

European Commission Approves Brineura™ (cerliponase alfa), the First Treatment for CLN2 Disease, a Form of Batten Disease and Ultra-Rare Brain Disorder in Children

Dosing includes all ages from birth for this fatal and rapid pediatric neurodegenerative condition

Brineura is among first therapies to go through European Medicine Agency's new accelerated assessment process

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BioMarin Pharmaceutical Inc. →

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SAN RAFAEL, Calif., June 1, 2017 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq: BMRN) today announced the European Commission (EC) has granted marketing authorization for Brineura™ (cerliponase alfa), the first treatment approved in the European Union for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. The dosing administration includes all ages from birth.

On April 21, 2017, the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), adopted a positive opinion for the company's Marketing Authorization Application (MAA) for Brineura™ (cerliponase alfa) following an accelerated review procedure, reserved for medicinal products expected to be of major public health interest. The EMA revised process for accelerated assessment came into effect June 1, 2016. Brineura is one of the first therapies to go through this process.

CLN2 disease is an ultra-rare, rapidly progressive fatal brain condition, which affects an estimated 1,200 to 1,600 children worldwide, many of whom are undiagnosed. These affected children completely lose the ability to walk and talk around 6 years of age. During the later stages of the disease, feeding and tending to everyday needs become very difficult with death usually occurring between 8 and 12 years of age.

"Today represents several important milestones for the medical and patient communities, and also for me, both professionally and personally. For the first time since entering this field nearly 15 years ago, I can now tell families affected by CLN2 disease that there is a meaningful treatment that may help their child, and provide hope," said Angela Schulz, M.D. Ph.D., Department of Paediatrics, Children's Hospital, University Medical Center Hamburg-Eppendorf and principal investigator of the Brineura studies. "We are committed to furthering the study of Brineura and believe that the medical knowledge gained from the Brineura studies can help us learn more about treating other neurodegenerative diseases."

Brineura, an enzyme replacement therapy, is the first to be directly administered to the brain, treating the underlying cause of the condition by helping replace the deficient TPP1 enzyme. Using an established route of administration most often used in oncology – intracerebroventricular administration– the therapy is delivered directly into fluid surrounding the brain, known as the cerebrospinal fluid.

"Thank you to the European Commission for recognizing the medical benefits of Brineura for children affected by CLN2 disease. We are also grateful to the families and study investigators and their teams, who dedicated their time to the clinical program to make this treatment a reality for affected children in the EU," said Jean-Jacques Bienaimé, Chairman and Chief Executive Officer of BioMarin. "The physicians and patient families that form the Batten disease community have been integral to the approval of this treatment. We are also working to reduce the diagnostic journey for patients, who are often not diagnosed until the age of five, nearly two years after their first seizure. With a treatment now available, accelerating early diagnosis will be critical."

In Europe, BioMarin supports programs for molecular and enzymatic diagnosis of CLN2 disease, including the early use of gene panels with the goal of helping reduce the average age of CLN2 diagnosis.

On Apr. 27, 2017 the U.S. Food and Drug Administration (FDA) approved Brineura™ to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Clinical Trial Results

The Brineura Marketing Authorization Application (MAA) was based on an open-label, dose-escalation study for Brineura in 24 patients with CLN2 disease between 3 and 8 years of age, as well as an open-label extension study. The primary objectives were to evaluate the safety and tolerability of intracerebroventricular-administered Brineura and to evaluate effectiveness using a CLN2 disease-specific rating scale score in comparison with natural history data after 48 and 72 weeks of treatment.

The clinical study has shown that at 48 weeks, 87 percent or 20 of the 23 children who completed the trial did not decline in motor and language score. In the study, the mean rate of decline in patients treated with Brineura at 300 mg. every other week was 0.40 points per 48 weeks. When compared to the expected rate of decline based on the natural history, the study results are statistically significant ($p < 0.0001$). The observed treatment effect was considered clinically meaningful in light of the natural history of untreated CLN2 disease. In the ongoing study as of June 3, 2016, the rate of decline in patients treated with Brineura compared to the natural history control group (N=42 patients) continues to show durability of the treatment effect.

