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.

**CLN2 disease progresses rapidly. Diagnose earlier to treat sooner.**

Brineura, an enzyme replacement, is the first and only product to treat CLN2 disease, a form of Batten disease.

Please see Important Safety Information inside.
Brineura® (cerliponase alfa) helps replace the deficient TPP1 enzyme in children with CLN2 disease.

**Brineura was assessed over 96 weeks in a nonrandomized, single-arm study with extension vs a natural history cohort**

- 24 patients, aged 3 to 8 years, were treated with 300 mg of Brineura every other week for 48 weeks and continued to receive treatment during the extension period
  - Brineura-treated patients were compared to an independent natural history cohort that included 42 patients who satisfied inclusion criteria for the clinical study
- The study was designed to assess disease progression using the CLN2 Clinical Rating Scale, which includes a Motor and a Language domain, each with a 0-to-3 score representing a range of function and with each score representing a range of function (6 is the highest possible combined score)
  - Patients were evaluated for efficacy if they had a combined Motor plus Language CLN2 score of < 6 at screening
- In this study, only the Motor domain was used to measure Brineura efficacy. With the Motor domain, 3 indicates normal motor function and 0 indicates immobility
  - Due to the inability to establish comparability for the Language domain ratings between the clinical study with extension and the natural history cohort, efficacy of Brineura for the Language domain cannot be established

**95% of Brineura patients did not show Decline on the Motor domain vs 50% in the natural history cohort**

**Decline** was defined as a sustained 2-point loss or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.

- The only Brineura-treated patient deemed to have Decline withdrew from the study after 1 infusion due to inability to continue with study procedures
- Ten Brineura-treated patients experienced 1-point loss on the Motor domain of the CLN2 Clinical Rating Scale while on the 300 mg dose

Brineura is contraindicated in patients with acute intraventricular access device–related complications (eg, leakage, device failure, or device-related infection) or ventriculoperitoneal shunts. Cardiovascular and hypersensitivity reactions related to Brineura may occur.
BRINEURA WAS GENERALLY WELL TOLERATED

The safety of Brineura was evaluated in 24 patients with CLN2 disease who received at least 1 dose of Brineura in a clinical study with extension of up to 161 weeks.4

Adverse reactions reported in ≥8% of patients treated with Brineura at week 964:

- Pyrexia
- ECG abnormalities
- Decreased CSF protein
- Vomiting
- Seizures
- Hypersensitivity
- Increased CSF protein
- Hematoma
- Headache
- Irritability
- Pleocytosis
- Device-related infection
- Bradycardia
- Feeling jittery
- Hypotension

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

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.

TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT:

BioMarin Pharmaceutical Inc. 
Phone: 1-866-906-6100 
Email: drugsafety@BMRN.com

FDA
Phone: 1-800-FDA-1088
Web: www.fda.gov/medwatch

FOR MEDICAL INFORMATION INQUIRIES:

Email: medinfo@BMRN.com
Phone: 1-800-983-4587
Fax: 1-866-524-0038

For any additional information about Brineura, please visit Brineura.com/HCP

Inform caregivers of the signs and symptoms of anaphylaxis, hypotension, bradycardia, and device-related complications. Instruct them to seek immediate medical care should any of these signs and symptoms occur.
This rare, progressive pediatric disease is\textsuperscript{1,2}:

A NEURODEGENERATIVE disorder caused by enzyme deficiency\textsuperscript{1}

- An autosomal recessive lysosomal storage disorder caused by pathogenic variants (mutations) in the \textit{TPP1} gene (also referred to as the \textit{CLN2} gene)\textsuperscript{1,3}
- Results in absence of or reduced activity of the tripeptidyl peptidase 1 (TPP1) enzyme\textsuperscript{1}
  - This enzyme deficiency is associated with accumulation of lysosomal storage materials leading to neuronal dysfunction and cell death\textsuperscript{4,5}
- Molecular or enzymatic genetic testing can be diagnostic\textsuperscript{6}

Associated with a PREDICTABLE and RAPID decline in function

- Classically presents with a late-infantile onset\textsuperscript{3}
- As the disease progresses, children commonly experience a complete loss of cognitive abilities, motor function, vision, and premature death\textsuperscript{3}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{disease_progression.png}
\caption{Watch for the early, nonspecific signs of CLN2 disease\textsuperscript{1,3,7-10}}
\end{figure}

\textbf{DISEASE PROGRESSION}

\begin{itemize}
  \item \textbf{1 TO 3 YEARS} Language development delay
  \item \textbf{2 TO 4 YEARS} New onset, unprovoked seizures
  \item \textbf{3 TO 4 YEARS} Ataxia
  \item \textbf{4 TO 5 YEARS} Drug resistant seizures
  \item \textbf{5 TO 6 YEARS} Wheelchair dependent/bedridden
  \item \textbf{7 TO 8 YEARS} Blindness
  \item \textbf{8 TO 12 YEARS} Premature death
\end{itemize}

\textit{ON AVERAGE, THERE'S A 2-YEAR DELAY FROM FIRST SEIZURE TO DIAGNOSIS}\textsuperscript{11,*}

\textit{*Average age at first seizure: 3 years, average age at diagnosis: 5 years.}

\textbf{Act now if you see these early, nonspecific symptoms—rule out or confirm a CLN2 disease diagnosis with genetic testing}
**IMPORTANT SAFETY 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 acute intraventricular access device-related complications and with ventriculoperitoneal shunts.

Brineura must only be administered via the intraventricular route and using aseptic technique to reduce the risk of infection. Healthcare professionals should inspect the scalp for skin integrity to ensure the intraventricular access device is not compromised prior to each infusion. Brineura is contraindicated if there are signs of acute intraventricular access device-related complications (e.g., leakage, device failure or signs of device-related infection such as swelling, erythema of the scalp, extravasation of fluid, or bulging of the scalp around or above the intraventricular access device). In case of intraventricular access device complications, discontinue the Brineura infusion and refer to the manufacturer’s labeling for further instructions. Routinely send cerebrospinal fluid (CSF) samples for testing to detect subclinical device infections.

Material degradation of the intraventricular access device reservoir may occur after approximately 105 perforations of the intraventricular access device and may require replacement as soon as, or prior to, 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 occurred 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 pressure. 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 premedicated 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, CSF protein decreased, vomiting, seizures, hypersensitivity, CSF protein increased, 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.

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. In both cases, 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.

Inform caregivers of the signs and symptoms of anaphylaxis, hypotension, bradycardia, and device-related complications. 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, or visit www.Brineura.com.
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.

Recognize early, nonspecific signs and symptoms of CLN2 disease

New-onset, unprovoked seizures, plus ANY of the following:

- Language development delay
- Motor disturbances (ataxia)
- Abnormal EEG: PPR with low-frequency (1-2 Hz) IPS
- Abnormal MRI (cerebellar atrophy or periventricular white matter hyperintensities)

Shorten the diagnostic journey with early genetic testing