NA
		Cerliponase alfa	9.90	$18,674,820	$1,848,013
4	**Removal of caregiver productivity losses**	BSC	–0.57	$224,588	NA
		Cerliponase alfa	9.67	$18,672,957	$1,803,000
5	**Application of utilities derived using PedsQL**	BSC	1.46	$225,075	NA
		Cerliponase alfa	15.47	$18,672,813	$1,316,605
6	**CADTH best estimate**	BSC	1.90	$223,835	NA
		Cerliponase alfa	6.25	$7,687,465	$1,718,976

BSC = best supportive care; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

Several scenario analyses were undertaken to consider alternate scenarios from those in the CADTH best estimate (Table 4):

a. initial distribution based on study 201 patient scores at baseline

b. different stopping rules:

   i. treatment with cerliponase alfa is stopped at a combined motor and language score of 1 instead of 0

   ii. treatment with cerliponase alfa is stopped at a combined motor and language score of 2 instead of 0

c. caregiver disutility applied.

Table 4: Results of CADTH Scenario Analyses

	Scenario	Treatment	QALYs	Cost	ICUR (Cost per QALY)
a	**Initial distribution based on study 201 patient scores at baseline**	BSC	1.44	$210,257	NA
		Cerliponase alfa	3.64	$4,749,979	$2,069,907
b-i	**Cerliponase alfa stopped at a score of 1 instead of 0**	BSC	1.94	$223,143	NA
		Cerliponase alfa	6.31	$6,723,219	$1,488,569
b-ii	**Cerliponase alfa stopped at a score of 2 instead of 0**	BSC	1.90	$223,831	NA
		Cerliponase alfa	5.19	$4,984,688	$1,449,359
c	**Caregiver disutility applied**	BSC	1.42	$223,372	NA
		Cerliponase alfa	5.58	$7,687,417	$1,795,128

BSC = best supportive care; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

CADTH undertook two exploratory analyses in an attempt to address uncertainty in the clinical effectiveness of cerliponase alfa; the results are reported in Appendix 5.

CADTH undertook a price-reduction analysis based on the manufacturer-submitted and CADTH base-case analyses, assuming proportional price reductions for cerliponase alfa (Table 5). In both analyses, a price reduction of approximately 94% and 99% was required for cerliponase alfa to achieve an ICUR of $200,000 per QALY and $100,000 per QALY, respectively, compared with BSC.

Table 5: CADTH Reanalysis Price-Reduction Scenarios

ICURs of Cerliponase Alfa Versus BSC (Cost/QALY, $)		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CADTH**
Submitted	1,811,059	1,718,976
20% reduction	1,465,500	1,398,283
40% reduction	1,117,830	1,064,665
60% reduction	778,745	740,484
80% reduction	430,624	414,685
90% reduction	258,442	251,771
95% reduction	172,967	171,643
99% reduction	104,114	105,797

BSC = best supportive care; ICURs = incremental cost-utility ratios; PedsQL = Pediatric Quality of Life Inventory; QALY = quality-adjusted life-year.

Clinical expert feedback on the CADTH reanalyses was received, indicating that the revisions undertaken were appropriate; however, the limitations associated with the disease pathway modelled and the uncertain effect of cerliponase alfa on aspects of the disease other than motor and language scores were considered to impact the confidence that could be placed in any reanalyses undertaken.

Patient Input

CADTH is unaware of a Canadian patient group for CLN2 that could provide patient input. However, given the rarity of the condition, CADTH accepted a description of the experiences of a Canadian family with a child with Batten Disease (CLN2) whose physician provided the family with CADTH's contact information for the purpose of providing input to this review.

The family had experience with cerliponase alfa and noted it was the only medication available for children with CLN2. The family indicated that the patient experienced seizures, difficulty walking and coordinating movements, speech difficulties, and decline of intellectual ability. The majority of these aspects were incorporated into the manufacturer's economic model by considering aspects of CLN2 in the model health state utility values; however, transitions between the health states focused only on a combined motor and language score scale. Impacts on the family and caregivers were raised as an aspect of the condition, as well, and were considered in the manufacturer's economic submission.

