CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Level Decisional Memo

Date	April 27, 2017
From	Victor Crentsil, MD MHS FCP
Subject	Office Level Decisional Memo
BLA #	761052
Applicant Name	BioMarin Pharmaceutical Inc.
Date of Submission	May 27, 2016
PDUFA Goal Date	April 27, 2017
Proprietary Name / Established (USAN) Name	Brineura (cerliponase alfa)
Dosage Forms / Strength	Intraventricular injection 150mg/5ml (30 mg/ml) solution in a single-dose vial co-packaged with intraventricular electrolytes injection (5ml) in a single-dose vial
Applicant Proposed Indication(s)/Populations	Treatment for patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency
Recommended Action	Approval
Approved/Recommended Indication/Population(s)	Slowing the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
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DGIEP= Division of Gastroenterology and Inborn Errors Products
OND=Office of New Drugs
OB= Office of Biostatistics
OCP= Office of Clinical Pharmacology
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDRH = Center for Devices and Radiological Health
PMHS= Division of Pediatric and Maternal Health
OSE= Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brineura (cerliponase alfa), a recombinant human tripeptidyl peptidase-1 (TPP1), has been evaluated as a biologic-device combination enzyme replacement therapy (ERT) for treatment of Late Infantile Neuronal Ceroid Lipofuscinosis type 2 (CLN2 or LINCL), a rare inherited lysosomal storage disease caused by TPP1deficiency that is characterized by a progressive and fatal pediatric neurodegenerative disease. Brineura (cerliponase alfa), a zymogen (pro-enzyme) which becomes activated after lysosomal uptake to introduce normal TPP1 activity to mitigate the progression of CLN2 disease, is infused intraventricularly into cerebrospinal fluid (CSF) through a surgically implanted device.

CLN2, a form of Batten disease, is estimated to occur in 1 per 100,000 live births and there is a steady-state of about 400 to 500 patients in the United States.[1] Progressive loss of motor function is among the cardinal features of CLN2 and the decline in motor function is such that loss of voluntary movement occurs by age six, when the patients usually become unable to sit or walk without support; premature death frequently occurs in mid-adolescence.[2, 3] There is no approved disease-modifying therapeutic agent for CLN2 and current management approaches are palliative.

I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve Brineura (cerliponase alfa) for slowing the loss of ambulation in symptomatic CLN2 patients aged 3 years or older. The recommended dosage is 300 mg Brineura (cerliponase alfa) administered as an intraventricular infusion followed by intraventricular electrolytes infusion over 4.5 hours every other week. The safety and effectiveness of Brineura (cerliponase alfa) in asymptomatic CLN2 patients or patients less than 2 years of age have not been established.

An FDA Advisory Committee Meeting was not held to discuss this application because the application did not raise significant safety or efficacy concerns that were not expected for this biologic and device combination.

The data submitted to the BLA supported the efficacy and safety of Brineura (cerliponase alfa) for the proposed indication. The primary efficacy endpoint was the proportion of patients meeting the responder criterion which is the absence of an unreversed (sustained) 2 categorical units of decline or an unreversed score of zero (0) in the Motor domain of the CLN2 Clinical Rating scale over 96 weeks. In a matched analysis, the Brineura-treated patients in Studies 201/202 were matched with the untreated patients in the natural history cohort in Study 901 on baseline

[1] Geraets RD, Koh SY, Hastings ML, Kielian T, Pearce DA, Weimer JM (2016): Moving towards effective therapeutic strategies for Neuronal Ceroid Lipofuscinosis. Orphanet Journal of Rare Diseases; 11:40

[2] Williams RE, Adams HR, Blohm M, et al. (2017): Management strategies for CLN2 disease. Pediatric Neurology; 69:102-112

[3] Worgall S, Kekatpure MV, Heier L, et al. (2007): Neurological deterioration in late infantile neuronal ceroid lipofuscinosis. Neurology; 69: 521-535

motor score, age, and genotype, a responder comparison of the 17 matched pairs showed a 59% difference (95% CI: 24%, 83%) at 96 weeks in favor of Brineura.[4] The robustness of the Brineura (cerliponase alfa) treatment effect at 96 weeks was demonstrated in several other analyses in which Brineura (cerliponase alfa) favorability over absence of treatment remained; these analyses included a time-to-decline of motor score analysis, ordinal analysis of motor scores, and binary logistic regression analysis for motor scores. I concur that the observed slowing of the loss of ambulation in symptomatic CLN2 patients aged 3 years or older treated with Brineura (cerliponase alfa) was substantially in favor of Brineura (cerliponase alfa) and clinically meaningful to Late Infantile CLN2 patients and their families.

