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.

Brineura® (cerliponase alfa)

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

EARLY DIAGNOSIS IS CRITICAL FOR CHILDREN WITH CLN2 DISEASE

This rare, progressive pediatric disease is[1,2]:

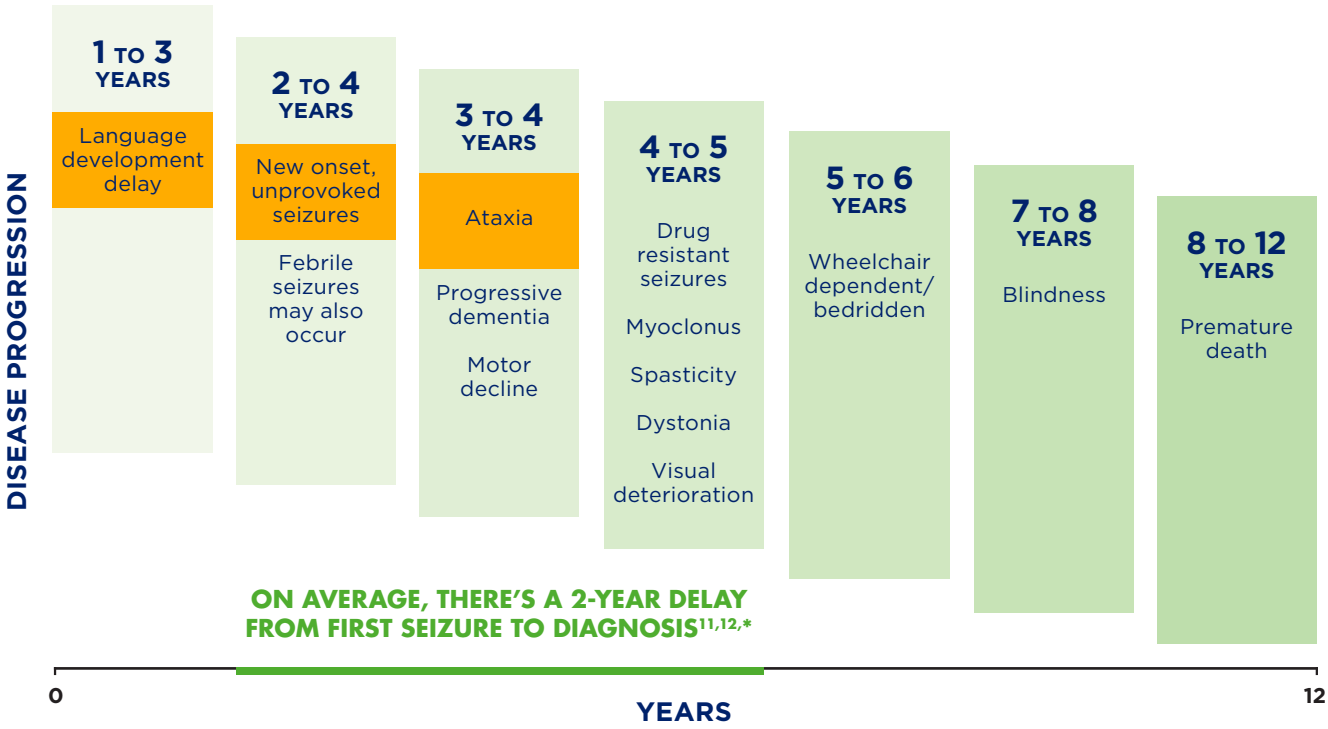
A NEURODEGENERATIVE disorder caused by enzyme deficiency[1]

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

Associated with a PREDICTABLE and RAPID decline in function

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

WATCH FOR THE EARLY, NONSPECIFIC SIGNS OF CLN2 DISEASE[1,3,7-10]



*Average age at first seizure: 3 years; average age at diagnosis: 5 years.

Act now if you see these early, nonspecific symptoms—rule out or confirm a CLN2 disease diagnosis with genetic testing