Issues for Consideration

- As described within the Limitations section, the costs of the ICV devices are typically covered by the institution where the device is implanted. Should cerliponase alfa be publicly funded, it is possible institutions will no longer cover the costs and these costs will shift to the public health system or consumers. This would increase the costs associated with cerliponase alfa, though the clinical experts consulted by CADTH noted that the device cost is quite minimal relative to the costs of cerliponase alfa.
- The estimated population size of patients with CLN2 eligible for treatment with cerliponase alfa is between [redacted] and [redacted] patients. Epidemiological data suggests that the distribution of patients may not be uniform across Canada. Data suggest that the incidence of CLN2 may be as high as nine cases per 100,000 live births in Newfoundland and Labrador.[13,14]
- Implementation of cerliponase alfa may be limited to areas where there are sites with those with the expertise to implant ICV devices and administer infusions. This may require patients to travel long distances regularly to obtain their infusions and may pose challenges to remote patients.

Conclusions

CADTH identified several important limitations with the model structure and comparative effectiveness that could not be adequately addressed in its reanalyses.

CADTH's best estimate was that cerliponase alfa was associated with an ICUR of $1,718,976 per QALY compared with BSC, which is similar to the ICUR estimated by the manufacturer; however, given the limitations that could not be addressed, there is substantial uncertainty whether CADTH's estimate reflects the true ICUR for cerliponase alfa compared with BSC.

Neither the CADTH- or manufacturer-estimated ICUR is considered cost-effective at a conventional willingness-to-pay threshold, and both are highly uncertain given the limitations identified with the model, particularly the lack of comparative clinical effectiveness information and uncertainty regarding the historical cohort, as well as the modelling of disease progression. The probability that cerliponase alfa was cost-effective assuming that the threshold value for a QALY was $500,000 was 0%. Price reductions of 75% and more than 99% are required to achieve willingness-to-pay thresholds of $500,000 and $100,000 per QALY, respectively.

Based on the manufacturer's submitted price, the annual cost of treatment with cerliponase alfa is $844,202 in persons aged two years or older.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Costs are the manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: CADTH Common Drug Review Cost Comparison Table for Cerliponase Alfa in Neuronal Ceroid Lipofuscinosis Type 2

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Cerliponase alfa (Brineura)	150 mg in 5 mL (30mg/mL)	Solution for infusion (vial)	16,190.1700 [a]	300 mg once every other week	2,312.88	844,202

[a] Manufacturer's submitted price.

Source: Product monograph for cerliponase alfa.[2]

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Cerliponase Alfa Relative to Best Supportive Care Using the CADTH Base Case?

Cerliponase Alfa vs. BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$1,718,976 per QALY					

BSC = best supportive care; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The methods described in the report for the base-case analysis were not those used to obtain the base-case analysis results. For example, no treatment stabilization was applied despite being a part of the base case according to the pharmacoeconomic report submitted by the manufacturer, among other differences between the submitted model and report. Additionally, CADTH requested an updated model from the manufacturer incorporating standard statistical methods to derive parameter input probability distributions. This revised model only worked under the base-case settings due to the revised coding for parameter distributions.[15] As a result, the previous version of the submitted model was used.		
Was the material included (content) sufficient?			X
Comments	CADTH submitted multiple requests for additional information in order to appraise the manufacturer's submission.		
Was the submission well organized and was information easy to locate?		X	
Comments	Some references could not be identified and were coded with an error.		

Table 9: Authors information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of global model/Canadian model done by the manufacturer

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

The cost-effectiveness of cerliponase alfa has been assessed by the National Institute for Health and Care Excellence (NICE) in the UK,[16] Australia's Pharmaceutical Benefits Advisory Committee (PBAC),[17] and France's Haute Autorité Santé (HAS);[18] it is currently being reviewed by Ireland's National Centre for Pharmacoeconomics (NCPE).[19] Summaries from NICE and PBAC are provided in Table 10.

