
## INDICATION AND IMPORTANT SAFETY INFORMATION

**What is Brineura used for?**
Brineura® (cerliponase alfa) is a prescription medication used to slow loss of ability to walk or crawl (ambulation) in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2 disease), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

**What is the most important safety information I should know about Brineura?**
Severe and life-threatening allergic reactions, including anaphylaxis, can occur during Brineura infusions and up to 24 hours after infusion. These reactions can occur in people receiving Brineura for the first time or in people who have previously received Brineura without having an allergic reaction. Your child's doctor should ensure appropriately trained personnel and equipment for emergency resuscitation (including epinephrine and other emergency medicines) are readily available during your child's Brineura infusion.

Your child's doctor will tell you about the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and when to seek immediate medical care. Signs of anaphylaxis can include cough, rash, throat tightness, hives, flushing, changes in skin color, low blood pressure, shortness of breath, chest pain, and gastrointestinal symptoms such as nausea, abdominal pain, retching, and vomiting. If a severe allergic reaction (e.g., anaphylaxis) occurs during infusion, the infusion should be stopped immediately, and your child should receive medical attention. Contact your child's doctor or get medical help right away if your child develops any severe symptoms after infusion.

If anaphylaxis occurs, you and your child's healthcare providers should consider the risks and benefits of readministration of Brineura. If the decision is made to readminister Brineura after the occurrence of anaphylaxis, the healthcare providers should ensure appropriately trained personnel and equipment for emergency resuscitation (including epinephrine and other emergency medicines) are readily available during infusion.

**Please see Important Safety Information throughout, including important warning for risk of anaphylaxis, and full Prescribing Information.**

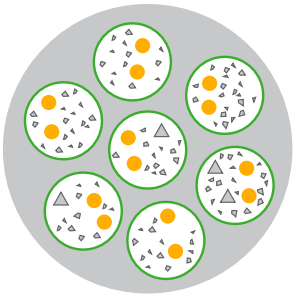
## What is CLN2 disease?

### CLN2 disease is a rare neurodegenerative disease that affects children[1]

- CLN2 disease is a part of a larger group of conditions called neuronal ceroid lipofuscinoses (NCLs). This group of disorders is commonly known as Batten disease[1]
- CLN2 is caused by variations in the *TPP1* gene, also referred to as the *CLN2* gene[1]
- CLN2 disease is an inherited disease and is referred to as an autosomal recessive disorder[1]

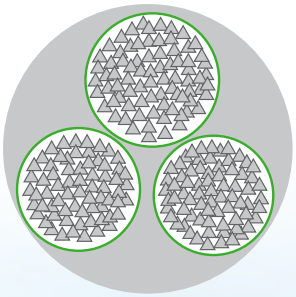
### CLN2 disease is a type of lysosomal storage disease, or LSD, that primarily affects cells in the brain[2]

There are lysosomes inside every cell. Lysosomes contain enzymes that break down material in the cell. One of these enzymes is called tripeptidyl peptidase 1, or TPP1. Over time, without functioning TPP1, cells stop functioning normally. As this happens, symptoms of CLN2 disease appear.[2,3]



#### HEALTHY CELL

In healthy brain cells, lysosomes use TPP1 enzymes to break down materials.[1]



#### CLN2 CELL

In CLN2 disease, TPP1 enzymes are missing or not working properly, and the lysosomes can't use TPP1 to break down materials. Instead, the lysosomes store materials.[1,4] This buildup of storage materials is associated with damage to cells in the brain and eyes.[5]

○ Lysosomes △ Storage material ● TPP1 enzymes

**CLN2 disease–specific language, which may require further explanation, is used in this brochure. Definitions can be found on page 13.**

## What is CLN2 disease? (continued)

**In CLN2 disease, there is usually a rapid and predictable decline in a child's functional abilities, especially in his or her ability to move independently[4,6]**

- At first, children may fall down frequently and appear to be unsteady or clumsy on their feet or while walking
- Over time, children will need more help with walking and moving, relying on support from mobility devices or their caregiver
- Eventually, children lose all mobility, including the abilities to walk or crawl, and will need to use a wheelchair and other equipment

**In addition, children with CLN2 disease may experience a range of symptoms, including language development delay, seizures, loss of cognition, and vision loss[6]**

*"Layla is touching lives—not only has she touched other people's lives, I feel like she's made me a better person. I feel like I'm way more empathetic.... Learning and going through this is something that really makes you realize what's important."*

