APPLICATION NUMBER:

761052Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<tr>
<td><strong>Application Number</strong></td>
<td>761052</td>
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<td><strong>Review Completion Date</strong></td>
<td>April 25, 2017</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>Cerliponase alfa</td>
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<td><strong>Trade Name</strong></td>
<td>Brineura™</td>
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<tr>
<td><strong>Name of Applicant</strong></td>
<td>BioMarin Pharmaceutical Inc.</td>
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<td><strong>Therapeutic Class</strong></td>
<td>Enzyme replacement therapy</td>
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<tr>
<td><strong>Formulation(s)</strong></td>
<td>150 mg/5 mL solution</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>300 mg given by intraventricular (cerebral) infusion every 2 weeks</td>
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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Brineura™ (cerliponase alfa) is necessary to ensure the benefits of this product outweigh its risks. BioMarin Pharmaceuticals (BioMarin) submitted a Biologics License Application (BLA 761052) on May 27, 2016, for cerliponase alfa with the proposed indication of treatment of late infantile neuronal ceroid lipofuscinosis (CLN2 disease). On August 29, 2016, the Agency received a major amendment to the application and subsequently extended the PDUFA goal date to April 27, 2017. Cerliponase alfa is administered by intraventricular access into the brain. The risks associated with the use of cerliponase alfa include access device-related complications and hypersensitivity. The Applicant did not submit a REMS with the application but proposed risk management activities that include the use of the labeling, long-term data collection in ongoing open label studies, and routine pharmacovigilance.

CLN2 disease is an extremely rare, serious, debilitating, progressive and ultimately fatal neurodegenerative childhood disease with no approved therapy. Cerliponase alfa showed substantial evidence of efficacy in the treatment of CLN2 and fulfills an unmet medical need. The primary serious risks observed in the supporting clinical studies are related to the intraventricular access device and include infectious complications and cerebral bleeding. Hypersensitivity reactions are an additional serious risk that will require patient monitoring. It is expected the drug will only be administered by healthcare professionals with expertise in intraventricular drug delivery, as stringent measures are necessary to prevent complications. DRISK recommends that a REMS is not necessary to ensure the benefits of cerliponase alfa outweigh the risks.

## 2 Background

### 2.1 Product Information

Brineura™ (cerliponase alfa), a new molecular entity\(^a\), is a recombinant form of human tripeptidyl peptidase 1 (TPP1), which is an enzyme deficient in patients with CLN2 disease. TPP1 is a soluble lysosomal enzyme that cleaves polypeptides that accumulate in the lysosome. Cerliponase alfa is supplied as a 150 mg/5 mL solution in single-use vials stored frozen. The recommended dose is 300 mg

\(^a\) FDAAA factor (F): Whether the drug is a new molecular entity.
administered as chronic therapy once every other week by intraventricular infusion into the brain over 4-5 hours using a surgically implanted reservoir and catheter. Cerliponase alfa received orphan product designation on April 1, 2013 and Breakthrough Therapy designation on August 27, 2015. Although cerliponase alfa is not currently approved in any other country, the European Medicines Agency (EMA) adopted a positive opinion for BioMarin’s cerliponase alfa application on April 21, 2017.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for BLA 761052 relevant to this review:

- 04/1/2013: Orphan product designation granted for the treatment of neuronal ceroid lipofuscinosis type 2
- 08/27/2015: Breakthrough Therapy designation granted for the treatment of patients with CLN2 disease
- 05/27/2016: BLA 761052 submission for the treatment of CLN2 disease received
- 07/20/2016: Multiple information requests sent to Applicant related to updating and clarifying clinical study efficacy data, natural history registry data, clinical outcome assessments, statistical analyses, and device design issues
- 08/29/2016: BLA 761052 major amendment received
- 12/16/2016: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the need for a REMS is still under review.
- 02/21/2017: A late-cycle meeting was held between the Agency and the Applicant. There was no discussion related to the need for a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Neuronal ceroid lipofuscinosis (NCL), also referred to as Batten disease, is a rare autosomal recessive neurodegenerative lysosomal storage disorder predominantly of childhood that is caused by genetic mutations within one of at least 14 different genes. The genetic heterogeneity results in different protein deficiencies, age of onset, clinical features, cell biology, and rate and characteristics of disease progression. Nearly all forms of NCL result in death and there are currently no therapies other than supportive care. c

Late infantile NCL (CLN2 disease) is caused by mutations in the tripeptidyl peptidase 1 (TPP1) gene in neurons and other cells of the body. In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate as intracellular deposits (ceroid- and lipofuscin-like pigments) in

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b FDAAA factor (D): The expected or actual duration of treatment with the drug.
c FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
many organs, and accumulation in the central nervous system (CNS) leads to neuronal cell death and the neuro-degenerative pathophysiology. CLN2 has an age of onset between 2-4 years and is typically characterized by language delay, speech degeneration, seizures, movement disorders, progressive motor decline, blindness, cognitive decline, and dementia. Death typically occurs in mid-childhood. The estimated incidence of CLN2 is 0.5-1/100,000 live births per year and the U.S. prevalence is estimated to range from 400 to 500 patients.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no approved treatments for CLN2. Current disease management is supportive and aims to provide seizure control and maintain the patient's quality of life. Physical therapy, occupational therapy, and speech therapy as well as other palliative care should be initiated early.