From the available guidance documents, NICE did not recommend cerliponase alfa for treating ceroid lipofuscinosis type 2; however, the manufacturer requested that NICE consider additional information at an upcoming meeting. No economic information was identified relating to the HAS submission, but HAS considered that cerliponase alfa provides an improvement in moderate medical service (ASMR III) in the management of ceroid lipofuscinosis type 2. Starting criteria were identified within the conclusions.[18]

Table 10: Other Health Technology Assessment Findings

	NICE (February 2018)[16]	PBAC (July 2018)[17]
Treatment	Cerliponase alfa administered via ICV infusion to the cerebrospinal fluid every two weeks.	
Price	£20,107.00 for a pack of cerliponase alfa (consisting of two 150 mg vials).	Not reported.
Similarities with CDR submission	Model health states, comparator, 95-year (lifetime) time horizon, discount rate of 1.5%, and transition probabilities appear to have been derived from same data sources and calculated via combined groups of scores, same source of utility values was used.	95-year time horizon, two week cycles, and transition probabilities appear to have been derived from same data sources, and calculated via combined groups of scores; similar application of disease-related mortality and age-related mortality; stabilization assumptions not incorporated.
Differences from CDR submission	Distribution of starting population at model entry, stabilization assumptions were applied in the base case.	Model structure based on eight health states (the vision and palliative care states were excluded). PBAC reported significant differences in model results from the NICE submission. PBAC uses a 5% discount rate. PedsQL utility values were used for the base case.
Manufacturer's results	Redacted	
Issues noted by the review group	Deviation from NICE discount rate of 3.5% not appropriately justified; discrepancy in calculation of transition probabilities; assumption of long-term stabilization highly uncertain given limited evidence; mortality assumptions are inappropriate; modelled population does not reflect current diagnostic practice and assumes improvement in diagnosis; omission of progressive vision loss by cerliponase alfa patients; utility values inappropriate; SAEs excluded in the base case; relevant costs excluded.	Discrepancy in calculation of transition probabilities; combination of treatment groups; extrapolation of patient benefit with cerliponase alfa inappropriate; substantial uncertainty regarding mortality assumptions; model didn't consider vision loss; patients moved too quickly through memoryless model; extra-neurological progression symptoms not considered.

Results of reanalyses by the review group	The manufacturer reported that cerliponase alfa patients incurred approximately 30 more QALYs compared with BSC. In the committee's preferred analysis, the incremental QALYs were reduced to 3.32. ICURs were redacted.	PBAC assessed costs per QALY and cost per LYG. ICURs were redacted, but reported to be between $105,000/QALY and $200,000/QALY and more than $200,000/QALY depending on assumptions used.
	NICE (February 2018)[16]	**PBAC (July 2018)[17]**
Recommendation	Cerliponase alfa was not recommended for treating CLN2 in part due to the extremely high ICUR.	Cerliponase alfa was not recommended for treating CLN2 in part due to the extremely high ICUR.

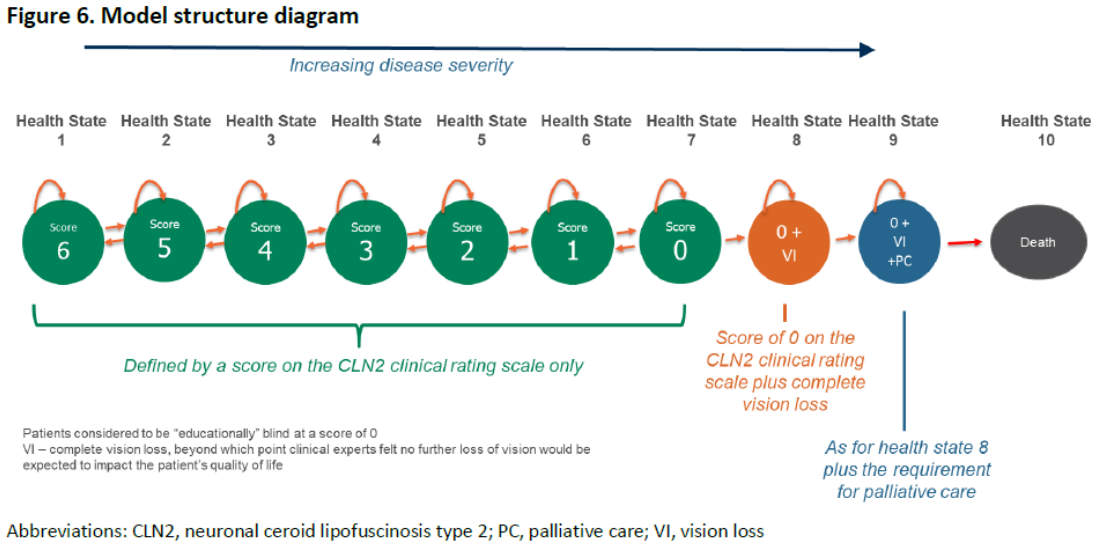
BSC = best supportive care; CDR = CADTH Common Drug Review; CLN2 = ceroid lipofuscinosis type 2; ICUR = incremental cost-utility ratio; ICV = intracerebroventricular; LYG = life-years gained; NICE = National Institute for Health and Clinical Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; PedsQL = Pediatric Quality of Life Inventory; QALY = quality-adjusted life-year; SAEs = serious adverse events.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The diagram of the manufacturer's model structure is provided in Figure 1.