In the clinical study, intraventricular access device-related infections were observed in two patients. In each case, antibiotics were administered, the intraventricular access device was replaced and the patient continued on Brineura treatment.

Hypersensitivity reactions have been reported in 14 (58%) Brineura treated patients during the clinical studies. The most common adverse reactions are convulsions, pyrexia, decreased cerebrospinal fluid (CSF) protein, ECG abnormalities, vomiting, upper respiratory tract infection, hypersensitivity, irritability, increased CSF protein, headache, needle issue and CSF pleocytosis.

About CLN2 Disease

Children with CLN2 disease typically begin experiencing seizures between the ages of 2 and 4 years old, preceded in the majority of cases by language development delay. The disease progresses rapidly with most affected children losing the ability to walk and talk by approximately 6 years of age. Initial symptoms are followed by movement disorders, motor deterioration, dementia, blindness, and death usually occurring between the ages of 8 and 12 years of age. During the later stages of the disease, feeding and tending to everyday needs become very difficult. BioMarin estimates the incidence of CLN2 disease is approximately one in 200,000 with up to 1,200 to 1,600 children in the regions of the world where BioMarin operates, many of whom are undiagnosed.

The neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of lysosomal storage disorders that includes the autosomal recessive neurodegenerative disorder CLN2 disease. CLN2 disease is caused by mutations in the TPP1 gene resulting in deficient activity of the enzyme tripeptidyl peptidase 1 (TPP1). In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate in many organs, particularly in the brain and retina. Buildup of these storage materials in the cells of the nervous system contributes to the progressive and relentless neurodegeneration which manifests as loss of cognitive, motor, and visual functions.

About Brineura

Brineura is a recombinant form of human tripeptidyl peptidase 1 (TPP1), the enzyme deficient in patients with CLN2 disease. It is an enzyme replacement therapy designed to restore TPP1 enzyme activity and break down the storage materials that cause CLN2 disease. In order to reach the cells of the brain and central nervous system, the treatment is delivered directly into the fluid surrounding the brain (cerebrospinal fluid) using BioMarin's patented technology.

Brineura administered via intracerebroventricular infusion every other week was well tolerated, and no patients discontinued treatment due to adverse events (AEs). Most AEs were Grade 1 or 2, and the majority are consistent with severe, chronic neurologic disease in pediatric patients. The most common events associated with treatment included: pyrexia, hypersensitivity, seizure, epilepsy, vomiting and headache. In Europe, dosing for children under two has been estimated based on brain mass. Limited data are available for children aged 2 years, and no clinical data is available in children below 2 years of age. While safety and efficacy of Brineura in children less than 3 years of age has not yet been established, BioMarin is conducting a study in this patient population.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for patients with serious and life-threatening rare and ultra-rare genetic diseases. The Company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.BioMarin.com.

Forward-Looking Statement

This press release contains forward-looking statements, including, without limitation, statements regarding the potential benefits and commercial availability of Brineura™ (cerliponase alfa). These forward-looking statements are based on the Company's current beliefs and expectations and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others, risks related to: uncertainties inherent in research and development, including unfavorable new clinical data and additional analyses of existing clinical data; the commercialization of Brineura; the Company's ability to manufacture sufficient quantities of Brineura for clinical trials and the commercial launch of Brineura; the market potential for Brineura as a treatment for CLN2 disease; competitive developments; and those other risks detailed from time to time under the

caption "Risk Factors" and elsewhere in the Company's Securities and Exchange Commission (SEC) filings, including the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, and future filings and reports by the Company. The Company undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information, future events or changes in its expectations.

BioMarin® is a registered trademark and Brineura™ is a trademark of BioMarin Pharmaceutical Inc.

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