4 Benefit Assessment

The clinical study (Study 190-201) supporting this application is a single-group, Phase 1/2, open-label, dose escalation study in 24 patients aged 3-8 years with mild-moderate CLN2 as defined by a combined motor-language scoring system. Patients received cerliponase alfa 300 mg administered every other week for 48 weeks. Patients who completed treatment in 190-201 could enroll in an open-label extension study (Study 190-202) and receive treatment for up to 240 weeks. Efficacy and safety of cerliponase alfa were compared with 42 untreated patients from the DEM-CHILD® natural history registry (Study 190-901). Patients were assessed for efficacy at 48, 72, and 96 weeks. The primary efficacy endpoint was based on a responder analysis using the motor domain score of the Hamburg University CLN2 clinical rating scale to assess disease progression on a 0 to 3-point scale. Possible scores ranged from 3 (grossly normal) to 0 (profoundly impaired). A non-responder was defined as a patient whose score declined to 0, or who had a sustained decline of 2 points.

Of 22 patients treated with cerliponase alfa who were evaluated for efficacy at Week 96, 21 (95%) did not experience a 2-point decline or a decline to 0 in the motor domain score, compared with 21 (50%) of 42 untreated patients in the natural history registry.

An evaluation of 17 matched pairs from Study 201/202 and Study 901 found 16 of 17 (94%) patients in the treatment group were responders at Week 48 compared with 13 of 17 (76%) natural history patients, for a response rate difference of 18% [95% CI (-19, 51)]. At Week 96, 16 of 17 (94%) patients in the treatment group remained responders whereas 6 of 17 (35%) natural history patients were responders, for a response rate difference of 59% [95% CI (24, 83)].

The clinical team concluded that substantial evidence of efficacy has been demonstrated for the use of cerliponase alfa to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with CLN2.

d FDAAA factor (A): The estimated size of the population likely to use the drug involved.

e DEM-CHILD® is a multinational research project of NCL disorders as a major cause of dementia in childhood (http://www.dem-child.eu/index.php/background-16.html).

f FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
5 Risk Assessment & Safe-Use Conditions

The safety population is comprised of 24 subjects in Studies 201/202 treated with cerliponase alfa for up to 108 weeks of treatment every other week.

5.1 Serious Adverse Events

No deaths were reported during the study. A total of 45 serious adverse events (SAEs) were reported in 19 (79%) patients during the total dosing period. Infections were the most commonly reported SAE category, with 17 infections reported in 12 patients. There were two serious device-related bacterial infections (Propionibacterium; Staphylococcus epidermidis) in two patients detected by CSF monitoring. The infections resolved after removal and replacement of the device and treatment with antibiotics. There were no adverse events of meningitis. In addition, there were 15 non-CNS serious infections, of which bacterial pharyngitis (n=3) and gastroenteritis (n=2) were the most frequently reported events.

Two patients experienced SAEs of CNS bleeding. One adverse event involved an intracranial hemorrhage that occurred at the time of surgery for placement of the intracranial access device. The patient improved symptomatically and was discharged three days after surgery; a follow-up MRI one week later showed a small amount of hemorrhage and edema in the frontal lobe along the shunt track. The second patient experienced a subdural hematoma that was identified on routine MRI approximately 6 months after the patient had entered the cerliponase alfa stable dosing period. The patient was asymptomatic, received no treatment for the event and continued to receive cerliponase alfa. The hematoma was reported to have resolved.

5.2 Hypersensitivity

Hypersensitivity reactions were reported in 11 of 24 patients (46%) treated with cerliponase alfa during or within 24 hours after completion of the infusion, despite pre-medication with antihistamines with or without antipyretics or corticosteroids. Common symptoms included fever, vomiting, and irritability.

Two patients experienced hypersensitivity reactions that could be broadly assessed as possible anaphylaxis using the Sampson criteria. The first patient (who was enrolled in an expanded access protocol) developed hypoxia 8 hours after completion of the infusion followed 7 hours later by a low mean arterial pressure. The patient received oxygen and intravenous fluids and recovered. The second patient experienced hypoxia and decreased diastolic blood pressure 45 minutes after the start of the infusion. The patient was repositioned, received oxygen, and recovered while the infusion continued.

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6 Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

h FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Reference ID: 4089205
5.3 Device-related Adverse Reactions

In addition to the serious device-related infections and CNS bleeding events described in Section 5.1 above, other device-related adverse events included needle issues (such as needle dislodgement), CSF pleocytosis, device leakage, device migration, hematoma, and other events. Overall, adverse reactions related to the device were observed in 12 of 24 (50%) of patients.