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's pharmacoeconomic submission.[3]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Based on patient characteristics in the cerliponase alfa studies 201 and 202.[4,5]	Distribution of patients upon model entry was based on optimistic assumption of future improvements in diagnostic testing which would allow earlier identification of CLN2. This is not appropriate in the base case as it does not represent current clinical practice.
Natural history	Data on natural history of disease were derived from a historical cohort of patients identified through one-to-ones with the population from the cerliponase alfa trials.[6]	Acceptable.
Efficacy	Transition probabilities for patients receiving cerliponase alfa across health states derived from the disease progression of patients in studies 201 and 202.[4,5] Transition probabilities for the BSC group were derived from the historical cohort. Rates for progressive symptoms of CLN2 not captured by the rating scales, including distress, dystonia, myoclonus, requirement	The clinical trials of cerliponase alfa were non-comparative trials and may be subject to bias. A limited amount of information was provided around the matched comparison used to derive transition probabilities within the model, which limited CADTH's appraisal of this information. The use of separate sources of data for cerliponase alfa and BSC may be biasing results in favour of cerliponase alfa, given some of the data for BSC was from a much earlier time point than the cerliponase alfa trials, with patients experiencing a different standard of care. There

Data Input	Description of Data Source	Comment
	of a feeding tube, and epilepsy, were identified within the literature[13] and through trial and natural history data.[4,5]	are also concerns with the different scales used and assessors of disease progression. In a request for additional information, the clinical review team requested the manufacturer indicate which of the populations identified in the clinical data was the most appropriate for the matched analysis and achieved the best minimization of bias. The manufacturer indicated this was a population with a total of [redacted] patients, yet the transition probabilities within the model were derived from a population of 23 patients. The [redacted] additional patients included within the data set to calculate transition probabilities are likely to be the [redacted] patients who began treatment with cerliponase alfa at a combined motor and language scale score of [redacted] and did not experience any decline. The inclusion of these [redacted] patients in the calculation of transition probabilities is likely to have increased treatment efficacy in favour of cerliponase alfa, decreasing health state costs and increasing utilities in favour of cerliponase alfa. This lack of congruence with the clinical effectiveness evaluated in the CADTH Clinical Report could not be addressed in the CADTH reanalyses.
Utilities	The manufacturer used utility values derived from a manufacturer-funded study in which eight clinical experts were presented with a set of vignettes derived by the manufacturer in consultation with clinical experts representing each of the model health states and asked to complete the EQ-5D-5L based on these vignettes. These results were then mapped to the EQ-5D-3L.[7]	The methods used to derive the utility values from the manufacturer's base case were associated with substantial uncertainty. The use of patient proxies are not ideal and may not accurately reflect the quality of life of the patient, especially in this case, which used clinicians as opposed to family members or caregivers. Furthermore, at least one of the clinical experts that validated the vignettes was involved in the study to derive the utility values. Additionally, the vignettes used to derive the health state utilities conferred additional benefit to cerliponase alfa, despite patients being in the same health state as those with BSC. This led to substantial differences in the health state utilities derived from this study. CADTH also noted that the vignettes specify that scores of 5, 3, and 1 on the motor and language scale are based on higher language scores (e.g., for combined score of 5, language equals 3, motor equals 2, etc.). The manufacturer undertook several scenario analyses using alternate sets of utility values. CADTH considered that the values derived from the PedsQL from the cerliponase alfa trials (studies 201 and 202) provided a more plausible

