Fimea
Finnish Medicines Agency
23rd of February 2021

Dear Members of the Fimea Agency,

Thank you for completing the therapeutic assessment for cerliponase alfa (Brineura®) indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease in patients of all ages. BioMarin would like to comment on some points of the document:

Point	**Biomarin clarification**
p. 5, Section 2.1 "CLN2 leads to neurodegeneration, loss of nervous system function and death at approximately 10-16 years of age." p.17, Section 3.5 "CLN2 is an extremely rare incurable disease that usually leads to death between the age of 10 and 16."	The company would like to clarify that according to the bibliography, death occurs typically between the ages of 8 and 12 years. [1,2,3,4,5]
p. 5, Section 2.1 "The incidence and incidence of CLN2 are not known precisely. In Sweden, Norway and Finland, the prevalence of CLN2 is estimated to be around 0.6–0.7 per million people, al.g. not quite recent data are available."	The exact prevalence and incidence of CLN2 disease is unknown. However, CLN2 is an ultra-rare disease with extremely low prevalence in Finland. According to literature reports, the estimated incidence of CLN2, worldwide, is 0.5 per 100,000 live births.[6,7,8]
p. 5, Section 2.2 "Treatment should be continued as long as the patient benefits from it."	The treatment should be continued as long as the benefit outweighs the risk as assessed by the treating clinician.
p. 7, Section 3.1, Table 3, Studies on the efficacy and safety of cerliponase alfa	The table doesn't include study 190-203, data from latest interim analysis was presented at WORLD conference in February 2021 and poster is included in the response.
p. 17, Section 3.4, "Cerliponase alfa is administered to patients every two weeks for 144 weeks and the estimated primary end time of the study is 10/2021. The study includes five patients who are ≤ 3 years old."	Estimated primary end time for study 190-203 is 10/2022. Regarding the patients' demographics, eight patients are below 3 years old and 5 patients are below 2 years old.
p.19, Section Limited data on the efficacy and safety of cerliponase alfa ≤ 2 years of age	As mentioned in our clarification responses above, study 190-203 includes 5 patients aged below 2 years old. The interim results suggest an efficacy profile comparable to that observed in prior studies and show that cerliponase alfa is generally well-tolerated and has an acceptable safety profile in the population study, including subjects <3 years of age.[9]
p. 19, Section No information for the treatment of more serious CLN2, "The 190-201 and 190-202 studies	Study 190-201 had an inclusion criterion of ML score between 3 and 6 at screening and as described in Schulz et al.[10] all

included patients with scores of CLN2 ML assessment scale was at least 3 (in addition, 1 point for motor and linguistic scales). Efficacy or safety data are not available in patients with the more serious disease cerliponase alfa"	patients enrolled in study 190-201 had a recorded ML score of 3 or above at screening. However, between screening and 300mg baseline (see footnote to Table 1, Schulz et al.[10]), two patients' ML scores declined to a score of 2, and one patient's score declined to 1, serving to highlight the rapidly progressive nature of the disease in untreated patients.
p.20, Section 4. Costs p. 24, Section Annual care costs are high	The ex-factory price for cerliponase alfa is 19,230.77 EUR per 300mg (2x 150mg) and is exclusive of VAT. The annual cost per patient is estimated at 500.000 euros, which is the lowest public price in Europe. As stated in the responses above, CLN2 is an ultra-rare disease with a low prevalence of patients. In Sweden there is currently one identified patient in a total population of 10 million people. Norway has no identified patients; Denmark has one identified patient and has a population similar to Finland. Given the ultra-rare nature of disease, the company expects the budget impact to be extremely limited.
p.22 Section 5, Table 10, Summary of HTA assessments in other countries	We would also add to the countries listed in table 10: • Sweden: One patient is receiving cerliponase alfa treatment which is reimbursed on regional level. • Denmark: One patient receiving cerliponase alfa treatment which is reimbursed on regional level. • Scotland: Cerliponase alfa has conditional reimbursement in Scotland for 3 years as it is going through the ultra-rare evaluation pathway.
Annex 4, Ongoing investigations into cerliponase alfa	From table XX, there are two additional studies (190- 504 and 190-506) that should be added. Study 190-504 is currently recruiting participants is an observational study and aims to evaluate the long-term safety of cerliponase alfa in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease) in patients across EMA states. This study is currently recruiting participants, is an observational study and aims to evaluate the long-term safety of cerliponase alfa in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease) in Japanese patients. Regarding study NCT03862274, the aim should be clarified to state that it compares cognitive and developmental outcomes of patients with CLN2 receiving treatment to a natural history cohort.

Many thanks for taking the time to review cerliponase alfa and please let us know if there are any further questions or points of clarification that we can address.

Sincerely,

Mattias Janzen

Director, Country Manager Nordics

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[1] Nickel M SA, Jacoby D, et al. Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression in an international cohort of 137 patients. Manuscript on File. 2016.

[2] Steinfeld R, Heim P, von Gregory H, Meyer K, Ullrich K, Goebel HH, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet. 2002;112(4):347-54.

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[5] Perez-Poyato MS, Marfa MP, Abizanda IF, Rodriguez-Revenga L, Sanchez VC, Gonzalez MJ, et al. Late infantile neuronal ceroid lipofuscinosis: mutations in the CLN2 gene and clinical course in Spanish patients. J Child Neurol. 2013;28(4):470-8

[6] M. Chang JDC, B.L. Davidson, O.P. van Diggelen, M. Elleder, H.H. Goebel, A.A. Golabek, E. Kida, A. Kohlschütter, P. Lobel, S.E. Mole, A. Schulz, D.E. Sleat, M. Warburton, and K.E. Wisniewski. Chapter 7 CLN2. In: Sara Mole RW, and Hans Goebel, editor. The Neuronal Ceroid Lipofuscinoses (Batten Disease). second edition ed: Oxford University Press; 2011.

[7] Moore SJ, Buckley DJ, MacMillan A, Marshall HD, Steele L, Ray PN, et al. The clinical and genetic epidemiology of neuronal ceroid lipofuscinosis in Newfoundland. Clin Genet. 2008;74(3):213-22

[8] Williams R.E.,The Neuronal Ceroid Lipofuscinoses (Batten Disease) second edition ed: Oxford University Press; 2011. Chapter 23 Appendix 1: NCL Incidence and Prevalence Data.

[9] Schulz A., de los Reyes E., Specchio N., Gissen P., Slasor P., Bondade S., Jacoby D., Cerliponase Alfa for the Treatment of CLN2 Disease in an Expanded Patient CohortIncluding Children Younger than Three Years: Interim Results from an Ongoing Clinical Study, presented at the 17th Annual World Symposium: 8-12 February, 2021

[10] Schulz A, Ajayi T, Specchio N, et al. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. N Engl J Med. 2018;378(20):1898-1907. doi:10.1056/NEJMoa1712649