In general, treatment with Brineura (cerliponase alfa), a biologic-device combination, was well tolerated by the Late Infantile CLN2 patients. The commonly reported adverse events were pyrexia (fever), electrocardiographic (ECG) abnormalities including bradycardia, hypersensitivity, CSF protein changes and pleocytosis, vomiting, seizures, hematoma, headache, and irritability. Other important adverse events reported were hypotension, feeling jittery, and device-associated complications including infections.

The safety issues associated with Brineura (cerliponase alfa) in CLN2 patients can be adequately communicated and managed through professional labeling and routine postmarketing pharmacovigilance. Prescribers of Brineura (cerliponase alfa) will likely be practitioners with expertise or experience in the management of CLN2 disease and Brineura (cerliponase alfa) infusion will be given in settings that are able to provide the aseptic conditions required for the preparation and administration of the infusion as well as the patient monitoring during and after the infusion. Furthermore, Brineura (cerliponase alfa) infusion is contraindicated in patients with ventriculoperitoneal shunts and during acute intraventricular device-related complications including device failure and presence of infections.

A Risk Evaluation Mitigation Strategy (REMS) will not be required for ensuring that the benefit of Brineura (cerliponase alfa) outweighs its risks. A required postmarketing clinical trial will address the need for further product labeling to maintain or enhance the safe and effective use of Brineura (cerliponase alfa) in CLN2 patients, especially patients below the age of 2 years. Also, a required long-term postmarketing observational study will evaluate the immunogenic potential of Brineura (cerliponase alfa) and development of anti-drug antibodies as well as provide further assessment of device complications, and occurrence of serious hypersensitivity and cardiovascular adverse events in patients followed for a minimum of ten years. Moreover, the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales will be assessed in these studies.

[4] Brineura (cerliponase alfa) did not demonstrate an efficacy advantage in slowing motor score decline over the absence of treatment at follow-up through 48 weeks and 72 weeks

Dimension	Evidence, Uncertainties, and Conclusions
Analysis of Condition	Late Infantile Neuronal Ceroid Lipofuscinosis type 2 (CLN2 or LINCL) is a rare autosomal recessive lysosomal storage disease caused by mutations in the CLN2 gene (on chromosome 11p15), which results in deficient activity of tripeptidyl peptidase-1 (TPP1). The TPP1 deficiency in CLN2 leads to intralysosomal accumulation of storage material (ceroid) causing progressive degeneration, which predominantly affects the brain and retina. The classical late infantile type of CLN2 presents between 2 and 4 years of age, and the late onset type, which is less common, begins between 4 and 10 years of age. Although there is heterogeneity in the phenotypic presentation of CLN2 gene mutations, clinical manifestations include progressive language deterioration, seizures (which may be refractory), relentless motor decline, myoclonus (which can be sleep-interrupting), dysphagia, ataxia, cognitive and visual impairments, and behavioral disturbances.[2] While there is considerable inter- and intra-familial variability in disease severity, classical late infantile CLN2 has a predictable clinical course characterized by an unremitting functional decline.[5] Patients eventually become disabled and fully dependent for activities of daily living including dependence on gastrostomy tube for nutrition. Ultimately, CLN2 leads to developmental regression and loss of speech, voluntary motor movements, vision, ability to swallow, and cognition. Premature death, which usually occurs between 10 to 15 years of age in late infantile CLN2[6], is commonly due to cardiopulmonary failure and sepsis complicating aspiration pneumonia.[2] *Comment:* Brineura (cerliponase alfa) is being developed for replacement of the deficient TPP1 in the central nervous system (CNS) of CLN2 patients; therefore, the target population should match the prevalence of CLN2, which is estimated at 400 to 500 in the United States. The availability of Brineura (cerliponase alfa) will offer an FDA-approved therapy that may reduce the motor complications associated with the progressive neurodegeneration, which contributes to the life-threatening effects of CLN2. Since there is currently no disease-modifying therapeutic option for CLN2, Brineura (cerliponase alfa) has a potential to fill a critical and unmet need, especially if its capacity to delay motor decline of Late Infantile CLN2 patients is enduring.
Current Treatment Options	Currently, there are no therapeutic options for modifying the outcome of CLN2; disease management approaches are palliative. Experimental strategies have included ERT, gene therapy, stem cell approaches, use of small molecule carriers (e.g., nanocarriers or peptide modification that facilitate penetration of the blood-brain barrier for effective therapeutic delivery), and a number of evolving novel approaches.[1]