Data Input	Description of Data Source	Comment
		set of utility values, despite the limitations associated with the derivation of these values.
	Caregiver disutilities were applied for all health states, with differing levels of disutility.[3]	Caregiver disutilities are typically only considered in the non-reference case and should not be included in the reference case. CADTH considered a scenario analysis in which caregiver utilities were re-incorporated.
Adverse events (pyrexia, hypersensitivity, headache, vomiting, infection)	Adverse event rates were obtained from the 201 and 202 clinical studies for cerliponase alfa,[4,5] as well as patient narratives.[20]	ICV adverse events besides infection were not considered within the model. In the model, data suggested that infections requiring replacement of the ICV device occurred in approximately 0.25% of infusions. One of the clinical experts consulted by CADTH had experience with the ICV device and noted that there were several adverse events not considered in the model that may require the ICV device be replaced and that the incidence of ICV replacement is likely higher than estimated, while the other clinical expert indicated infection was the only reason. This had limited impact on the overall model results.
Mortality	Mortality from disease was only applied to the final health state as a constant rate based on an assumption.[21] All-cause mortality rate was obtained from Statistics Canada life tables and applied to other health states.[3]	The clinical experts consulted by CADTH indicated that the while patients on cerliponase alfa may not progress as rapidly in terms of score on motor and language scales, other disease-related mortality is applicable due to neurological and extra-neurological progression. One of the clinical experts consulted by CADTH noted five additional life-years from cerliponase alfa was a reasonable estimate.
Resource Use and Costs		
Drug	Cerliponase alfa costs were based on the manufacturer-submitted price and resource use associated with product monograph suggested dosing.[3] For additional medications associated with seizure and other progressive symptoms, drug costs were obtained from the ODB e-formulary.[11]	Appropriate source.
Administration	Administration costs related to the insertion of the ICV and in-hospital infusion costs were obtained using insertion of a shunt in the CIHI patient cost estimator and revisions or replacement of intracranial catheter in the Ontario Schedule of Benefits and Physician Service[9] as proxies, respectively. Additionally, replacement costs for ICV were applied based on the proportion of infusions that lead to infection multiplied by the proportion of infections that require a replacement ICV from Cohen-Pfeffer et al.[22] Cost used was that for a minor	The sources for these costs are highly uncertain and there is insufficient information for their costing. Due to the relatively low cost of the ICV device compared with drug costs, this is not likely to have a large impact on the results. This may, however, pose an implementation issue that limits the capacity of institutions to administer cerliponase alfa, or require additional costs to equip more institutions with the resources to undertake this procedure to administer cerliponase alfa.

Data Input	Description of Data Source	Comment
	intervention, used as a proxy for ICV replacement, from the CIHI patient cost estimator.	
AEs	Costs for serious infections were obtained from the CIHI patient cost estimator, while costs related to pyrexia, hypersensitivity, headache, and vomiting were based on an assumption of additional nurse time and validated based on clinical expert opinion.	Appropriate.
Event	Progressive symptom resource use and costs were included in the model for requirement of a feeding tube, epilepsy, reported distress, dystonia, and myoclonus. Resource use for each were obtained from a combination of Delphi panels, trial data, and assumptions, while costs were obtained from the ODB e-formulary[11] and Ministry of Health Schedule of Benefits.[9]	Appropriate.
Health state	Resource use for each health state was obtained from a global Delphi panel,[8] with modification and validation from global expert opinion. Costs were obtained from the Ministry of Health Schedule of Benefits,[9] CIHI patient cost estimator, and livingin-canada.com.	Health state costs included family caregiver productivity losses, which are not appropriate from the Canadian health care payer perspective.

