

5.02 CERLIPONASE ALFA, 150mg/5mL vial for infusion, Brineura™, Biomarin

1 Purpose of application

- 1.1 Section 100 Highly Specialised Drug listing for cerliponase alfa administered via intracerebral ventricular (ICV) injection for treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a rare neurodegenerative genetic condition which is caused by deficiency of the enzyme TPP1 and usually manifests in late infancy. Patients with CLN2 disease have a short life expectancy with an average age of death between 8 and 12 years. Cerliponase alfa has not been considered by the PBAC previously.
- 1.2 The basis for listing is a cost-effectiveness analysis based on life years gained (LYG) and cost-utility analysis of cerliponase alfa plus standard care versus standard care alone. No evidence regarding improved survival with cerliponase alfa treatment is presented in the submission, rather an observed reduction in the rate of progression of disease is used to assume improved survival. Table 1 summarises the key components of the clinical issue addressed by the submission.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) also known as TPP1 deficiency
Intervention	Cerliponase alfa 300 mg administered every other week (in patients >2 years of age, with modified dosing for those < 2 years of age) via an intracerebroventricular (ICV) reservoir and catheter~
Comparator	Standard care
Outcomes	Motor-language scale score
Clinical claim	In CLN2 disease, cerliponase alfa 300 mg is superior to standard care in terms of response as assessed by the CLN2 clinical Motor-Language (ML) scale and inferior in safety.

Source: Table 1.1-1, p17 of the submission

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
Cerliponase alfa Vial for infusion, 150mg/5mL	4 units	5	\$ [REDACTED] (Public) \$ [REDACTED] (Private)	Brineura	Biomarin

Category / Program:	Section 100 Highly Specialised Drugs Program
PBS Indication:	Neuronal ceroid lipofuscinosis type 2 disease
Treatment phase:	Initial treatment
Restriction:	Authority required
Treatment criteria:	Must be treated by a specialist physician with expertise in the management of patients with neuronal ceroid lipofuscinosis type 2 disease.
Clinical criteria:	Patient must have a confirmed diagnosis of neuronal ceroid lipofuscinosis type 2; AND Patient must not receive more than 24 weeks of treatment under this restriction
Prescriber Instructions	The initial authority application must be in writing and include documented confirmed diagnosis of neuronal ceroid lipofuscinosis type 2 disease.
Category / Program:	Section 100 Highly Specialised Drugs Program
PBS Indication:	Neuronal ceroid lipofuscinosis type 2 disease
Treatment phase:	Continuing
Restriction:	Authority required
Treatment criteria:	Must be treated by a specialist physician with expertise in the management of patients with neuronal ceroid lipofuscinosis type 2 disease.
Clinical criteria:	Patient must have CLN2 disease AND Patient must not have had an unreversed motor-language (ML) score = 0 for 6 months
Prescriber Instructions	Must have documented evidence of ML scores

Source: Table 1.4-2 and 1.4-3, p31 of the submission

- 2.1 Under the proposed restriction, all patients diagnosed with CLN2 disease, irrespective of severity, are eligible for initial treatment. The identification of the causative gene in CLN2 disease has allowed for an accurate diagnosis by TPP1 enzyme activity and/or pathogenic mutations in the CLN2 gene, with over one hundred different mutations in the CLN2 gene reported to be pathogenic. Specific tests for TPP1 are currently not funded by the Commonwealth. However the PSCR confirmed that the costs for the testing of TPP1 enzyme activity and CLN2 genotype sequencing carried out at the National Referral Laboratory are met by the referring hospital laboratory. The PSCR indicated that it would be appropriate for the restriction to include criteria specifying confirmation of diagnosis by TPP1 enzyme activity testing and CLN2 genotype sequencing.
- 2.2 The PSCR also stated it would also be appropriate for the restriction to specify that the patient must be treated by or in conjunction with a specialist physician with expertise in the management of patients with CLN2 disease.
- 2.3 Under the proposed restriction, patients are eligible for continued treatment until disease progression to the point where a patient has an adapted CLN2 motor-language (ML) score of 0 for six months. The ML score is a composite score from the motor and language domains of an adapted CLN2 disease rating scale, which has a total of 4 domains (motor, language, vision and seizures). Each domain is scored out of

3, with a maximum score of 6 possible for the ML score, which corresponds to normal motor function and language, and a minimum score of 0, which indicates the patient can no longer walk or crawl and has no intelligible words or vocalisation. The ESC noted there was no specified clinical rationale for treating patients for an additional 6 months once patients decline to an ML score of 0. The ESC was uncertain whether improvement in a patient condition and quality of life with continued treatment once a patient declines to an ML score of 0 would be realistic.

- 2.4 The requested listing is consistent with the proposed TGA listing but is broader than the clinical evidence presented. In Study 201/202 (the primary source of evidence for the submission), only patients with stable seizures, and either asymptomatic or only have early-moderate symptoms (ML score of 3-6 at baseline) aged between 3-15 years were included in the study and were treated with cerliponase alfa. The PSCR argued that at the time that patients commenced treatment with cerliponase alfa in Study 201/202, the trial population was reflective of the patient population in Australia as two patients declined to an ML score of 2 and one patient declined to an ML score of 1. The PSCR also noted that the inclusion criteria for Study 201/202 for patients to have stable seizures was unlikely to have restricted the population as all patients with a diagnosis of CLN2 disease at screening were included in the main study phase. The PSCR further argued that while Study 201/202 only enrolled patients between 3-15 years, and the mean age at diagnosis in Australia is unknown, it was unlikely that patients would be diagnosed prior to the age of 3 given that the mean time from first symptom onset to diagnosis is between 2 to 3 years. The ESC noted it was currently not possible to compare the Australian patient population with that of Study 201/202 or Study 901 as formal ML scoring is not currently used in Australian clinical practice.
- 2.5 The ESC was uncertain whether all patients with CLN2 disease would benefit equally from treatment with cerliponase alfa given the burden of treatment (i.e requires ICV device) and severity of the disease particularly at the lower end of the ML scale.
- 2.6 The PSCR stated there was currently no specific access program for cerliponase alfa in Australia.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 **TGA status at time of PBAC advice:** TGA status: – Cerliponase alfa was submitted under the parallel process. The TGA delegate's overview was expected by the end of June 2018. The proposed TGA indication is: "Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency." Cerliponase alfa was granted orphan drug status by

the TGA (effective date 8 November 2017, lapse date 8 August 2018) for the same indication.

4 Population and disease

- 4.1 CLN2 disease is a rare (35 reported cases in Australia between 2000-2016, corresponding to an incidence of 1:135,000 live births) type of neuronal ceroid lipofuscinosis (NCL) caused by mutation in the CLN2 gene which leads to deficient activity of the enzyme TPP1. CLN2 is a neurodegenerative disease with seizures usually being the first symptom, followed by rapid loss of learned language over 2.5 years and loss of motor function. Myoclonus/abnormal movements and loss of vision develop. Patients eventually become blind, unable to walk or communicate and will have respiratory and feeding problems. Death due to respiratory failure is likely to eventuate and the average age of death for CLN2 patients is between 8-12 years.

5 Comparator

- 5.1 The nominated comparator was standard care only. The main argument provided in support of this nomination was that there are no disease-modifying treatments for CLN2 disease in Australia. This is reasonable.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented an overview of the natural history of CLN2 disease and the diagnostic pathway and affirmed that both the TPP1 enzyme activity test and CLN2 gene mutational analysis are required to confirm a diagnosis of CLN2 disease. In relation to disease prognosis, the clinician indicated there was limited variability apart from a small amount of heterogeneity in age of presentation which affects time of death (i.e. earlier onset is associated with an earlier age of death). The clinician discussed the effect of treatment with cerliponase alfa in the context of the trial evidence from Study 201/202, and highlighted that 87% of patients in the trial were classified as responders.
- 6.2 Preliminary long term data which had not been included in the submission was also presented as evidence of the long term efficacy of cerliponase alfa. On the basis of this data, the clinician claimed that cerliponase alfa halts the progression of CLN2 disease. In support of the assumption in the submission that patients die from CLN2 disease only when patients decline to an ML score of 0, the clinician noted that for most patients in the natural history cohort (Study 901), the last ML score on or known prior to death was 0. The clinician indicated that the benefits which patients value most from a treatment for CLN2 disease were the control of seizures, preservation of vision and motor function.

