Japanese Regulatory Authority, MHLW Approved Brineura (cerliponase alfa) for the Treatment of CLN2 Disease, Ultra-Rare Pediatric Neurodegenerative Disorder in Children

BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) announced that the Ministry of Health, Labor and Welfare (MHLW) in Japan approved Brineura (cerliponase alfa) on September 20, 2019 in patients with ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. Brineura is the first CNS enzyme replacement therapy approved to treat children with CLN2 disease, a form of Batten disease.

CLN2 disease is an ultra-rare, rapidly progressive fatal brain condition. 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 often occurring at early teenage.

In clinical trials, Brineura, an enzyme replacement therapy, was shown to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with CLN2 disease. It is the first enzyme replacement therapy to be directly administered to the brain, treating the underlying cause of the condition by replacing the deficient TPP1 enzyme. Using an established technique most often used in oncology – intraventricular administration– the therapy is delivered directly into CSF fluid surrounding the brain, known as the cerebrospinal fluid.

“CNL2 is a devastating disorder that robs families of life with their children much too young,” said Yoshikatsu Eto M.D. Ph.D., Director, Advanced Clinical Research Center & Institute for The Treatment of Genetic Diseases, Southern Tohoku Research Institute for Neuroscience and Emeritus Prof. of Tokyo Jikei University. “The approval of Brineura brings a treatment option to children and their families with CLN2 where there was no treatment before.”

Brineura is now available in Japan. BioMarin will begin the promotion of Brineura immediately.

IMPORTANT SAFETY INFORMATION FROM THE U.S. PRESCRIBING INFORMATION

Indication

Brineura® (cerliponase alfa) injection for intraventricular use is indicated 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.

Important Safety Information

Brineura is contraindicated in patients with any sign or symptom of acute, unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or suspected or confirmed CNS infection (e.g. cloudy CSF or positive CSF gram stain, or meningitis), any acute intraventricular access device-related complications (e.g., leakage, extravasation of fluid, or device failure), and with ventriculoperitoneal shunts.

Brineura must only be administered via the intraventricular route using aseptic technique to reduce the risk of infection. Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage, failure or potential infection. Brineura is contraindicated if there are acute intraventricular access device-related complications (e.g., leakage, extravasation of fluid, device failure, or bulging of the scalp around or above the intraventricular access device); or sign or symptom of acute, unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or suspected or confirmed CNS infection (e.g. cloudy CSF or positive CSF gram stain, or meningitis). Consultation with a neurosurgeon may be needed to confirm the integrity of the device. In case of intraventricular access device complications, discontinue the Brineura infusion and refer to the device manufacturer’s labeling for further instructions. Prior to each infusion of Brineura and when clinically indicated, send cerebrospinal fluid (CSF) samples for testing of cell count and culture.

Material degradation of the intraventricular access device reservoir was reported after approximately 4 years of administration, which may impact the effective and safe use of the device. During benchtop testing such material degradation was recognized after approximately 105 perforations of the intraventricular access device. The intraventricular access device should be replaced prior to 4 years of single-puncture administrations, which equates to approximately 105 administrations of Brineura.

Monitor vital signs before infusion starts, periodically during infusion, and post-infusion in a healthcare setting. Perform electrocardiogram (ECG) monitoring during infusion in patients with a history of bradycardia, conduction disorder, or with structural heart disease. In patients without cardiac abnormalities, regular 12-lead ECG evaluations should be performed every 6 months.

Hypotension was reported in 2 patients during or up to 8 hours after Brineura infusion. Patients did not require alteration in treatment, and reactions resolved spontaneously or after intravenous fluid administration.

One patient experienced hypoxia 8 hours after Brineura infusion, followed by a low mean arterial pressure at 15 hours post infusion. Symptoms resolved after oxygen administration, airway repositioning, and normal saline infusion. One patient reported decreased oxygen saturation, 45 minutes after starting Brineura, with associated low diastolic blood pressures. Hypoxia resolved after oxygen administration. No treatment was administered for the low diastolic blood pressure, which returned to normal while the patient continued to receive Brineura infusion without change to the infusion rate or dose.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when Brineura is administered. If anaphylaxis occurs, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion.

Hypersensitivity reactions were reported in 11 patients during or within 24 hours after completion of the Brineura infusion. The signs and symptoms observed concomitantly with hypersensitivity reactions include pyrexia, vomiting, pleocytosis, or irritability. Patients were routinely pre-medicated with antihistamines with or without antipyretics or corticosteroids, prior to infusion of Brineura.

The management of hypersensitivity reactions should be based on the severity of the reaction and may include temporarily interrupting the infusion, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. If a severe hypersensitivity reaction occurs, immediately discontinue the infusion and initiate appropriate medical treatment.

Brineura has not been studied in pregnancy or lactation.

Safety and effectiveness in pediatric patients below 3 years of age have not been established.

In clinical trials, the most frequently reported adverse reactions (≥8%) were pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and

hypotension.

Seizures were reported in 12 patients and included atonic, generalized tonic-clonic, focal, and absence. Seizures were managed with standard anticonvulsive therapies and did not result in discontinuation of Brineura treatment.

In clinical studies with Brineura, device-related adverse reactions were reported in 12 patients and included infection, delivery system–related complications, and pleocytosis. Intraventricular access device-related CNS infections were observed in 2 patients; antibiotics were administered, the intraventricular access device was replaced, and treatment continued. Device-related complications did not result in discontinuation of Brineura treatment. Other device-related adverse reactions included 1 patient with leakage of the intraventricular access device and 1 with pleocytosis.

Hematoma adverse reactions were reported in 5 patients and presented as hematoma, post procedural hematoma, traumatic hematoma, and subdural hematoma. Hematomas did not require treatment and did not interfere with Brineura infusion.

Anti-drug antibodies (ADAs) were detected in serum (79%) and CSF (33.3%) in patients treated with Brineura. No association was found between serum or CSF ADA titers and incidence or severity of hypersensitivity.

Intraventricular access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura. The signs and symptoms of infections may not be readily apparent in patients with CLN2 disease. Healthcare providers should be vigilant for the development of signs and symptoms of infection, including meningitis. In clinical studies, antibiotics were administered, the intraventricular access device was replaced, and the patient continued on Brineura treatment.

Inform caregivers of the signs and symptoms of anaphylaxis, hypotension, bradycardia, and device-related complications and meningitis. Instruct them to seek immediate medical care should any of these signs and symptoms occur.

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088, or go to www.fda.gov/medwatch.

Please see accompanying full Prescribing Information (here), or visit www.Brineura.com.

DISEASES

Lysosomal Storage Disorders (MPS I, MPS IVA, MPS VI, CLN2 disease) PKU, LEMS

PRODUCTS

PALYNZIQ®
Brineura®
Vimizim®
Kuvan®
Naglazyme®
Aldurazyme®
Firdapse®

PATIENT/PHYSICIAN SUPPORT CONTACT INFORMATION

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