AEs = adverse events; BSC = best supportive care; CIHI = Canadian Institutes for Health Information; CLN2 = ceroid lipofuscinosis type 2; EQ-5D-3L = EuroQol 5-dimensions 3-levels; EQ-5D-5L = EuroQol 5-dimensions 5-levels; ICV = intracerebroventricular; ODB = Ontario Drug Benefit; PedsQL = Pediatric Quality of Life Inventory.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
The distribution of patients across the health states at the beginning of the model reflects the expected population to be treated given future improvements in diagnosis.	Feedback from the clinical experts consulted by CADTH suggested that the proportions assumed by the manufacturer are likely appropriate based on expected diagnostic practices in Canada. Given that this assumption does not align with the data available, and the limitation that CADTH has highlighted with this approach, the distribution of CLN2 Clinical Rating Scale scores at baseline in the cerliponase alfa clinical study 201 was used in a scenario analysis.
The starting age of patients in the model, which affects age-related mortality and dosages of cerliponase alfa, was assumed to be the mean starting age across Study 190-201 and the natural history study.	Feedback from the clinical experts consulted by CADTH suggests that this is likely to be appropriate; although improvements in the diagnostic techniques for CLN2 may allow for diagnosis at a younger age. This aligns with the feedback regarding detection of CLN2 at an earlier stage.
When calculating transition probabilities, health states 1 and 2 were grouped together; health states 3, 4, and 5 were grouped together; and health states 6 and 7 were grouped together, for both treatment groups of the model.	May not be appropriate. While issues with data, including limited sample size, arose, each of these states is distinct and should have its own transition probability; the grouped value may not be representative of the clinical data.
The proportion of patients in each health state experiencing progressive symptoms (epilepsy, reported distress, dystonia, myoclonus, and the requirement of a feeding tube) is the same in the cerliponase alfa group as the standard of care group.	Appropriate. There is no evidence of improvement of these symptoms due to the administration of cerliponase alfa.

Assumption	Comment
Mortality risk is tied to lower health states within the model.	Inappropriate. This implicitly assumes a survival benefit with cerliponase alfa as it is assumed to delay progression in CLN2 motor and language scores, which results in increased survival. There is no clinical data to support a survival benefit with cerliponase alfa.
Patients stop receiving cerliponase alfa treatment when they reach health state 7 (CLN2 Clinical Rating Scale score of 0). Upon discontinuing cerliponase alfa, patients switch to transition probabilities and utility values observed in the BSC group.	Appropriate, though the clinical experts consulted by CADTH noted that this is a decision that should be made on a case-by-case basis and some patients and caregivers may choose to stop therapy earlier should disease continue to progress.
Replacements of the ICV delivery device were assumed to only be required if an infection occurred.	Inappropriate. Replacements for ICV devices may be required for a number of reasons beyond infection based on feedback from the clinical expert consulted by CADTH.
Patients receiving cerliponase alfa treatment for more than 16 weeks are assumed to either be early stabilizers or late stabilizers. Early stabilizers remain in the health state that they are in at 16 weeks for the rest of the model time horizon, while late stabilizers continue to progress at a rate of 1 point on the CLN2 Clinical Rating Scale (i.e., one health state) per 80 weeks until 96 weeks, after which point they remain in the health state that they are in for the rest of the model time horizon. These assumptions about transitions are only observed for patients while they are receiving treatment — if treatment has been discontinued then they will transition in accordance with the transition probabilities applied to the standard care group.	Given a lack of long-term clinical evidence, the assumption regarding stabilization and accompanying mortality benefit is highly uncertain.
Vision loss (52 weeks after achieving score of 0) and palliative care (52 weeks after achieving score of 0 and vision loss) were incorporated only after patients reached a score of 0 on the combined motor and language scale.	Inappropriate. The manufacturer primarily based disease progression within its model on the combined score on the CLN2 motor and language scales, which may not appropriately capture important milestones of disease progression. Additionally, patients could only achieve vision loss or require palliative care upon reaching a score of 0 on the CLN2 motor and language scales. According to feedback from the clinical experts consulted by CADTH, patients responding on cerliponase alfa and with a slowed disease progression based on the combined motor and language scale score may experience vision loss before a score of 0 given cerliponase alfa cannot cross the blood-brain barrier and prevent vision loss. Patients on either cerliponase alfa or BSC may require palliative care at higher scores than 0 and without vision loss. CADTH considered an alternate assumption of 0 weeks for each, but neither change had an impact on results.
Assumption of the EQ-5D values derived from the manufacturer-created vignettes as the most appropriate set of utilities to use.	Inappropriate. The methods used to derive the utility values used in the manufacturer's base case were associated with substantial uncertainty and there are concerns that these values do not meet face validity.
Time receiving palliative care before disease-related mortality (52-weeks post palliative care).	Inappropriate. There is no evidence to suggest disease-related mortality is only likely to occur after 52 weeks of palliative care. CADTH considered an alternate assumption of 0 weeks, but this did not impact results.