[5] Chang M, Cooper JD, Davidson BL, et al. CLN2. In: Mole SE, William RE, Goebel HH, eds. *The Neuronal Ceroid Lipofuscinoses (Batten Disease)*. Oxford: Oxford University Press;2011:80-109

[6] Simpson NA, Wheeler ED, Pearce DA (2014): Screening, diagnosis and epidemiology of Batten disease. Expert Opinion on Orphan Drugs, 2(9):903-910

Dimension	Evidence, Uncertainties, and Conclusions
Benefit	The efficacy of Brineura (cerliponase alfa) was established through a comparison of Brineura (cerliponase alfa)-treated CLN2 pediatric patients in Study 190-201 **[**Study 201] and its long-term extension Study 190-202 **[**Study 202] with untreated CLN2 patients from an independent natural history cohort (external control group). **Brineura Treatment Studies [Studies 201/202]** • **Study 201:** A Phase 1/2 single-arm open-label dose-escalation multicenter clinical study in which 24 CLN2 disease patients with confirmed CLN2 gene mutation and TPP-1 deficiency were enrolled and underwent surgical implantation of the intraventricular access device for a planned Brineura infusion dose-escalation scheme of 30 mg, 100 mg, and a 48-week treatment with 300 mg Brineura every other week. Twenty three (23) patients completed this study.[7] • **Study 202:** An extension study in which patients who completed the 48-week treatment in Study 190-201 were enrolled to continue their Brineura stable dose every other week. Of the 24 patients eligible for the efficacy analysis[8], two had the highest Motor plus Language CLN2 score of 6 and did not experience any functional decline; therefore, they were not included in the efficacy analysis. The 22 Brineura-treated patients included in the efficacy analysis consisted of 15 female (68%) and 7 male (32%) CLN2 patients with a mean age of 4.3 years (standard deviation: 1.2 years; range: 3 to 8 years). **Natural History CLN2 Cohort (Study 190-901)** The source population of the control group was a natural history cohort of untreated CLN2 patients whose information has been maintained in the DEM-CHILD database/registry.[9] From the CLN2 patients in the DEM-CHILD database, 42 (25 males and 17 females) untreated CLN2 patients met criteria for comparability to the 22 Studies 201/202 Brineura-treated patients. The inter-rater weighted Kappa for the Motor domain[10] of the CLN2 Clinical Rating scale was 0.88 and that of the Language

[7] One patient dropped out after one dose of 300 mg Brineura. The patient was found to have intracranial hemorrhage that may have occurred during surgery for placement of the intraventricular device.
[8] Of the 24 three- to eight-year-old Brineura-treated CLN2 patients, 96% were Caucasian and 4% Asian, 63% were female and 37% were male.
[9] Schulz A, Simonati A, Laine M, Williams R, Kohlschutter A, Nickel M (2015): The DEM-CHILD NCL Patient Database: A tool for the evaluation of therapies in neuronal ceroid lipofuscinoses (NCL). European Journal of Paediatric Neurology 19S:S16
[10] The Motor domain scores of the CLN2 Clinical Rating scale ranges from 3 (grossly normal) to 0 (profoundly impaired); sustained decline by 2 categorical units from screening or a sustained score of 0 was defined as a clinically important change.