- 6.3 The clinician indicated that given the severity and rarity of the disease, there is unlikely to be a large undiagnosed population with CLN2 disease. The PBAC considered the hearing was informative as it provided a clinical perspective of the diagnosis of CLN2 and the disease course.
- 6.4 The PBAC noted that there were approximately [REDACTED] patients globally with CLN2 disease receiving treatment though there was no specific compassionate access program for Australian patients.

Consumer comments

- 6.5 The PBAC noted and welcomed the input from individuals (446), health professionals (11) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the rapid progression, debilitating symptoms and significant burden of CLN2 disease on the patient and family and emphasised that there are currently no other treatment options for these patients. The comments also described the benefits of treatment in children currently receiving cerliponase alfa including reduction of seizures and maintenance of mobility and speech functions.
- 6.6 Batten Disease Support and Research Association (BDSRA) Australia and BDSRA North America expressed their strong support for the subsidisation of cerliponase alfa and indicated the importance of access to this treatment for families of patients diagnosed with CLN2 disease regardless of whether the treatment is curative. BDSRA Australia presented several narratives about the management of CLN2 disease from families of children with CLN2 disease with and without access to treatment to cerliponase alfa to highlight the positive impact that treatment could have on patients and their families.

Clinical trials

- 6.7 The submission is based on a 1:1 matched comparison of two single arm studies: Study 201 (and the extension Study 202, referred to as Study 201/202 herein) (n=24) and Study 901 (n=49).
- 6.8 Study 201/202 enrolled and treated 24 patients with early to moderate symptoms (ML score 3-6) and aged between 3-8 years with cerliponase alfa. Four different dosage regimens were used during initiation but the same maintenance dose of 300mg fortnightly was used in all patients in Study 201/202. Patients enrolled in Study 201/202 were assessed using an adapted CLN2 disease rating scale, with the motor-language (ML) domains used to measure the primary outcome (number of patients who experience fewer than 2 points decline on the ML score from baseline in 48 weeks).
- 6.9 Study 901 was a longitudinal quantitative clinical registry for patients with CLN2 which has expanded over time. In 2015, the original study contained data from patients in two large cohorts in Hamburg, Germany (n=[REDACTED]) and the Weill Cornell Medical College in New York, US (n=[REDACTED]). A subsequent update included patients from another

collaborative database, the DEM-CHILD (n=█), which was formed from patients from two clinical sites (Hamburg, Germany and Verona, Italy). The data from the submission includes only the latest Study 901 update, which includes 49 patients, of which █ were from the original Hamburg study. Patients enrolled in Study 901 were assessed using the Hamburg rating scale for CLN2, and the motor-language score from the Hamburg rating scale (HML) was assumed by the submission to be equivalent to the ML score in Study 201/202. This is likely to be reasonable as the ratings of the two scales appear comparable.

- 6.10 The submission also describes two databases: the DEM-CHILD database (N=█) and the Weill Cornell Medical College (WCMC) cohort (N=█), which contain longitudinal data about the disease progression of patients with CLN2 treated with standard care only. Study 901 contains data from some (but not all) patients from both databases. Longitudinal data from 58 patients in DEM-CHILD database and █ patients in the WCMC cohort was published in Nickel et al 2016.
- 6.11 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Main cerliponase alfa studies		
Study 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.	27 April 2016
Study 202	A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease. Interim cutoff date: 1 November 2016.	13 October 2017
Study 201/202	Statistical analysis of data from Study 190-201/202.	April 2017
Supplementary cerliponase alfa clinical studies		
Study 203	A Phase 2, Open-Label Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Patients < 18 years of age with CLN2 Disease. Interim cut-off date: 1 November 2016.	23 October 2017
Natural history studies		
Study 901	Natural History of Late-Infantile CLN2 Disease: Quantitative Assessment of Disease Characteristics, Rate of Progression, and Magnetic Resonance Imaging Findings. Updated Analysis of the Natural History of CLN2 Disease: Estimated Rate of Decline from the DEM-CHILD Multi-Center Clinical NCL Database (data transfer July 2015) Updated Analysis of the Natural History of CLN2 Disease: Estimated Rate of Decline from the DEM-CHILD Multi-Center Clinical NCL Database (data transfer: August 2016)	30 June 2015. Report date: 1 May 2016 Report date: 21 July 2017
Nickel et al., 2016b	Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression in an international cohort of 137 patients	Not yet published, Manuscript in preparation

Source: Table 2.2-1, p42, Table 2.2-2, p44 and Table 2.2-4 p47 of the submission

6.12 Study 203 was a trial which enrolled and treated siblings of patients who were enrolled in Study 201/202 with cerliponase alfa. At the time of submission only four patients were enrolled in Study 203 and only data up to 36 weeks was available, therefore it was not utilised as part of the matched 1:1 comparison. The submission also identified 14 total studies for natural history of CLN2 disease which reported patient outcomes However only data from Study 901 was used in the submission. The submission inappropriately did not explicitly justify the exclusion of the 13 studies, but it is likely because none of the 13 studies included ML score measurements.

6.13 The key features of the clinical studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Study 201/202	24	OL, SA, 96 weeks	High	Early to moderate CLN2 disease (treated with cerliponase alfa 300mg fortnightly)	Response rate	Matched to study 901 to derive transition probabilities
Study 901	49	OL, SA, NR ¹	High	All CLN2 disease (treated with standard care)	Estimated rate of decline	Matched to study 201/202 to derive transition probabilities

OL=open label; SA = single arm; NR = not reported

¹Was a study of patient database, no estimated follow up period reported but patients were followed up till death, which is a matter of years in patients with CLN2 disease.

Source: compiled during the evaluation

6.14 Patients enrolled in Study 201/202 were matched in a 1:1 ratio with patients enrolled in Study 901 based on two criteria: (i) patients must have the same ML score just prior to the first dose of fortnightly administered cerliponase alfa 300mg in Study 201/202 and baseline HML score (Study 901), and (ii) both patients' age at baseline must be within 12 months. Using these criteria, the submission claimed that 21 out of 23 patients from Study 201/202 were matched to patients in Study 901.

6.15 There were inconsistencies with the number of patients reported in 1:1 matching. In the NICE assessment of cerliponase alfa in the UK, the same 1:1 matched comparison was conducted between the same studies, but 22 patients were reportedly matched instead of 21. Moreover, when the submission used patient level data from the matched comparison to estimate the transition probabilities in the economic evaluation (Appendix 21 of the submission), [REDACTED] matched pairs were identified. The PSCR stated that the discrepancy between the number of matched pairs in the NICE assessment and the submission was due to an update of the DEM-CHILD database between the 72-week data analysis used in the NICE evaluation and the 96-week data analysis in the submission which resulted in a new set of patients and an additional patient from Study 201/202 being unmatched in the 96-week data analysis. The PSCR further explained that the discrepancy in the number of matched pairs in the 1:1 matched comparison and the matched comparison used to estimate the transition probabilities was due to more than one patient from Study 201/202 being matched to the same patient in Study 901 in some instances.

6.16 The 1:1 matching did not consider other characteristics such as residual TPP1 activity or uncommon genotype in CLN2 mutation which are likely to be more prognostic of CLN2 disease progression than baseline age. There were twice as many patients with uncommon genotypes ([REDACTED]) in Study 201/202 than there were in Study 901 ([REDACTED]), which may bias the results in favour of cerliponase alfa as Nickel et al 2016 noted that uncommon genotypes are potentially associated with delayed onset or prolonged course of disease (i.e. slower rate of decline). The PSCR presented results from Schulz

et al., 2018¹ of an additional 1:1 matched comparison adjusted for genotype. In the 1:1 matched comparison adjusted for genotype, the mean rate of decline in ML score per 48 weeks was an incremental difference of 1.70 points (cerliponase alfa: 0.20 ± 0.67 ; standard care: 1.90 ± 1.23) compared with an incremental difference of [REDACTED] points in the unadjusted 1:1 matched comparison in the submission. The PSCR noted that these results did not differ significantly from the results of the 1:1 matched comparison in the submission.