BSC = best supportive care; EQ-5D = EuroQol 5-dimensions; ICV = intracerebroventricular; PedsQL = Pediatric Quality of Life Inventory.

Manufacturer's Results

Table 13: Summary of Results of the Manufacturer's Base Case

	Total Life-Years[a]	Total Costs ($)	Incremental Cost of Cerliponase Alfa ($)	Total QALYs	Incremental QALYs of Cerliponase Alfa	Incremental Cost per QALY
BSC	4.94	225,268	–	–0.56	–	–
Cerliponase alfa	22.57	18,672,046	18,446,778	9.62	10.19	$1,811,059

BSC = best supportive care; QALY = quality-adjusted life-year.

[a] Based on the deterministic analysis. Probabilistic life-years not reported. Deterministic analysis results aligned with the probabilistic results.

Source: Manufacturer's pharmacoeconomic submission.[3]

Table 14: Manufacturer's Scenario Analyses

Scenario Number	Description	Resulting ICUR ($/QALY)
Manufacturer's base case	Not applicable	$1,811,059
Scenario 1	Starting population of patients evenly split across health states 1 and 2	$1,784,271
Scenario 2	All starting population starts in health state 1	$1,676,234
Scenario 3	Starting population matches the population of studies 190 to 201, and 202 at baseline	$2,013,762
Scenario 4	Utility values obtained using the PedsQL values from the trial, mapped to EQ-5D, with the assumption of the same utility values across both groups of the treatment	$1,314,834
Scenario 5	Unmapped EQ-5D-5L utility values from the utility study	$1,651,625
Scenario 6	Utility values for cerliponase alfa group assumed to be the same as the standard care group, from the utility study	$1,799,414
Scenario 7	Utility values for health state 1 are reduced by 10%	$1,815,620
Scenario 8	Utility values decrease with age	$1,845,987
Scenario 9	Patients stop receiving cerliponase alfa treatment at health state 6	$1,619,151
Scenario 10	Patients do not stop receiving cerliponase alfa treatment until death	$1,950,941
Scenario 11	Patients are split into "early" and "late" stabilizers after 26 weeks (instead of 16 weeks)	$1,803,550
Scenario 12	No caregiver or sibling disutility is applied in the model, for the cerliponase alfa group	$1,849,237
Scenario 13	Discount rate of 0% for costs and benefits	$1,862,834
Scenario 14	Discount rate of 3.0% for costs and benefits	$1,764,786
Scenario 15	Time horizon of 50 years	$1,782,307

EQ-5D = EuroQol 5-dimensions; EQ-5D-5L = EuroQol 5-dimensions 5-levels; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PedsQL = Pediatric Quality of Life Inventory.

Source: Manufacturer's pharmacoeconomic submission.[3]

CADTH Exploratory Analysis Results

Table 15: CADTH Exploratory Analyses

Exploratory Analysis	Treatment	QALYs	Cost	ICUR (per QALY)
Two-year time horizon (similar to the 96 weeks of clinical data from studies 201 and 202)	BSC	1.26	$81,924	NA
	Cerliponase alfa	1.51	$1,748,700	$6,553,981
Same efficacy for cerliponase alfa as BSC from 96 weeks onward	BSC	1.91	$224,005	NA
	Cerliponase alfa	2.85	$3,439,340	$3,390,786