Additionally, there is potential for damage to the access device reservoir membrane over time due to repeated punctures for administration of the infusion, which could lead to device leakage, infection, or other problems. Based on the results of a material degradation study provided by the Applicant, the Agency determined that degradation of the access device membrane may occur after approximately 105 perforations (4 years of regular administration of drug) and require device replacement.

6 Expected Postmarket Use

Cerliponase alfa is likely to be prescribed at specialty centers by pediatric neurologists and medical geneticists who are involved in the care of patients with CLN2. It is expected that cerliponase alfa will be infused at specialized outpatient facilities that have the experience and capacity to administer intraventricular therapy. Infusions may also be administered in the hospital setting. Although the physician is the healthcare professional usually responsible for injecting drugs into a CSF access device, specially trained nursing personnel may also perform the procedure depending on local facility policy and state nursing law. The duration of the infusion and monitoring will likely be managed by nursing personnel with appropriate privileges to do so per their institution.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS with the application but proposed risk management activities that include the use of the labeling, long-term data collection in ongoing open label studies, and routine pharmacovigilance.

8 Discussion of Need for a REMS

CLN2 disease is an extremely rare, serious, debilitating, progressive and ultimately fatal neurodegenerative disease of children with no treatment options other than symptomatic and supportive care.

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1 The Applicant recently published a literature review of intracerebroventricular drug delivery. Ninety-seven publications with adequate data were identified. Although only eight publications provided details about the setting where therapies were administered, all specifically stated patients were treated in an outpatient center (Cohen-Pfeffer JL, et al. Intracerebroventricular delivery as a safe, long-term route of drug administration. Pediatr Neurol 2017; 67:23-35).
The open-label study and extension found there were more responders in the group of patients who received cerliponase alfa compared with the matched natural history control group, based on slowing the loss of ambulation.

The potential serious adverse events associated with the access device include infections and other complications such as CNS bleeding. The labeling will include recommendations for routine CSF culture with each infusion to test for subclinical infection, as well as recommendations related to the lifespan of the device and its replacement schedule. Risks such as CNS hemorrhage or subdural hematoma are inherent risks related to the device itself. Hypersensitivity reactions, which include possible anaphylaxis, are also risks associated with the drug. Therefore, the labeling will include a warning and precaution for hypersensitivity, with recommendations for the use of antihistamines with or without antipyretics and corticosteroids prior to the start of infusion, as well as the need for appropriate medical support and management if anaphylaxis occurs. The labeling will also include a warning and precaution for patient monitoring in a healthcare setting before and during the infusion, and post-infusion as clinically indicated.

It is expected that cerliponase alfa will be administered by healthcare professionals with expertise in intraventricular drug delivery, as stringent measures are necessary to prevent complications associated with this method of administration. As intraventricular drug administration has been used for many years to treat pediatric and adult patients for malignancies, infections, or intractable pain for a range of CNS conditions, there are healthcare professionals well-versed in this route of drug administration. BioMarin submitted a use-risk analysis of the steps involved in using cerliponase alfa to the cerliponase alfa IND (122472) on August 28, 2015, and the Applicant asserted the residual risks are acceptable. After review of that analysis, the Division of Medication Error Prevention and Analysis concluded a Human Factors study was not necessary. Additionally, the CDRH Office of Device Evaluation evaluated the safety of the access device and determined the device is acceptable to use up through approximately 105 perforations or 4 years of chronic use. The need to replace the device at that time will be addressed by a warning and precaution in the label.

Based on the observed benefit of cerliponase alfa, the progressive and fatal nature of the disease, the unmet medical need, and the expectation that cerliponase alfa will only be administered by physicians and healthcare providers with the necessary technical expertise, DRISK is not recommending a REMS for the management of the potential risks of cerliponase alfa therapy.

9 Conclusion & Recommendations

Based on the available information a REMS is not necessary to ensure the benefits of cerliponase alfa outweigh the risks. CLN2 disease is treated at specialty centers by pediatric neurologists and medical geneticists who specialize in the care of patients with CLN2. Intraventricular drug delivery is an established method of administration and has been used for many years for the treatment of other CNS conditions. Although cerliponase alfa may be administered more frequently than other drugs

\[\text{IND 122472, Cerliponase, Type C Meeting Minutes, October 28, 2015.}\]
administered by the intraventricular route, the Applicant's material degradation study demonstrates that the device can be accessed at the dosing frequency for approximately 4 years before necessitating replacement.

Should DGIEP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:

- Cerliponase alfa IND 122472 Type C Meeting Minutes, October 28, 2015.
- BioMarin. Clinical Overview for cerliponase alfa, BLA 761052 (Serial 003), June 27, 2016.
- Center Director Briefing Slides, BLA 761052, December 15, 2016.
- Center Director Briefing Slides, BLA 761052, January 27, 2017.
- BioMarin. Response to Request for Information, BLA 761052 (Serial 120), March 27, 2017.
11 Appendices

11.1 REFERENCES


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/s/

ROBERT G PRATT
04/25/2017

JAMIE C WILKINS PARKER
04/25/2017