- 6.17 Although the 1:1 matching of patients in Studies 201/202 and 901 aimed to emulate a randomised trial, the exclusion of 13 natural history studies (where it is acknowledged there may be some overlap in the patients enrolled in each) and/or more than half the patients in Study 901 (all patients with CLN2 disease which is more likely to reflect the requested PBS population than those enrolled in Study 201/202 (patients with early-to-moderate progression of CLN2 disease) may bias the estimates of the natural progression of this rare disease. A more appropriate approach may have been to provide an estimate of the natural progression of CLN2 disease using all available data, in addition to the 1:1 matching to assess and quantify any potential bias. Although noting that the exclusion of data was based on earlier Food and Drug Administration advice, the ESC considered that the exclusion of additional data may not have been appropriate in the context of the small population size and matched comparison.

Comparative effectiveness

- 6.18 The primary outcome in Study 201/202 was a responder analysis, where a responder was defined by an absence of an unreversed 2-point decline or score of 0 on the ML scale (either adapted CLN2 rating scale or Hamburg rating scale) per 48 weeks. The responder analysis was not an outcome in Study 901. Instead, the submission estimated the response rate (a different definition of 'responder' was used) in patients from Study 901 in the matched 1:1 comparison using patient level data. The responder analysis in Study 201/202 is presented in Table 4 and the responder analysis in the 1:1 matched comparison is presented in Table 5.

¹ Schulz A., Ajayi T., Specchio N., de Los Reyes E., Gissen P., Ballon D., Dyke J., Cahan H., Slasor P. Jacoby D. & Kohlschutter A, 2018. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. NEJM;378: 1898-1907.

Table 4: Responder analysis (absence of an unreversed 2-point decline in ML or score of 0)

Population	48 weeks (Study 201)			96 weeks (Study 202)		
	N	% (95% CI)	1-sided p-value ¹	n	% (95% CI)	1-sided p-value ¹
Primary analysis						
ITT ² (N = 23)	20	87 (66, 97)	0.0002	■	■ (■, ■)	■
Sensitivity analysis ³						
Efficacy (N = 21)	■	■ (■, ■)	■	■	■ (■, ■)	■

¹ Tested against a null hypothesis that the responder rate would be ≤50%.

² ITT population excluded one patient who discontinued treatment after a single dose

³ Sensitivity analysis excludes two patients who maintained a ML score of 6 throughout the 96 weeks of Study 201/202

Source: Table 2.5-2, p83 of the submission

Table 5: Responder (fewer than 2 points decrease in motor language score in 48 weeks) analysis in 1:1 matched comparison

Response	Study 901	Study 201/202	Rate Difference	2-sided p-value
1:1 matched population				
Primary analysis				
ITT (N = 21)	■ (■%)	■ (■%)	■%	■
Sensitivity analyses¹				
Efficacy (N = ■)	■ (■%)	■ (■%)	■%	■
Responder analysis over 1000 replications using 1:1 matching				
Distribution of Response Rates (%)			Study 901 – Study 201/202	1-sided p-value
N	■	■	■	■
Mean (SD)	■ (■)	■ (■)	■ (■)	■ (■)
Median	■	■	■	■
25 th , 75 th Percentile	■, ■	■, ■	■	■, ■

¹ Efficacy matched population excluded 2 patients with ML scale scores of 6 with no decline

Source: Table 2.6-1, p106 and Table 2.6-2, p107 of the submission

6.19 There was an important difference in the results presented in the matched comparison and the results in the individual studies. Only 20/23 (87%) patients in Study 201/202 were classified as responders however in the matched comparison, this is reported as ■/21 (■%). It should be noted that despite the responder analysis being the primary outcome in Study 201/202 and the outcome upon which the clinical claim is based, it is NOT used directly to inform the economic evaluation. Instead, patient level data was used to construct transition probabilities through health states. The PSCR stated that a responder was defined as a patient who did not experience a 2-point decline or ML score of 0 over a 48-week period. In contrast, a responder in the 1:1 matched comparison was defined as a patient who experienced a rate of decline less than 2 points over a 48-week period. The ESC requested that the sponsor further clarify the difference between the two definitions of a responder including confirmation whether a responder in Study 201/202 may not be a responder in the 1:1 matched comparison. The Pre-PBAC Response clarified that based on the

definition of responder in the 1:1 matched population (patient with a rate of decline less than 2 points per 48 weeks), all patients who were considered responders in Study 201/202 (patients who did not experience a 2 point rate of decline from baseline or score of 0) would also be considered responders in the 1:1 matched comparison. However, patients in Study 201/202 who were considered non-responders based on the 2-point decline from baseline in the first 48 weeks may be considered a responder in the 1:1 matched comparison.

6.20 Additionally, the rate of decline in ML score was also estimated for patients in Study 201/202 and Study 901 (see Table 6). In a previous data cut (April 2016) of Study 901, results from a mixed-effect model repeated measures (MMRM) with unstructured variance and linear trend and adjustment by age of diagnosis was presented. The MMRM allows for non-uniformity in the interval between ML scores to be used and adjusts for the multiple measurements from the same patient and is considered to be a more sophisticated approach given the data than the simple linear regression presented as the base case in the submission. However no analysis with the MMRM in the latest data cut off (July 2017) in Study 901 was reported in the submission or attached report.

Table 6: Rate of decline of HML scale score in Study 901 using different methods at different data points

Study, time and method of estimation	Mean (SD)	(95% CI)
Study 201/202 – 48 weeks simple linear regression (N=23)	0.40 (NR)	0.05, 0.75
Study 201/202 – 96 weeks simple linear regression (N=23)	████ (██)	████, █████
Study 901 - Data cut from July 2017 (N=49)		
Estimation by first point/last point algorithm	████ (████)	████, █████
Simple linear regression	████ (████)	████
Study 901- Data cut from April 2016 (N=41)		
Simple linear regression	2.09 (0.966)	1.79, 2.40
Mixed-effect model repeated measures (MMRM)		
Post diagnosis, 0-72 months – AR variance	1.286 (NR)	1.03, 1.54
Post diagnosis, 0-30 months – UN variance	1.457 (NR)	1.12, 1.79
Follow up from age 36-144 months – AR variance	████ (██)	████, █████
Follow up from age 36-72 months – UN variance	████ (██)	████, █████
Matched 1:1 comparison		
Study 201/202 (N=21) simple linear regression	████ (████)	████, █████
Study 901 (N=21) simple linear regression	████ (████)	████, █████

AR = heterogeneous autoregressive, UN = unstructured, NR = not reported

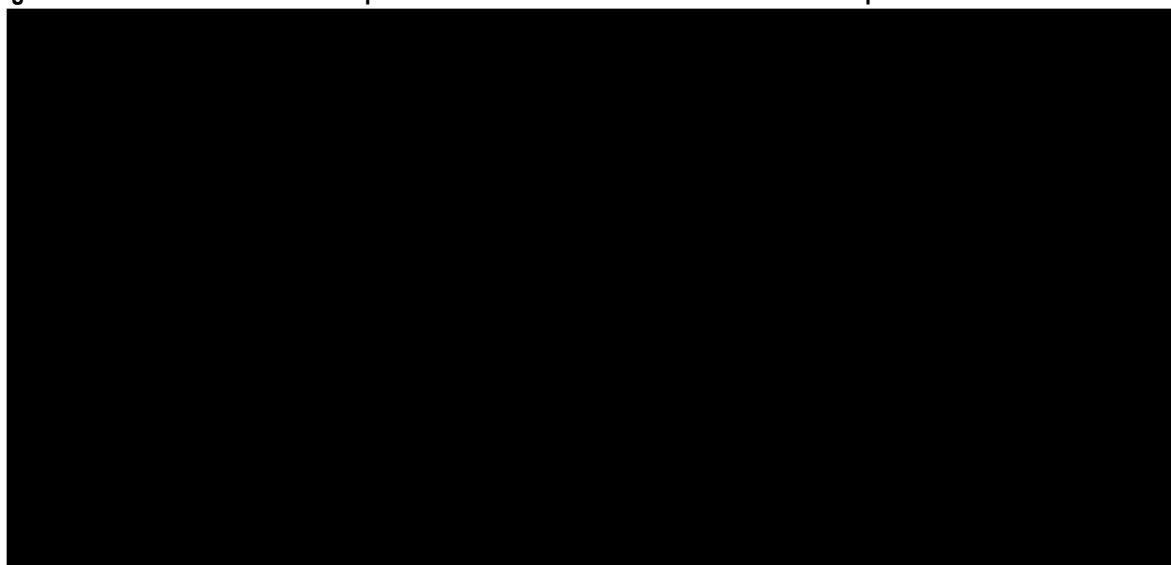
Source: Table 2.5-5, p87, Table 2.5-13, p95 and table 2.6-4, p108 of the submission, Table 9.1, p27 and Table 9.2, p29190-901 supplemental report final 20 Apr2016, Appendix 11 of the submission

6.21 The MMRM provides substantially lower estimates of rate of decline (between 1.3 to 1.5 points at the April 2016 data cut) compared to a linear regression or first point/last point algorithm (2.09 points at the April 2016 data cut) in the HML score in Study 901.