*—Maria, Layla's mom*

**Layla, age 7**
**Treated with Brineura**

# Brineura® (cerliponase alfa) addresses the underlying cause of CLN2 disease and is approved to slow the loss of ambulation[7]

Brineura® (cerliponase alfa)

## Brineura is a type of treatment called enzyme replacement therapy (ERT)

- Brineura is a prescription medication used to slow loss of ability to walk or crawl (ambulation) in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2), also known as TPP1 deficiency[7]
- Brineura is administered through intraventricular infusion to help replace the TPP1 enzyme, the enzyme that is missing or not working properly in children with CLN2 disease[7]
- Intraventricular infusion is a method in which a drug is infused directly into a ventricle in the brain. It is an established method with clinical experience in other disease areas[8]
- An intraventricular access device or reservoir will need to be placed just below your child's scalp, allowing Brineura to be directly infused into the fluid surrounding the brain, known as the cerebrospinal fluid, or CSF[7,8]

## The CLN2 Clinical Rating Scale was used to measure how Brineura works[7]

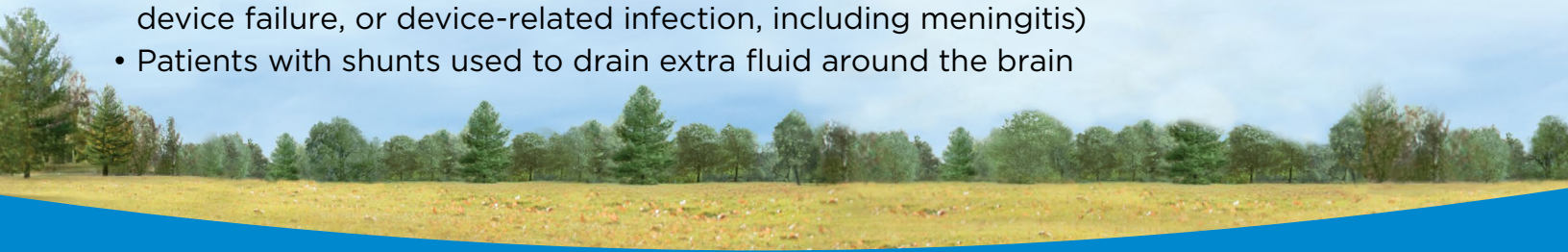
In a clinical study, each child's ability to walk, with or without assistance, was evaluated over approximately 2 years using the Motor domain of the CLN2 Clinical Rating Scale. Scores range from 3 (normal) to 0 (loss of walking/crawling abilities). Each score represents a range of function.[7]

### CLN2 CLINICAL RATING SCALE[9]

| | | |
|---|---|---|
| 3 | **Walks normally** | Mostly normal walking. No noticeable loss of body control; not constantly falling. |
| 2 | **Some difficulty walking** | Can walk independently without support for 10 steps. Will show obvious instability and may fall every so often. |
| 1 | **Needs help walking** | Needs help to walk, or can crawl only. |
| 0 | **Loss of walking/ crawling abilities** | Can no longer walk or crawl. |

## Who should not take Brineura?[7]

- Patients with any sign or symptom of acute or unresolved localized infection on or around the device insertion site (eg, cellulitis or abscess) or suspected or confirmed central nervous system (CNS) infection (eg, cloudy cerebrospinal fluid [CSF] or positive CSF gram stain, or meningitis)
- Patients with active intraventricular access device-related complications (eg, leakage, device failure, or device-related infection, including meningitis)
- Patients with shunts used to drain extra fluid around the brain



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# Brineura® (cerliponase alfa) helped maintain children's ability to walk, with or without assistance, over approximately 2 years of treatment[7]