Dimension	Evidence, Uncertainties, and Conclusions
	domain was 0.53 when the Studies 201/202 clinician ratings were compared with the Study 901 CLN2 developer ratings in the CLN2 scale comparability study. Therefore, the efficacy evaluation focused primarily on the Motor domain to ensure that a reliable outcome variable is used, so that measurement error is minimized. The primary efficacy endpoint was the proportion of patients meeting the responder criterion defined as the absence of an unreversed (sustained) 2 categorical units decline or an unreversed score of zero (0) in the Motor domain of the CLN2 Clinical Rating scale over 96 weeks. In a matched analysis, the Brineura-treated patients in Studies 201/202 were matched with the untreated natural history cohort in Study 901 on baseline motor score, age $\pm$ 3 months, and genotype; a responder comparison of the 17 matched pairs showed a 59% difference (95% CI: 24%, 83%) at 96 weeks in favor of Brineura (cerliponase alfa). The robustness of the Brineura (cerliponase alfa) treatment effect at 96 weeks was demonstrated in other analyses in which Brineura (cerliponase alfa) favorability over absence of treatment remained; these analyses included a time-to-decline of motor score analysis, ordinal analysis of motor scores, and binary logistic regression for motor scores (see below). **Other analyses:** All the analyses compared the Brineura-treated patients with the untreated patients in natural history cohort through 96 weeks follow-up • **Time-to-Decline Analysis:** A Cox proportional hazard model adjusted for screening motor score and genotype (0 key mutation [Yes/No]) was used to assess the time to unreversed (sustained) 2 categorical units decline or unreversed score of 0 in the Motor domain scores. The hazard ratio was 0.12 (95% CI: 0.015, 0.92) at 96 weeks in favor of Brineura (cerliponase alfa). • **Ordinal Analysis for Motor Score:** This analysis assumed proportional odds and the included covariates were baseline age and genotype (0 key mutation [Yes/No]). The odds ratio was 0.17 (95% CI: 0.05, 0.60) at 96 weeks in favor of Brineura (cerliponase alfa). • **Binary Logistic Regression for Motor Scores:** This analysis adjusted for screening age, screening motor score, and genotype (0 key mutation [Yes/No]), and yielded an odds ratio of 13.1 (95% CI: 1.2, 146.9)[11] at 96 weeks in favor of Brineura (cerliponase alfa). ***Comment:*** The efficacy of Brineura (cerliponase alfa) for slowing the loss of ambulation in symptomatic CLN2 patients aged 3 years or older has been established in these studies in which motor scores of Brineura-treated patients in a single-arm open-label

[11] Note: The statistical review has the inverse of this result [OR=0.08 (95% CI: 0.007, 0.86)] and the interpretation remains unchanged.

Dimension	Evidence, Uncertainties, and Conclusions
	non-randomized multicenter clinical study were compared with motor scores of untreated patients in a natural history cohort, and all the results were in favor of Brineura (cerliponase alfa).[12] However, while Brineura (cerliponase alfa) has shown efficacy for delaying progression of motor loss, its efficacy for halting progression of motor loss in CLN2 or preventing motor loss in asymptomatic CLN2 patients, especially before the typical age of onset of CLN2 (<2 years old), has not been established. Since CLN2 is specifically attributed to deficiency of TPP1, reversal or prevention of its manifestations are theoretically possible if the replacement of TPP1 is durable or treatment is begun early in the course of the disease. The experience with Studies 201/202 suggests prolonged treatment (likely beyond 96 weeks) may be necessary to assess Brineura's ability to reverse or prevent manifestations of CLN2. A formidable challenge for the prolonged treatment with Brineura (cerliponase alfa) over several years is the need for intraventricular administration and the complications associated with maintaining the infusion device for many years. For the meantime, Brineura (cerliponase alfa) may provide an effect that is important for Late Infantile CLN2 patients and their families as well as delay complications associated with immobility until other forms of disease-modifying treatments are available. Despite the limitations of use of a single-arm, open-label, non-randomized design and historical controls, alternative strategies such as a randomized placebo-controlled clinical trial or cross-over designs could present feasibility and ethical challenges for such a rare disease with a limited number of patients worldwide and the need for prolonged treatment ($\geq$ 96 weeks) in a disease which can irreversibly progress at an appreciable rate when untreated. Continued follow-up of the cohort of treated patients should be informative for the long-term safety and effectiveness of Brineura (cerliponase alfa).
Risk	The safety assessment of Brineura (cerliponase alfa) is based on data obtained from the open-label Studies 201/202. All of the 24 enrolled patients were exposed to Brineura (cerliponase alfa) for up to 107.6 weeks; the maximum duration for which any patient received the 300-mg dosage was 91 weeks. One patient withdrew from the study after one dose of the 300-mg infusion.[6] No death was reported and no adverse event has been reported to have resulted in permanent discontinuation of Brineura (cerliponase alfa). **Adverse Events:** The most frequent serious adverse events were hypersensitivity (46%), hematoma (21%), hypotension (8%), bradycardia (8%), and device-related infections (8%). Other frequent adverse events were pyrexia (71%), vomiting (63%), irritability (17%), and headaches (17%). Additional important adverse events were ECG abnormalities (71%), seizures (50%),

[12] Results of the analyses in which all 24 Brineura-treated patients were compared with the 42 natural history cohort patients were similar to those in which the 22 Brineura-treated patients were compared with the 42 natural history cohort patients.