In the NICE evaluation of cerliponase alfa (NICE evaluation consultation document for cerliponase alfa section 4.6, p10), NICE considered the mixed effects model was more appropriate to estimate the rate of decline in CLN2 score in the natural history population as it used all the data points available in Study 901. The PSCR claimed that linear analysis is the most appropriate approach for estimating the rate of decline in HML score since this analysis is informed by observed data only, whereas the MMRM relies on assumptions that are not consistent with the observed data. The ESC noted that both the linear regression analysis and MMRM assume that the outcome variable (HML score) is continuous and approximately normally distributed which may not accurately describe the HML rating scale. As such, the ESC considered that estimating the rate of decline using either method is uncertain. The ESC considered that the sponsor may wish to provide further information to inform the PBAC's considerations in relation to this matter, including the rationale for choosing each method and whether any alternative approaches were, or could be, explored. This might include for example the suitability of the model in reflecting the apparent different slopes of estimated effect across different HML scores. The Pre-PBAC Response presented examples of individual patient ML scale profiles from Study 901 to support that the decline in ML score between 5 and 1 is linear for most patients. On this basis, the pre-PBAC Response argued that the use of the first/last point algorithm and linear regression to estimate the rate of decline is supported.

6.22 Figure 1 shows the time to first unreversed 2 point ML/HML score decline in the matched 1:1 comparison and is a graphical representation of the rate of decline in ML score between the two studies.

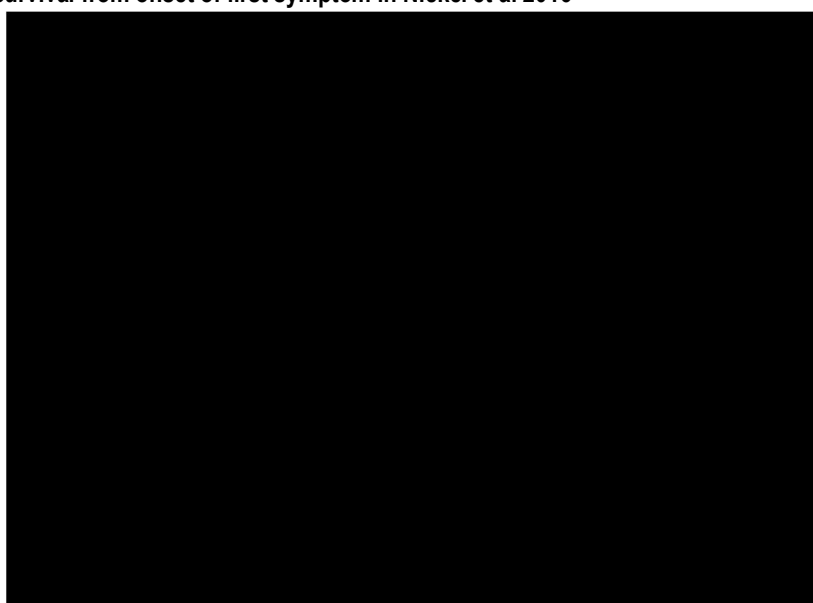
Figure 1: Time to first unreversed 2 point ML/HML score decline in matched 1:1 comparison



Study 201/202 (blue solid line) and Study 901 (red dotted line)
Source: Figure 2.6-1, p106 of the submission

- 6.23 Overall, the evaluation considered that rate of decline reported in Study 201/202 compared to Study 901 supported the clinical claim that treatment with cerliponase alfa is likely to slow the disease progression of CLN2 disease as measured by performance on the ML score. However, the exact magnitude of benefit is unknown, as both Study 201/202 and Study 901 have a high risk of bias given the single arm, open label design, and the rate of decline in Study 901 varies depending on the data cut and also the method of estimation.
- 6.24 Health related quality of life (HRQoL) data was collected in Study 201/202 with the PedsQL, a HRQoL instrument designed for use in children, and a CLN2 disease based QoL survey. EQ-5D data was collected in Study 202 only, but the exact results were not presented. It is difficult to draw conclusions based on the HRQoL data in Study 201/202 due to the lack of a comparative treatment. However there is a trend of an increase in HRQoL at 48 weeks which is unexplained, but a decrease in HRQoL at 97 weeks, which likely reflects the degenerative nature of CLN2 disease. In the base case of the economic evaluation, the submission uses the results from the PedsQL parent report for toddlers mapped using an algorithm from Khan et al 2014 to the EQ-5D to inform the utilities.
- 6.25 Only data up to 96 weeks was presented for Study 201/202 in the submission, and no deaths have been reported in the study thus far, hence no data on mortality could be presented for Study 201/202. Mortality from patients enrolled in Study 901 were similarly not presented separately; instead, the submission presented mortality results from Nickel et al 2016, which includes the patients enrolled in Study 901 as well as other patients with CLN2 disease who were part of the DEM-CHILD or WCMC databases. This is shown in Figure 2.

Figure 2: Overall survival from onset of first symptom in Nickel et al 2016



Source: Figure 2, Nickel et al 2016b

Benefits and harms

6.26 The naïve indirect comparison presented in the submission did not allow for a comparison of the benefits and harms of cerliponase alfa and standard care. Accordingly, a benefits/harms table has not been presented.

Interpretation of clinical evidence

6.27 The submission claimed that cerliponase alfa plus standard care is superior in terms of efficacy compared with standard care alone/no treatment based on responder analyses (response defined as an absence of an unreversed 2-point decline in ML score or ML score of 0). Cerliponase alfa is associated with increased toxicity when compared with standard care. Nonetheless, cerliponase alfa has an acceptable safety profile considering the severity of CLN2 disease.

6.28 The PBAC acknowledged that the evidence presented indicated that treatment with cerliponase alfa slows progression of CLN2 disease. However, the PBAC were uncertain of the magnitude of benefit given the issues raised above. Further, the PBAC considered there was insufficient evidence in the submission to support that the treatment benefit in terms of ML score would equate to a survival benefit.

6.29 The PBAC considered the claim of inferior safety over standard care was reasonable given the administration method of cerliponase alfa. The PBAC agreed that based on the data available, there were no major safety signals however, noted that the long term safety of cerliponase alfa is uncertain.