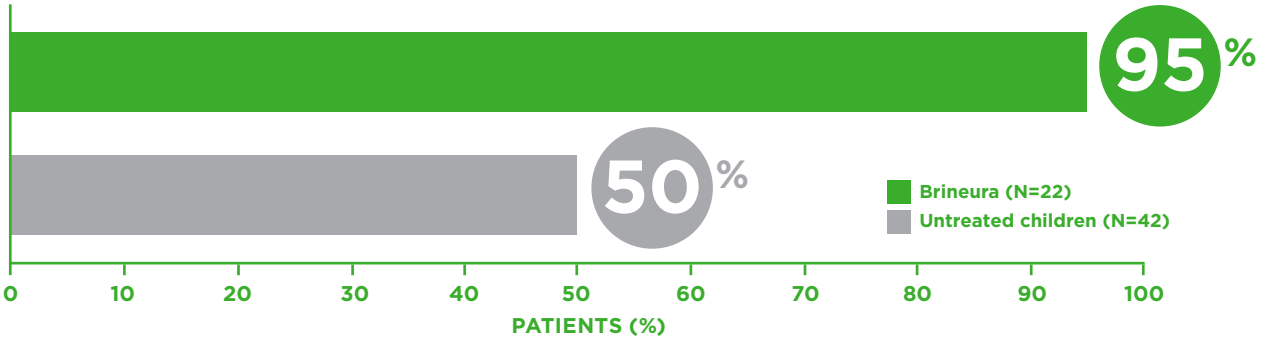
Brineura® (cerliponase alfa)

## Brineura was evaluated in 24 children with CLN2 disease in an ongoing clinical study[7,10]

- Patients in the study ranged from 3 to 8 years old; 15 of the patients were girls and 9 were boys[7,10]
- Average age at first symptom was 3.4 years (the age range was 2.5 to 6.3 years)[10]
- Data from patients with CLN2 disease was compared with data from an independent natural history study of disease progression in untreated children with CLN2 disease[7]

In the study, **Decline** was defined as a sustained drop of 2 points or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.[7]

### PATIENTS WHO DID NOT EXPERIENCE THIS DECLINE IN THEIR ABILITY TO WALK OR CRAWL AT APPROXIMATELY 2 YEARS[7]




- One patient withdrew after Week 1 due to inability to continue with study procedures, and was analyzed as having a decline at the time of termination[7]
- Ten children treated with the recommended dose of Brineura dropped 1 point over approximately 2 years on the Motor domain of the CLN2 Clinical Rating Scale[11]

## In another study, Brineura was evaluated in 14 children, 8 of whom were under 3 years of age,[7*†]

- Patients were between 1 and 6 years of age before starting treatment (baseline)
- None of the treated patients (N=14) had a 2-point decline or score of 0 in the Motor domain of the CLN2 Clinical Rating Scale by Week 169. 65% of the matched natural history comparators (N=31) had an unreversed 2-point decline or score of 0 by last assessment

*CLN2 disease progresses over time. Each child's experience with Brineura will be different.

**†Patients less than 3 years of age may be at increased risk for developing hypersensitivity reactions with Brineura use compared to patients 3 years of age and older. Brineura is not recommended for use in patients less than 37 weeks post-menstrual age (gestational age at birth plus post-natal age) or those weighing less than 2.5 kg.[7]**

**Low blood pressure and/or slow heart rate may occur during and following the infusion of Brineura. Contact your child's healthcare provider immediately if these reactions occur.**

**Infusion Associated Reactions (IAR) such as vomiting, seizure, rash, fever, hypersensitivity, and anaphylactic reaction have been observed in patients treated with Brineura. Your child's doctor may prescribe medicines for your child to take 30 to 60 minutes prior to the start of infusion.**

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# Getting started with the Brineura® (cerliponase alfa) treatment process

When your child is ready to begin Brineura, it's helpful to understand more about the infusion process. Every hospital has its own policies and treatment procedures. This guide can give you a sense of what you and your child may experience before, during, and after their Brineura infusions.

## Partner with your healthcare team every step of the way

Your healthcare team at the hospital will work on an individualized plan for your child, which your doctor will discuss with you. As a parent or caregiver, you are a source of support and comfort for your child, so staying informed and preparing ahead of time may help your child feel more at ease. Keep in close contact with your healthcare team about how your child is doing and any instructions for your child's care. They are your partners in this journey, so don't hesitate to reach out to them with any questions or concerns you may have.