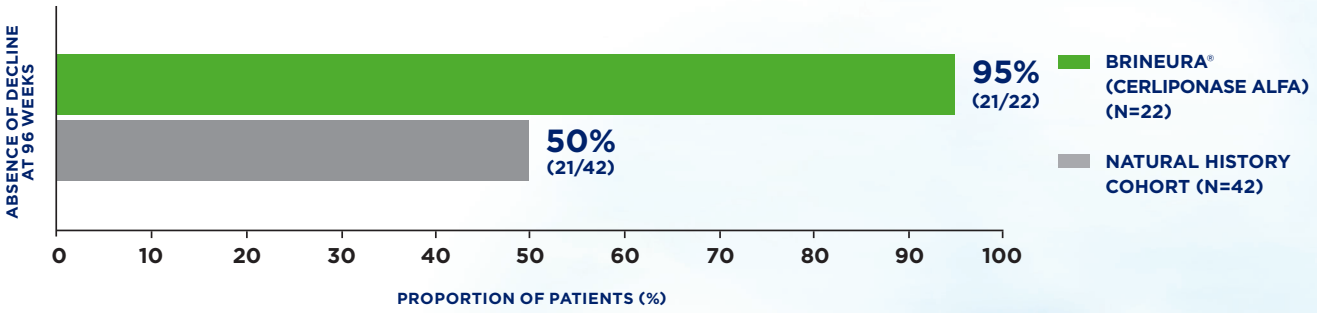
BRINEURA® (CERLIPONASE ALFA) HELPED MAINTAIN PATIENTS' MOTOR FUNCTION BY SLOWING THE LOSS OF AMBULATION[4]

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[4]

- 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[4]



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.[4]

- 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 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® (CERLIPONASE ALFA) WAS GENERALLY WELL TOLERATED

The safety of Brineura® (cerliponase alfa) 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 96[4]:

- Pyrexia
- ECG abnormalities
- Decreased CSF protein
- Vomiting
- Seizures
- Device-related complications
- Hypersensitivity
- Increased CSF protein
- Hematoma
- Headache
- Irritability
- Pleocytosis
- Device-related infections
- 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. Consider the risks and benefits of readministration of Brineura following an anaphylactic reaction.

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 and meningitis. Instruct them to seek immediate medical care should any of these signs and symptoms occur.

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.

Contraindications

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)
- ventriculoperitoneal shunts

Important Preparation and Administration Information

Brineura must only be administered via the intraventricular route using aseptic technique to reduce the risk of infection. Administer Brineura and the Intraventricular Electrolytes using the provided Administration Kit for use with Brineura components. Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage or failure and for potential infection. Prior to each infusion of Brineura and when clinically indicated, send cerebrospinal fluid (CSF) samples for testing of cell count and culture.

Special Populations

Brineura has not been studied in pregnancy or lactation.

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

WARNINGS AND PRECAUTIONS

Meningitis and Other Intraventricular Access Device-Related Infections

Bacterial meningitis requiring antibiotic treatment and removal of the device was reported during postmarketing use of Brineura. The signs and symptoms of infections may not be readily apparent in patients with CLN2 disease. To reduce the risk of infectious complications, Brineura should be administered by, or under the direction of, a physician experienced in intraventricular administration.

Intraventricular Access Device-Related Complications

During the clinical trial and in postmarketing reports, intraventricular access device-related complications were reported (e.g., device leakage, device failure, extravasation of CSF fluid, or bulging of the scalp around or above the intraventricular access device). In case of intraventricular access device-related complications, discontinue the Brineura infusion and refer to the device manufacturer's labeling for further instructions.

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. The intraventricular access device should be replaced prior to 4 years of single-puncture administrations, which equates to approximately 105 administrations of Brineura.

Cardiovascular Adverse Reactions

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.

Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Brineura-treated patients during clinical studies and postmarketing use. In clinical trials, a total of 11 out of 24 patients (46%) experienced hypersensitivity reactions during the infusion or within 24 hours of completion of the infusion.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when Brineura is administered. If a severe hypersensitivity reaction or anaphylaxis occurs, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion. Inform patients/caregivers of the signs and symptoms of hypersensitivity reactions and anaphylaxis and instruct them to seek immediate medical care should signs and symptoms occur. Consider the risks and benefits of readministration of Brineura following an anaphylactic reaction.

ADVERSE REACTIONS

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

Seizures were reported in 12 of 24 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.

Adverse reactions related to the device were observed in 12 of 24 patients. Device-related adverse reactions include infection, delivery system-related complications, and 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%) in patients treated with Brineura. No association was found between serum or CSF ADA titers and incidence or severity of hypersensitivity.

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)

DIAGNOSE AND TREAT BEFORE IRREVERSIBLE DISEASE PROGRESSION

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[6]:

- 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

Connect with BioMarin today

Call 1-866-906-6100 or email
support@biomarin-rareconnections.com

Brineura® (cerliponase alfa)

EEG, electroencephalogram; IPS, intermittent photic stimulation; MRI, magnetic resonance imaging; PPR, photoparoxysmal response.

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