Dimension	Evidence, Uncertainties, and Conclusions
	and CSF changes [decreased protein -71%, increased protein -21% and pleocytosis-17%]. ***Comment:*** Overall, Brineura (cerliponase alfa) [a biologic-device combination] was generally well tolerated especially given the increased risk for adverse effects in this population in which polypharmacy is common due to the need for management of multiple symptoms associated with CLN2. Since the biologic component of Brineura (cerliponase alfa) is a therapeutic protein with a potential for immunogenicity, the immune mediated events were expected. The adverse events were mild to moderate, self-limiting at times, responded to routine care and did not result in permanent treatment discontinuation. **Device-Associated Complications:** Adverse events attributable to the intraventricular infusion system include infections, device failure/malfunction, leakages, and needle-related issues. Notable infections reported in two patients were due to *propionibacterium*, which was recurrent in the affected patient, and *staphylococcus epidermidis* in another patient. Both organisms are skin commensals, and the infections resolved with antibiotic therapy and replacement of the device. ***Comment:*** The device-related complications temporarily interfered with treatment in some cases, however, after the complication was resolved, the patients were able to continue treatment with Brineura (cerliponase alfa). **Cardiovascular Adverse Events:** Two patients (8%) experienced hypotension during or after Brineura (cerliponase alfa) infusion. Electrocardiographic (ECG) abnormalities occurred in 71% of the patients and they included bradycardia, sinus tachycardia, non-specific repolarization changes, ST and T wave changes, intraventricular conduction delays, and extrasystoles. ***Comment:*** In one patient, the hypotension resolved after treatment with intravenous fluids. The other cardiovascular events resolved spontaneously. None of the events required modification of treatment with Brineura (cerliponase alfa). **Hypersensitivity Reactions:** 11 (46%) patients were reported to have experienced hypersensitivity reactions that were temporarily associated with Brineura (cerliponase alfa) infusion. Hypersensitivity presented as pyrexia (with a negative work-up for an infectious cause), vomiting, and irritability. ***Comment*:** There was no report of anaphylaxis; however, vigilance for such an occurrence and preparedness for immediate management should it occur is warranted. Routine pre-medication prior to Brineura infusion is a prudent approach to hypersensitivity risk management.

Dimension	Evidence, Uncertainties, and Conclusions
	Immunogenicity: Clinical antibody testing was performed on 24 CLN2 patients as part of Studies 201/202. Serum and CSF were evaluated for total anti-drug antibody (ADA), and serum IgE was assessed in patients suspected to have developed hypersensitivity during treatment with Brineura (cerliponase alfa). Neutralizing antibodies (Nabs) were measured only in the CSF due to the route of administration and the understanding that CNS will be the primary site of action of Brineura (cerliponase alfa). Approximately 79% of the patients had serum ADA after 49-107 weeks of treatment, and 21% had CSF ADA. Three of the patients had ADA titers of almost or above 100,000, although the titers for the other patients were low. The 15 of 24 patients who met criteria for hypersensitivity had a negative RAST test for anti- Brineura (cerliponase alfa) IgE. No Nabs were detected in CSF but the Nab assay used by the sponsor has poorly validated sensitivity, so the results are considered unreliable. ***Comment:*** Although the available data do not show immunogenicity that should preclude approval of Brineura (cerliponase alfa) for a life-threatening disease such as CLN2, the immunogenic potential of Brineura (cerliponase alfa) deserves further characterization. The negative anti-Brineura (cerliponase alfa) IgE results do not exclude a clinically significant risk for immunogenicity since a variety of scenarios can lead to false negativity. The sponsor will be required to assess development of Nabs using assays of acceptable sensitivity.
Risk Management	**Labeling:** Product labeling will include Warnings for intraventricular access device-related complications, cardiovascular adverse reactions, and hypersensitivity reactions observed during treatment of CLN2 patients with Brineura (cerliponase alfa). **Risk Mitigation:** A Risk Evaluation Mitigation Strategy (REMS) will not be required for Brineura (cerliponase alfa). **Postmarketing Required Studies** ***Pediatric Research Equity Act (PREA)*** Brineura (cerliponase alfa) has orphan product designation and is not subject to PREA provisions. ***Food and Drug Administration Amendments Act (FDAAA)*** The applicant will be required to: • Conduct an observational post approval safety study (Study 190-501) to evaluate the long-term safety of Brineura (cerliponase alfa) in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease), and further assess the occurrence of serious hypersensitivity reactions (including anaphylaxis), serious cardiovascular adverse events, and