**BRINEURA infusion is approximately 2 to 4.5 hours, depending on the dose and volume administered, every other week.[7]**

*"Every two weeks, Matty takes a drive down to Boston in the morning with his grandparents for his treatment, and he is home by dinnertime. Then he is back to school the next day. It's become routine for our family."*

*—Joe, Matty's dad*

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## How Brineura® (cerliponase alfa) is administered

Brineura® (cerliponase alfa)

### Brineura is delivered over 2 to 4.5 hours, depending on the dose and volume administered, by intraventricular infusion[7]

- Intraventricular drug delivery is an established method in other disease areas, including oncology[8]
- Knowledgeable members of your healthcare team will administer your child's Brineura infusions
- Before starting Brineura, your child will need to have an intraventricular access device surgically implanted[7]—an established procedure in pediatric neurology[8]
- Your child's doctor should ensure appropriately trained personnel and equipment for emergency resuscitation (including epinephrine and other emergency medicines) are readily available during your child's Brineura infusion

### Before your child's first infusion:

### MRI brain scans to help place the intraventricular access device

- MRI (magnetic resonance imaging) scans are used to help the surgeon locate where the intraventricular access device should be inserted, and to confirm placement after the surgery[12]

### Surgery to implant the intraventricular access device

- The intraventricular access device is implanted just below the scalp.[8] It has a reservoir about 19 mm in diameter, with a straw-like catheter that extends down from the reservoir so that Brineura can be infused directly into the ventricle[7]
- After the intraventricular access device is placed, your healthcare team will work with you to schedule infusions. It is recommended that Brineura treatment begin at least 5 to 7 days after your child's intraventricular access device is implanted[7]
- Before 4 years of Brineura infusions have been completed, the intraventricular access device will need to be replaced.[7] Your healthcare team will advise you when this is needed
- BioMarin can provide education around the intraventricular access device selection to the medical team

**Post-implant intraventricular access device area on Matty.**

**Intraventricular access device–related infections, including meningitis, were observed with Brineura treatment. If any signs of infection or meningitis occur, contact your child's doctor immediately[7]**

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## Preparing for infusion days

Brineura® (cerliponase alfa)

Below are important steps that will help prepare you and your child for infusion of Brineura® (cerliponase alfa).

**Talk** with your child about the infusion process in a way that is comfortable for both of you. Your child may look to you for guidance, so it's important to stay positive and reassuring.

**Plan ahead** for any items you may need to bring. It may be helpful to talk with your child about special things you will do on infusion days, like watching their favorite TV show or reading a favorite book.

- Your child will have to sit relatively still during the infusion process, so consider bringing comforting items to keep your child engaged and entertained. Items can include tablets or similar devices, books, toys, snacks, music, games, or favorite items
- You may want to wash your child's hair with a special antibacterial shampoo the day before the infusion, to prevent potential infections[13]
- You may want to bring hair clips to hold back your child's hair, or a hat or scarf for your child to wear home

**Update** your healthcare team on any changes to your child's medications.

**Carry** the contact information of your healthcare team with you at all times in case any questions or concerns arise.

> *"After the first few infusions we became more comfortable, because it simply became routine for us. The initial surgery for the port was scary, as is any surgery with your child, so we felt like that was the first hurdle to jump. Once Matty had a few infusions, we were very comfortable with the process."*
>
> *—Joe, Matty's dad*

**Preparation**

**Accessing the intraventricular access device**

**Infusion**

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# What to expect on infusion days

Brineura® (cerliponase alfa)

Below is an example of what you may expect on an infusion day. Your experience may be slightly different since each hospital has its own procedures.

**Prepare** by following your healthcare team's directions for what to do before the appointment. Directions vary, and **may** include:

- Removing a small patch of your child's hair to prepare for accessing the intraventricular access device.[8] You may want to use a clipper for the hair removal
- Applying numbing cream to a small area of your child's head[13]
- Giving your child pretreatment medication 30 to 60 minutes before the infusion begins, to reduce the risk of reactions, like fever or hypersensitivity—your healthcare team will provide instructions[7]

## During the appointment

### MAINTAINING A STERILE ENVIRONMENT

Your child's healthcare team will use an aseptic technique according to the institution's procedures to help reduce the risk of infection.