BSC = best supportive care; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

References

1. CDR submission: Brineura (cerliponase alfa) 150mg/5 mL solution administered by Intracerebroventricular (ICV infusion) [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): BioMarin Pharmaceuticals (Canada) Inc.; 2018 Jul 31.
2. Brineura (cerliponase alfa solution for infusion): solution for infusion for intracerebroventricular infusion 150 mg/5 mL (30 mg/mL) [product monograph]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018 Dec 19.
3. Pharmacoeconomic evaluation. In: CDR submission: Brineura (cerliponase alfa) 150mg/5 mL solution administered by Intracerebroventricular (ICV infusion) [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018 Jul 31.
4. Clinical Study Report: 190-201. A phase 1/2 open-label dose-escalation study to evaluate safety, tolerability, pharmacokinetics, and efficacy of intracerebroventricular BMN 190 in patients with late-infantile neuronal ceroid lipofuscinosis (CLN2) disease [**CONFIDENTIAL** internal manufacturer's report]. Novato (CA): BioMarin Pharmaceutical Inc.; 2016 Apr 27.
5. Clinical Study Report: 190-202. A multicenter, multinational, extension study to evaluate the long-term efficacy and safety of BMN 190 in patients with CLN2 disease [**CONFIDENTIAL** internal manufacturer's report]. Novato (CA): BioMarin Pharmaceutical Inc.; 2017 Oct 13.
6. Clinical Study Report: 190-901. Natural history of late-infantile CLN2 disease: quantitative assessment of disease characteristics, rate of progression, and magnetic resonance imaging findings [**CONFIDENTIAL** internal manufacturer's report]. Novato (CA): BioMarin Pharmaceutical Inc.; 2015 Jun 30.
7. CLN2 disease utility study report. In: CDR submission: Brineura (cerliponase alfa) 150mg/5 mL solution administered by Intracerebroventricular (ICV infusion) [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018 Jul 31.
8. Delphi workshop report: UK treatment practices for the management of CLN2 disease. In: CDR submission: Brineura (cerliponase alfa) 150mg/5 mL solution administered by Intracerebroventricular (ICV infusion) [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018 Jul 31.
9. Ontario Ministry of Health Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html. Accessed 2018 Jul 31.
10. Living in Canada. Medical and health jobs – Canada salary and wage guide. 2018; https://www.livingin-canada.com/salaries-for-health-jobs-canada.html. Accessed 2018 Nov 7.
11. Ontario Ministry of Health Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2018; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2018 Jul 31.
12. BioMarin Pharmaceutical (Canada) Inc. response to September 13, 2018 request for additional information regarding Brineura (cerliponase alfa) CDR review: revised economic model [**CONFIDENTIAL** additional manufacturer's information]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018.
13. Williams RE, Adams HR, Blohm M, et al. Management strategies for CLN2 disease. *Pediatr Neurol.* 2017;69:102-112.
14. Moore SJ, Buckley D, MacMillan A, et al. The clinical and genetic epidemiology of neuronal ceroid lipofuscinosis in Newfoundland. *Clin Genet.* 2008;74(3):213-222.
15. BioMarin Pharmaceutical (Canada) Inc. response to October 1, 2018 request for additional information regarding Brineura (cerliponase alfa) CDR review: 1:1 matching and updated probabilistic model to follow [**CONFIDENTIAL** additional manufacturer's information]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018
16. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 *(NICE highly specialised technology evaluation report ID943)*. London (GB): National Institute for Health and Care Excellence; 2018: https://www.nice.org.uk/guidance/gid-hst10008/documents/committee-papers. Accessed 2018 Nov 13.
17. Pharmaceutical Benefit Advisory Committee. Public summary document: cerliponase alfa, 150mg/5mL vial for infusion, Brienura™, Biomarin. Canberra (AU): Pharmaceutical Benefits Scheme; 2018: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-07/files/cerliponase-alfa-psd-july-2018.pdf. Accessed 2018 Nov 14.
18. Transparency Committee. Brineura (cerliponase alfa), classe simple. Saint-Denis (FR): Haute Autorité de Santé 2018: https://www.has-sante.fr/portail/upload/docs/evamed/CT-16359_BRINEURA_PIC_INS_Avis3_CT16359.pdf. Accessed 2018 Nov 14.
19. National Centre for Pharmacoeconomics. Cerliponase alfa (Brineura®). 2018; http://www.ncpe.ie/drugs/cerliponase-alfa-brineura/. Accessed 2018 Nov 13.
20. Study 190-201/202 integrated subject narratives. In: CDR submission: Brineura (cerliponase alfa) 150mg/5 mL solution administered by Intracerebroventricular (ICV infusion) [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; 2018 Jul 31.
21. Cerliponase alfa economic model workshop report. In: CDR submission: Brineura (cerliponase alfa) 150mg/5 mL solution administered by Intracerebroventricular (ICV infusion) [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): BioMarin Pharmaceutical (Canada) Inc.; ; 2018 Jul 31.
22. Cohen-Pfeffer J, Gururangan S, Lester T. Intracerebroventricular delivery as a safe, long-term route of drug administration. *Pediatr Neurol.* 2017;67:23-35.