Economic analysis

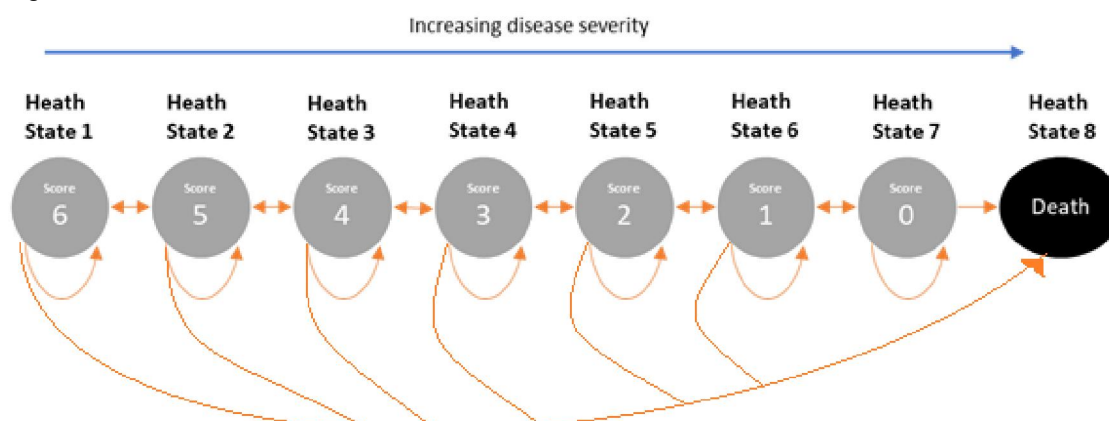
6.30 The submission presented a stepped economic evaluation, with a modelled cost effectiveness (life years gained) and cost utility analysis. A summary of the economic evaluation is presented in Table 7 and Figure 3.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	95 years in the model base case versus 96 weeks in study 201/202. Submission assumed transition probabilities at 96 weeks was extrapolated to beyond 96 weeks.
Outcomes	LYG and QALY gained
Methods used to generate results	Markov model
Health states	A total of 8 health states: 7 individual health states for each ML score (6 to 0) and death as an absorbing health state.
Utilities	PedsQL results from study 201/202 was mapped to EQ-5D using algorithm from Khan et al 2014 in the base case. Khan et al 2014 was a study which used mapped results from the PedsQL filled out by 559 children in England aged 11-15 to the youth version of the EQ-5D. Disutility for adverse events related to cerliponase alfa were sourced from literature. Details on why and how the specific published studies were chosen were not provided by the submission.
Cycle length	2 weeks. Submission claimed that this is consistent with the dosage frequency for cerliponase alfa. However this required interpolation of ML score measurements from both study 201/202 and study 901 as the interval between ML score readings were greater than 2 weeks.
Transition probabilities	<p><u>Transitions between ML score health states:</u> Observed transitions in the 1:1 matched population analysis of Studies 201/202 and 901 in 24-week intervals up to 96 weeks. The methods used to estimate transition probabilities in the submission were potentially inconsistent and arbitrary (see paragraphs 6.22 and 6.23).</p> <p><u>Mortality:</u> Disease-related mortality: Estimated from the manuscript by Nickel M et al, 2016 by estimating the time from a mean ML score of 0 to death for a cohort of CLN2 patients. Applied to the health state membership of ML score of 0. This may not be appropriate (see paragraph 6.24) Age-related mortality: Estimated from Australian life tables and assuming an equal gender distribution. Applied to the health state membership for all ML scores. It may not be reasonable to assume that patients with CLN2 would have the same baseline mortality as the general population.</p>

Abbreviation: LYG = life years gained, QALY = quality adjusted life years
 Source: reference sections/tables/spreadsheets within the submission

Figure 3: Model structure for economic evaluation



Score refers to ML score

Source: Edited from Figure 3.2-1, p135 of the submission during evaluation

- 6.31 There were discrepancies between the method and rules for determining the transition probabilities in the main body of the submission and Appendix 21 of the submission. For example, in the main body of the submission it was claimed that there were four periods: 0-24 weeks, 24-48 weeks, 48 to 72 weeks and 72 to 96 weeks. However in Appendix 21 of the submission (comment in cell B13) it was stated that data was to be divided into three periods (0-24 weeks, 24-48 weeks and 48 to 96 weeks). Moreover, the actual transition probabilities used in the submission did not in fact come from the stated time periods. The transition probabilities for patients treated with cerliponase alfa were informed by data from the 0-24 weeks, 24-48 weeks and 48+ weeks (time period 48-72 weeks, 72-96 weeks and 96+ weeks all have the same transition probability) time periods whereas the transition probabilities for patients treated with standard care were informed by data from the 0+ weeks (all time points) time period (all time periods in standard care have the same transition probability). No justification for the choice of these specific time periods was provided in the submission. It may be inappropriate to use different time periods to inform the transition probabilities for different treatment groups.
- 6.32 Additionally, the submission combined observations between consecutive ML scores (ML score = 6 was combine with ML score =5 and ML score = 4 was combined with ML score = 3 and ML score = 2) in order to boost the number of observations for each transition to make up for small number of patients with each ML score. The combination of ML scores appears to be arbitrary and not justified by the submission. The ESC noted that the sample sizes of the individual groups of observations was still likely to be small and therefore considered the resulting transition probabilities to be highly uncertain.
- 6.33 Extrapolation of the 96 weeks 1:1 matched comparison between Studies 201/202 and 901 to a lifetime using 48+ weeks transition probabilities is likely to be optimistic given there is no efficacy data for cerliponase alfa after 96 weeks. It may have been more

conservative to assume the same rate of disease progression/transition probabilities for both treatment arms after 96 weeks. The ESC considered that a constant rate of progression throughout the disease course was not adequately supported by the evidence in the submission and considered it would be more likely that the rate of progression increases once patients begin to decline. The ESC advised it would have been more appropriate to assume the same transition probabilities for patients in the cerliponase alfa as the standard care arm after patients in the cerliponase alfa arm complete a transition to a worse health state. The Pre-PBAC Response argued that the evidence presented in the submission indicates that cerliponase alfa slows progression of CLN2 disease noting that the mean rate of decline in ML score in Study 201/202 at 48 weeks of 0.40 points was reduced to [REDACTED] points at 96 weeks. The Pre-PBAC Response contended assuming the same transition probabilities for patients in the cerliponase alfa as the standard care arm after patients in the cerliponase alfa arm complete a transition to a worse health state would be inappropriate.

- 6.34 The economic evaluation presented in the submission is not based around responders in the ML score but around increased survival and QALY gains. The submission stated that as no patients died in Study 201/202 or Study 203, it was not possible to estimate overall survival in patients treated with cerliponase alfa. Instead, the submission argued that CLN2 disease-related mortality occurs almost exclusively from an ML score of 0, and that slowing the decline in motor and language function and increasing the time to an ML score of 0 is a surrogate for improved survival. In the NICE evaluation consultation document for cerliponase alfa, it was postulated (Section 4.12, p16 of the NICE evaluation consultation document) that “while death usually occurs because of complications from neurological degeneration, the expression of TPP1 is not limited to the central nervous system and untreated accumulation of ceroid lipofuscin may lead to pancreatic, intestinal, cardiac and hepatic impairment.” though it was also acknowledged that “without longer-term data, the effect of CLN2 on mortality due to affects in other body systems was completely unknown”. Overall, any assumptions about long-term disease stabilisation and mortality are associated with substantial uncertainty given the lack of data beyond 96 weeks. The use of increasing the time to progress to an ML score of 0 used as a proxy for improved survival requires consideration. Background mortality based on age and gender was applied in each cycle independently of ML score. The ESC considered there was insufficient evidence in the submission to determine whether the assumption in the model that death occurs only from an ML score of 0 was appropriate. The Pre-PBAC Response argued that based on data that most patients ([REDACTED]%) who died had a last recorded ML score of 0 in Study 901, the assumption that death occurs from an ML score of 0 is reasonable. Further, the Pre-PBAC Response claimed that this assumption has been reviewed and considered appropriate by Australian clinicians with experience in managing patients with CLN2.
- 6.35 The model presented in the submission is similar to the published economic evaluation by NICE. The structure and underlying assumptions of the NICE model do

not appear to differ significantly with the current submission however, there are SIGNIFICANT discrepancies in the modelled outcome, with the NICE model reporting greater than ■ times the incremental life year gain compared with the submission (40.04 incremental LYG vs ■■ incremental LYG).

6.36 There are several plausible reasons for this discrepancy:

- The NICE model has an ‘early stabiliser’ (will maintain ML score after 16 weeks of treatment) and ‘late stabiliser’ (decline by 1 health state every 80 weeks but will maintain ML score after 96 weeks of treatment) cohort for patients treated with cerliponase alfa, whereas there is only one cohort in the PBAC submission;
- The NICE model used a lower discount rate (1.5% annually) than the PBAC submission (5% annually);
- There is a difference in the initial ML score distribution;
- Baseline mortality could be different between the two models; and
- The NICE model has more health states (two additional health states beyond ML score = 0; ML score = 0 + vision loss, and ML score = 0 + vision loss + palliative care).