Dimension	Evidence, Uncertainties, and Conclusions
	serious device related complications in patients followed for a minimum of ten years. In addition, this study will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales. (PMR 3207-1) • Develop and validate a cellular uptake assay with sensitivity adequate to evaluate the neutralizing capacity of anti-drug antibodies of Brineura (cerliponase alfa) detected in patient serum and CSF samples (PMR 3207-2). • Develop and validate an assay to measure the capacity of anti-drug antibodies detected in the patient serum and CSF samples to neutralize Brineura (cerliponase alfa) enzymatic activity after uptake into lysosomes (PMR 3207-3). • Conduct an immunogenicity study to evaluate the relationship between Brineura (cerliponase alfa) treatment and neutralizing anti-drug antibody (ADA) status. ADA-positive serum and CSF samples detected in Studies 190-201 and 190-202 will be re-tested with validated neutralizing antibody assays (developed in PMRs 3207-2 and 3207-3) for enzyme neutralization and cellular uptake, and patient serum and CSF samples will be collected and analyzed for immunogenicity assessment in Study 190-203. (PMR 3207-4) • Conduct a clinical trial (Study 190-203) to evaluate the short-term safety of Brineura (cerliponase alfa) in CLN2 patients below the age of 2 years. The trial will assess the risks of serious hypersensitivity reactions, and serious device related complications with short-term use. Perform a root-cause analysis on any device-related complications and/or failures including, but not limited to, an analysis of the material integrity of the intraventricular access device reservoir. In addition, this trial will evaluate the effects of serious adverse events on patient performance on the CLN2 motor and language clinical scales. (PMR 3207-5) **Postmarketing Commitments** The applicant has agreed to the following: • For patients in Studies 190-203 and 190-501, obtain a blood sample prior to cerliponase alfa treatment to determine TPP1 enzyme activity at baseline and collect the *TPP1* genotype information. Evaluate the association of enzyme activity with efficacy and safety data from PMR 3207-1 and PMR 3207-5. Derive the predicted protein function from the *TPP1* genotype for each patient, and compare efficacy and safety in patients with different *TPP1* genotypes based on their predicted protein function. In addition, perform similar analyses using a combined dataset from 4 clinical studies, including Studies 190-203, 190-501, 190-201 and 190-202. • Add cellular uptake as a release assay for drug product, Brineura (cerliponase alfa), and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested. • Develop and validate an additional identity test method for the Intraventricular Electrolytes Injection (b) (4)

Dimension	Evidence, Uncertainties, and Conclusions
	(b) (4) • Revalidate RP-HPLC and SEC-HPLC release and stability assays using impurities generated by subjecting Brineura (cerliponase alfa) to stressed stability conditions. ***Comment:*** The safety issues identified in Studies 201/202 can be adequately managed by product labeling. The required postmarketing clinical trial (Study 190-203) will further inform product labeling regarding the safe and effective use of Brineura (cerliponase alfa) in pediatric patients below the age of 2 years. Additional required studies will assess the immunogenic potential of Brineura (cerliponase alfa) and development of anti-drug antibodies. The required long-term postmarketing observational study (Study 190-501) will provide further assessment of device complications, occurrence of serious hypersensitivity and cardiovascular adverse events in patients followed for a minimum of ten years. In addition, the effect of adverse events on patient performance on the CLN2 motor and language clinical scales will be assessed in both Study 190-203 and Study 190-501. The results of these required postmarketing studies may enhance product labeling with information on the long-term safety and effectiveness of Brineura (cerliponase alfa) for Late Infantile CLN2 patients.

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/s/

VICTOR CRENTSIL
04/27/2017

JULIE G BEITZ
04/27/2017
I concur with the efficacy and safety findings discussed in this summary review, and with the recommendation to approve this application.