6.37 Adjusting the current submission’s model to have a discount rate of 1.5% and to have the same initial ML score distribution to the NICE model, the incremental LYG increases from ■ in the base case to ■■, which is closer to, but still significantly lower than, the 40.04 years in the NICE model. It is likely that the assumption behind the ‘early stabiliser’ and ‘late stabiliser’ cohorts in the NICE model, which assumes that 74% of patients treated with cerliponase alfa would maintain their ML score after 16 weeks of treatment, is the key driver for this difference in modelled outcome.

6.38 Despite these differences, there were several comments by NICE Evidence Review Group (NICE public committee slides Model slide 3) which were applicable to the current model:

- Some patients progressed through the ‘memoryless’ model too quickly;
- Model structure does not account for progressive vision loss; and
- Extra-neurological progression symptoms are not included.

6.39 The submission also assumed that patients stop treatment with cerliponase alfa once they reach health state 7 (ML score = 0). This is inappropriate, as the requested restriction allows patients to continue on cerliponase alfa for six months even if ML score does not improve from 0. This will underestimate the total cost of cerliponase alfa.

6.40 The ESC noted the utilities applied to each health state were derived by mapping PedsQL data collected in Study 201/202 to EQ-5D-5L using the algorithm in Khan et al., 2014, a study which used mapped results from PedsQL filled out by children (11-15 years) older than the population in Study 201/202 to EQ-5D-Y, a version of EQ-5D adapted for youths. The ESC considered this method of deriving utilities to be uncertain and advised that it would have been more appropriate to use the utility

values from the NICE model (see Table 8 below) which were based on EQ-5D-5L responses from 33 individuals (caregivers or siblings of patients with self-reported CLN2) in the base case analysis. The ESC further advised that although the utility values from the NICE model differed for patients treated with cerliponase alfa and standard care in each health state, it would be more appropriate to apply the same utility value for patients treated with cerliponase alfa and standard care in each health state. The ESC noted that the utility value for the health state ML=2 for patients treated with cerliponase alfa is higher than that for the health state ML=3 and requested that the sponsor confirm whether this is an error.

Table 8: Utility values used in the NICE model

ML	CA	SC
6	0.985	1.00
5	0.762	0.731
4	0.629	0.553
3	0.464	0.341
2	0.366	0.131
1	0.218	0.064
0	-0.163	-0.358
0+VS	-0.198	-0.326
0+VS+PC	-0.211	-0.389
Dead	0	0

Abbreviation: ML = motor-language, PC = palliative care, VS = vision loss
Source: p127 of the submission

- 6.41 The Pre-PBAC Response noted that the ESC was incorrect in stating that the utilities from the NICE model were based on EQ-5D-5L responses from 33 individuals (caregivers or siblings of patients with self-reported CLN2). The Pre-PBAC Response confirmed that the utilities from the NICE model were EQ-5D-3L values converted from EQ-5D-5L values from a UK utility study which used the EQ-5D-5L instrument to elicit preferences from a survey of 8 clinicians experienced in the treatment of patients with CLN2 disease.
- 6.42 The submission also used costings from Round 19 (financial year 2014-2015) of the National Hospital Cost Data Collection, Public Hospitals Cost Report to inform the costs for inserting an ICV device and feeding tube. The Round 20 (financial year 2015-2016) data is now available, and a sensitivity analysis using these more recent estimates was conducted during the evaluation.
- 6.43 The key drivers of the model are presented in Table 8. Overall, the incremental costs of the economic evaluation is largely driven by the drug cost for cerliponase alfa, whilst the incremental outcome (LYG and QALY) is largely driven by the difference in transition probabilities based on the 1:1 matched comparison of Studies 201/202 and 901 and the extrapolation of treatment effect beyond 96 weeks for patients treated with cerliponase alfa.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Cost of cerliponase alfa	Taken from requested DPMQ (\$█████ per fortnight)	High. Responsible for █████% of all incremental costs.
Extrapolation	Treatment effect continued beyond 96 weeks (study 201/202) for up to 95 years.	High. Assuming 96+ weeks transition to be the same as standard care for both treatment arms leads to increase in ICER by █████% in LYG and █████% in QALY. Favours cerliponase alfa
Transition probabilities	Patients treated with cerliponase alfa + standard care in general have a higher probability to maintain or improve their ML score/health state (and therefore lower probability to worsen) compared to patients treated with standard care only. This differential in transition probability is likely to be the key driver in the outcomes in the economic model, as death from CLN2 disease is assumed to only be possible when patients decline to ML score = 0, and patients in higher ML score health states also have higher utility	High. Responsible for both QALY and LYG observed. Favours cerliponase alfa. Magnitude of effect may not be supported by data which has high risk of bias and short duration (only up to 96 weeks).
Utility values	There were other potential sources of utilities which could have been applied to the different health states in the model. In the base case, the submission nominated the results of PedsQL mapped to EQ-5D-Y from Study 201/202 as the source of utilities, but also presented a sensitivity analysis using the utilities from the NICE model. The utilities from the NICE model were derived by converting utilities elicited from a UK utility study which included results from 8 CLN2 experts in the UK to EQ-5D-3L values. Whilst there was little difference in the ICER between using utility results from PedsQL and the UK Delphi results, applying the utility values from the NICE model (for health states 1 to 7 only) led to an increase of █████% (from approximately more than \$200,000 per QALY to approximately more than \$200,000 per QALY).	Potentially high (up to 50% difference in cost per QALY gained). Favours either cerliponase alfa or standard care depending on perspective.

Source: compiled during the evaluation

- 6.44 The submission also nominated two methods for estimating disease related mortality. One method involves regression of data from Nickel et al 2016, and an alternative method which maps the estimated ML score for patients treated with standard care in the economic model to the survival at the corresponding ML score reported in Nickel et al 2016 over time, and then adjusting the disease related mortality for the modelled patients such that the area under the curve for both the mapped and actual survival curves were the same. It is unclear which method of estimating disease related mortality is more appropriate. However, the method of estimation does not have a significant impact on the ICER.
- 6.45 The results of the stepped economic evaluation are summarised in Table 9. The first step, a cost per responder analysis, was not presented by the submission. Instead, results for the cost per responder analysis was conducted during the evaluation using values from the submission. Moreover, the submission inappropriately applied

discounting from cycle 1 onwards. This has been corrected during the evaluation such that there was no discounting from week 0 to week 50 (cycle 1 to 26).

Table 10: Results of the stepped economic evaluation

Step and component	Cerliponase alfa	Standard care	Increment
Step 1: Responder (<2 point decrease in ML score every 48 weeks) at 96 weeks of treatment			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Number of responders	[REDACTED]/21 ([REDACTED]%)	[REDACTED]/21 ([REDACTED]%)	[REDACTED]%
Incremental cost/extra responder gained			\$ [REDACTED]
Step 2: trial evidence transformed from surrogate to life year gained (LYG)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG			\$ [REDACTED]
Step 3a: trial evidence transformed to quality adjusted life year (QALY) gained using PedsQL			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 3b: trial evidence transformed to QALY gained using UK utility study			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Note that values differ from results presented in table 3.8-3 of the submission as the results above indicate no discounting from week 0-50

Text in italics indicate values calculated during evaluation

Source: Constructed during evaluation Brineura (cerliponase alfa) Economic Evaluation .xlsx

The redacted table shows ICERS in the range of more than \$200,000/QALY.

- 6.46 The ESC was uncertain whether a [REDACTED] incremental LYG was plausible given the limited long term data and uncertainty around the method used to estimate the rate of decline in Study 901 (see paragraph 6.16).
- 6.47 Utilising the UK utility study data results in potentially implausible utility outcomes in patients treated with standard care, in which the aggregate utility for these patients over the remainder of their life in the model is negative.
- 6.48 Key univariate sensitivity analyses conducted by the submission and during the evaluation are summarised in Table 10.

Table 11: Results of univariate sensitivity analyses

Univariate analyses	Incremental costs	Incremental life year gained	Incremental QALY gain	ICER (LYG)	ICER (QALY)
Base case	\$██████	██████	██████	\$██████	\$██████
Base case with corrected discounting (no discounting in weeks 0-50)	\$██████	██████	██████	\$██████	\$██████
Survival – Nickel et al 2016 (vs Matched AUC)	\$██████	██████	██████	\$██████	\$██████
Discount rate: 0%	\$██████	██████	██████	\$██████	\$██████
Assume all patients start at ML score = 6 (baseline distributed as in Study 201/202)	\$██████	██████	██████	\$██████	\$██████
Assume patients don't stop cerliponase till death (base case stop when ML score =0) see 6.29	\$██████	██████	██████	\$██████	\$██████
Using round 20 costs for ICV and feeding tube insertion ³ (base case round 19 costs) see 6.30	\$██████	██████	██████	\$██████	\$██████
Key drivers (discussed in table 8)					
Lowering cost of cerliponase alfa by 90%	\$██████	██████	██████	\$██████	\$██████
Assume 96+ week transition to be same as standard care in both treatment arms	\$██████	██████	██████	\$██████	\$██████
Using utility values from NICE ²	\$██████	██████	██████	\$██████	\$██████

¹ Slight difference to base case due to more adverse events from longer cerliponase alfa treatment and higher disutility in cerliponase alfa treatment arm

² See Table 3.3-2, p129 of the submission.

³ Base case \$██████ and \$██████ for ICV and feeding tube insertion respectively. Round 20 estimates are \$██████ and \$██████ respectively. Cost of feeding tube based on AR-DRG G47A. *The sponsor clarified that the cost of a feeding tube should have been \$9,726 based on AR-DRG G46A.*

Text in italics indicate analyses conducted and values calculated during evaluation

Abbreviation: AUC = area under curve, ML = motor language, ICER = incremental cost effectiveness ratio, ICV = intracerebral ventricular, QALY = quality adjusted life year, LYG = life year gain

Source: Table 3.8-3, p158 of the submission, Brineura (cerliponase alfa) Economic Evaluation .xlsx

The redacted table shows ICERs in the ranges of \$105,000/LYG - \$200,000/LYG and more than \$200,000/LYG; and \$105,000/QALY - \$200,000/QALY and more than \$200,000/QALY.

6.49 The ESC considered that the base case should be informed by the utilities in the NICE model. However the ESC advised that it would be more appropriate to apply the same utility value for patients treated with cerliponase alfa and standard care in each health state (see paragraph 6.33). The ESC noted that when the utility values for cerliponase alfa from the NICE model were applied to both treatment arms, the ICER increased to more than \$200,000 per QALY gained.

- 6.50 Some of the sensitivity analyses shown in Table 10 correspond to the drivers described in Table 8 and updated Australian Refined Diagnosis Related Group (AR-DRG) costs. The undiscounted analysis shows that the economic model predicts an absolute increase in life expectancy by an additional [REDACTED] years in patients treated with cerliponase alfa compared to patients treated with standard care. Assuming that early diagnosis is possible such that all patients begin treatment at ML score = 6, leads to a marginal decrease in ICER to more than \$200,000/QALY.
- 6.51 Overall, given the high cost of cerliponase alfa, it is likely impossible to demonstrate cost-effectiveness. For example, in order to achieve an ICER of \$75,000/LYG - 105,000/LYG, [REDACTED] LYG would be required at the requested price for cerliponase alfa, or a price reduction in excess of [REDACTED] %.

Drug cost/patient/year: \$ [REDACTED]

- 6.52 The cost per patient per year was estimated to be \$ [REDACTED] based on 26 fortnightly doses of 300mg cerliponase alfa per year at \$ [REDACTED] per dose. The economic evaluation assumes only [REDACTED] % compliance, and hence a lower drug cost (\$ [REDACTED]) was applied in the economic evaluation. Treatment with cerliponase alfa is assumed to continue until patient declines to an ML score = 0 in the economic model, though the requested restriction allows patients to continue on cerliponase alfa for six months even if ML score does not improve from 0. The drug cost does not include the cost of ICV device insertion. The PBAC considered it would have been appropriate to include costs for the 6 months of treatment once a patient declines to an ML score of 0 consistent with the proposed restriction.

Estimated PBS usage & financial implications

- 6.53 This submission was not considered by DUSC. The submission takes an epidemiological approach to estimate the financial impact of listing cerliponase alfa on the PBS. The estimated financial impact is summarised in Table 11.

Table 12: Estimated use and financial implications of listing cerliponase alfa on the PBS

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of cerliponase alfa						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Copayments	\$0	\$0	\$0	\$0	\$0	\$0
Cost to PBS/RPBS less copayments	\$6█	\$█	\$█	\$█	\$█	\$█
Estimated financial implications for other drugs						
Additional Cost of coadministered drugs ^b	\$█	\$█	\$█	\$█	\$█	\$█
Reduction in standard care medication ^c	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost to PBS ^d	\$█	\$█	\$█	\$█	\$█	\$█
Net financial implications						
Net cost to PBS/RPBS	\$█7	\$█	\$█	\$█	\$█	\$█
Net cost to hospital budget ^e	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to MBS ^f	\$█	\$█	\$█	\$█	\$█	\$█
Total cost to health budget^g	\$█	\$█	\$█	\$█	\$█	\$█

^a █% compliance and 13 scripts assumed (each script contains medication for 2 fortnightly administrations) per year, for an expected 12.87 scripts per year per patient.

^bInclude loratadine, paracetamol and metoclopramide, used both as premedication and to treat adverse events

^cTotal cost for medications used to treat progressive disease related to CLN2 (Standard care) which will no longer be required due to patient not progressing as rapidly when treated with cerliponase alfa (estimated by applying rate of decline in table 6)

^dCost of cerliponase alfa plus cost of coadministered drugs and savings from reduction in progressive disease/standard care medication

^eIncludes costs for ICV device insertion and feeding tube insertion and replaced every 2 years based on round 19 costs

^fCosts for administration of cerliponase alfa and savings from reduced visits to health care professionals for disease monitoring due to less severe disease

^gNet cost to PBS/RPBS + net cost to hospital budget + net cost to MBS.

Source: Table 4.2-1, p176, Table 4.2-2, p177, Table 4.2-5, p179, Table 4.3-4, p185, Table 4.5-3, p188 of the submission

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the total cost to the health budget would be \$10 - \$20 million.

6.54 The submission underestimated the percentage of patients requiring ICV device replacement due to infection per year. In the financial estimates it was assumed that there was a █% chance of per year of needing an ICV device replacement, which is a significantly lower percentage compared to the economic evaluation which applied a █% chance (█% risk of infection every administration and █% requiring replacement) every 2 weeks, equal to █% chance per year. However changing this percentage and updating the costs for inserting an ICV device and feeding tube to Public Hospitals Cost Report Round 20 costs did not substantially increase the financial estimates (less than \$10 million per year in difference). The Pre-Sub-Committee Response (PSCR) clarified that the DRG for a feeding tube is G46A which is associated with a cost of \$9,726 instead of the value \$10,545 used in the submission.

- 6.55 The ESC noted that while the assumption of █% compliance is conservative, it does not account for the impact of ICV treatment which is likely to be significant especially for patients with low ML scores.
- 6.56 Ultimately, although the submission has accounted for cost-offsets which are likely to be delayed rather than eliminated, the ‘savings’ from these offsets are significantly smaller in magnitude compared to the drug and administration (e.g. ICV device insertion, fortnightly administration costs) costs for cerliponase alfa.
- 6.57 It should also be noted that, if cerliponase alfa increases life expectancy as claimed, the number of patients will continue to rise and will not plateau until the first incident patient discontinues treatment, which may be a significant number of years as the economic model predicts an undiscounted life year gain of █ years for patients treated with cerliponase alfa – therefore it likely, that the cost of listing cerliponase alfa will increase by approximately less than \$10 million per year (assuming approximately █ incident patients per year and less than \$10 million per year for drug costs alone), potentially all until Year █ of listing. Moreover, the cost of caring for disabled adults may also be greater than the cost of caring for disabled children, which has not been considered in the submission.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of cerliponase alfa for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease on the basis of unacceptable high cost-effectiveness at the proposed price and uncertainty that the treatment effect observed in the trial would equate to a survival benefit. The PBAC considered that the primary outcome of motor language (ML) score alone was not adequate to derive an informative model of survival benefit.
- 7.2 The PBAC acknowledged the many consumer comments received from health professionals, families and carers on behalf of patients with CLN2 disease and the correspondence from Batten Disease Support and Research Association (BDSRA) Australia and BDSRA North America. The PBAC acknowledged the high and urgent clinical need for treatments for CLN2 disease, particularly given the severity of this rare condition. The PBAC noted that in addition to symptoms relating to speech and motor function, the comments indicated that vision loss and seizures associated with CLN2 disease were equally debilitating. The PBAC noted the sponsor hearing also indicated that preservation of vision and seizure control were important to patients.
- 7.3 The PBAC considered that as all testing of TPP1 enzyme activity and CLN2 genotype sequencing in Australia is currently carried out by the National Referral Laboratory (South Australia) following referral from a hospital laboratory, there was unlikely to be

an issue of access, as patients could access testing through any hospital. Further, the PBAC noted that given the prevalence of genetic carriers for CLN2 disease, there would unlikely be a significant increase in testing if cerliponase alfa was subsidised.

- 7.4 The PBAC considered that the nominated main comparator of standard care was appropriate.
- 7.5 The PBAC noted the submission was primarily based on a 1:1 matched comparison (n=21) of the single arm Study 201 and its extension Study 202, and a natural history study (Study 901). The PBAC noted that the submission presented efficacy data from Study 201/202 up to 96 weeks to support efficacy of treatment over a life-time though follow-up for Study 201/202 was currently ongoing. The PBAC further noted that the primary outcome from Study 201/202 was a responder analysis defined by an absence of an unreversed 2-point decline or score of 0 on the Motor-Language (ML) scale score, a composite score from the motor and language domains of the adapted CLN2 disease rating scale (used in Study 201/202) which consists of 4 domains including motor, language, vision and seizures.
- 7.6 The PBAC noted the submission's claim of superior efficacy over standard care was based on a responder analysis in the 1:1 matched comparison, where a responder was defined as a patient with a rate of decline less than 2 points per 48 weeks. The PBAC noted that based on the definition of responder in the 1:1 matched comparison, █% (█/21) of the patients from Study 201/202 in the matched comparison were classified as responders compared to █% (█/21) of patients from Study 901. The PBAC considered that data from the 1:1 matched comparison was indicative of a treatment benefit of cerliponase alfa in terms of slowing progression. However, the Committee noted that based on the different definition of a responder used in Study 201/202, only 87% (20/23) of patients in Study 201/202 were classified as responders.
- 7.7 The PBAC considered the magnitude of benefit in ML score to be uncertain given the small sample size from which the treatment effect was estimated and the risk of bias in both Study 201/202 and Study 901 due to the single arm open label designs. Further, the PBAC noted that the comparability between patients in Study 901 and the Australian patient population was unknown.
- 7.8 The PBAC noted that the ML scale score consisting of only motor and language domains, does not capture the full extent of CLN2 disease severity or progression and therefore, considered the primary outcome of responder analysis based on ML score to be inadequate for providing an informative estimate of the magnitude of treatment benefit with cerliponase alfa. The PBAC noted that the progression and severity of CLN2 disease could be measured by three different four domain scales including the Hamburg rating scale (motor, language, vision, seizures), the Weill Cornell rating scale (motor, language, gait, feeding) and adapted CLN2 rating scale (an adaptation of the Hamburg rating scale). The PBAC noted that the change from baseline in adapted CLN2 clinical rating score varied significantly depending on the number of domains

included in the score. On this basis and given the significance of symptoms in addition to those of language and motor function, the PBAC considered that an outcome consisting of at least all four domains in the adapted CLN2 rating scale used in Study 201/202 would be required to inform a view on the magnitude of treatment benefit with cerliponase alfa. The PBAC noted the ESC's concerns around the methodology used to estimate the rate of decline of patients in Study 201/202 and Study 901, however, considered that more importantly, an outcome measure which reflects the full extent of CLN2 disease should be used in estimating the rate of decline. In particular, the PBAC considered there was insufficient evidence that a treatment benefit based only on ML score could be used to derive a reliable estimate of survival benefit.

- 7.9 The PBAC noted that the longer term follow up data of change in ML score from Study 201/202 presented during the sponsor hearing was supportive of the treatment effect of cerliponase alfa being maintained past 96 weeks.
- 7.10 The PBAC considered the base case ICER presented in the submission was unacceptably high at more than \$200,000 per QALY gained largely due to the cost of cerliponase alfa. The PBAC considered that given the high cost of cerliponase alfa, it would likely not be possible to demonstrate cost-effectiveness, as the ICER per QALY gained remained between the range of \$75,000/QALY - \$105,000/QALY even when the cost of cerliponase alfa was reduced by █%.
- 7.11 Further, the PBAC considered that the ICER presented in the submission was highly uncertain due to the following issues:
- The economic analysis inappropriately modelled increased survival using transition probabilities based on ML score, given ML does not capture the full extent of CLN2 disease severity and progression (see paragraph 7.7).
 - There is a lack of definitive clinical data to support that treatment with cerliponase alfa results in a survival gain. The modelled survival gain is based only on the surrogate of increased time to an ML score of 0.
 - The transition probabilities in the cerliponase alfa arm of the model are derived from a small sample size of individual patient data from Study 201/202 in the 1:1 matched comparison of Study 201/202 to Study 901. The PBAC noted the sample sizes of the individual groups of observations were combined in the submission to increase the number of observations for each transition, however noted that these groups of observations was still likely to be small.
- 7.12 The PBAC considered on the basis of the issues above, the modelled incremental LYG of █ years was highly uncertain.
- 7.13 The PBAC considered that the claim of inferior safety compared to standard care was appropriate given the administration of cerliponase alfa is via intracerebral ventricular

device. The PBAC noted that no major safety signals in the context of the severity of CLN2 disease was reported in Study 201/202 however, the long term safety of cerliponase alfa beyond 96 weeks is unknown.

7.14 The PBAC noted the submission requested that cerliponase alfa be considered for inclusion on the Life Saving Drugs Program (LSDP) if rejected by the PBAC for PBS listing. The PBAC further noted that the Commonwealth Chief Medical Officer (CMO) advises the Minister on drugs proposed to be included on the LSDP.

7.15 The PBAC considered that if cerliponase alfa was to be further considered for public subsidy, it would be relevant to obtain further information on the following:

- There are approximately [REDACTED] patients with CLN2 disease globally who are currently on treatment with cerliponase alfa. Based on this larger and more diverse patient population, a more informative model of disease progression and survival could be derived. The model should also account for all relevant baseline covariates and outcomes related to the progression of CLN2 disease given there were several outcomes measured in the trials in addition to ML score which as noted above, does not capture the full extent of CLN2 disease.
- There are currently [REDACTED] known patients with CLN2 disease in Australia of which there [REDACTED] patient who has decided not to receive treatment with cerliponase alfa. Given the severity and progressive nature of CLN2 disease and administration procedure of cerliponase alfa, it may be clinically appropriate for some patients not to receive treatment. Consultation with clinicians experienced in the management of patients with CLN2 disease would provide more clarity around the conditions which may render a patient not suitable for treatment with cerliponase alfa.

7.16 The PBAC considered that at the proposed price, the financial impact of listing cerliponase alfa of less than \$10 million in Year 1 increasing to \$10 - \$20 million in Year 6 is substantial. The PBAC agreed with the ESC that the cost-offsets claimed in the financial estimates were more likely to be delayed costs rather than true offsets given cerliponase alfa is not a cure for CLN2 disease. However, the PBAC noted that the estimated savings from these cost-offsets were not significant in the context of the costs for cerliponase alfa and its administration.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

BioMarin would like to recognise the input received from patients, families and health care professionals. BioMarin would also like to thank the PBAC for its consideration of CLN2, an ultra-rare disease affecting only 1 in 135,000 children. BioMarin looks forward to working with the Life Saving Drugs Program to make cerliponase alfa available to Australian patients with CLN2.