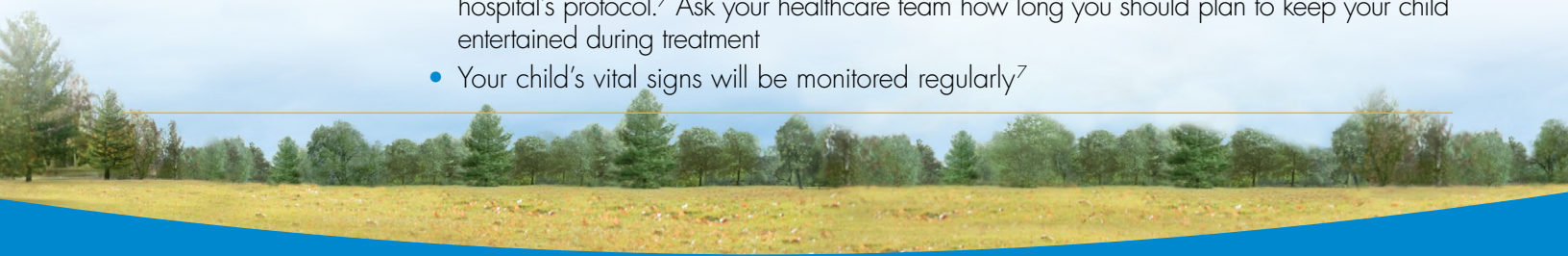
- You may be asked to wear a mask[8]
- The number of people in the room will be limited during the infusion, especially when accessing the intraventricular access device—ask your healthcare team who and what is allowed in the room[8]
- A healthcare team member may apply a numbing cream to the scalp before the infusion[13]
- Your child's doctor may take a sample of CSF for cell count and culture before each infusion[7]
- The skin over the intraventricular access device area will be cleaned by a healthcare team member[8]
- Please follow your healthcare team's instructions carefully—take care not to touch the skin over the access device once it is cleaned[8]

### ACCESSING THE INTRAVENTRICULAR ACCESS DEVICE

- You may be asked to hold your child or sit behind them on the bed while the access needle is inserted to minimize movement during this part of the infusion
- Your child's head may be wrapped in gauze during or after the infusion process[9]
- Intraventricular access device-related infections, including meningitis, were observed with Brineura® (cerliponase alfa) treatment. If any signs of infection—such as swelling or reddening of the skin—or signs of meningitis occur, contact your child's doctor immediately[8]

### DURING THE INFUSION

- Your child can sit or lie down in a bed, chair, or stroller during the infusion and play with games or electronics[8]
  - Take care to minimize your child's movement during the infusion to avoid disconnecting the needle
- Brineura infusion will take about 2 to 4.5 hours, and preparation of the intraventricular access device site and observation time after the infusion can vary depending on your hospital's protocol.[7] Ask your healthcare team how long you should plan to keep your child entertained during treatment
- Your child's vital signs will be monitored regularly[7]



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## Post-infusion care

Brineura® (cerliponase alfa)

### Immediately after infusion

- Follow your hospital's instructions for care and bandage removal
- You and your child should avoid touching or putting direct pressure on the intraventricular access device and surrounding area[8]

### First few days following infusion

- Follow your healthcare team's instructions about wetting your child's head, shampooing, and using public pools or other areas that may expose the device to water
- Ask your healthcare team if your child can wear hats, caps, or bows

### After your child's Brineura® (cerliponase alfa) infusion, watch for signs of the following[7]:

- Intraventricular access device-related complications
  - There is a risk of device-related infections. There are steps the doctor can take to reduce this risk with every treatment. If you see any signs of infection, such as swelling or reddening of the skin, contact your healthcare team immediately
  - There is a risk of meningitis. Signs of meningitis include flu-like symptoms, such as fever and nausea, or swelling of the treatment area[14]
- Cardiovascular adverse reactions
  - Low blood pressure or slow heart rate may occur during and following Brineura infusion. Contact your healthcare team immediately if either occur
- Hypersensitivity
  - Hypersensitivity reactions related to Brineura treatment may occur, including fever, vomiting, and irritability. Some patients may experience anaphylaxis (severe allergic reactions to medicine). Talk to your healthcare team about signs and symptoms of anaphylaxis, and contact them immediately if any occur

**Your healthcare team can let you know which activities are appropriate and safe for your child to do after their infusion. Your child may be able to return to regular routines and activities after infusion.**

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## Possible side effects of Brineura® (cerliponase alfa)[7]

Brineura can cause side effects. Talk to your healthcare team immediately if your child experiences any side effects.

The most common side effects reported during Brineura infusions included[7]:

- Fever
- Problems with the electrical activity of the heart (arrhythmia)
- Decreased or increased protein in the fluid of the brain
- Vomiting
- Seizures
- Device-related complications/ infections
- Hypersensitivity
- Collection of blood outside of blood vessels (hematoma)
- Headache
- Irritability
- Feeling jittery
- Increased white blood cell count in the fluid of the brain
- Slow heart rate
- Low blood pressure

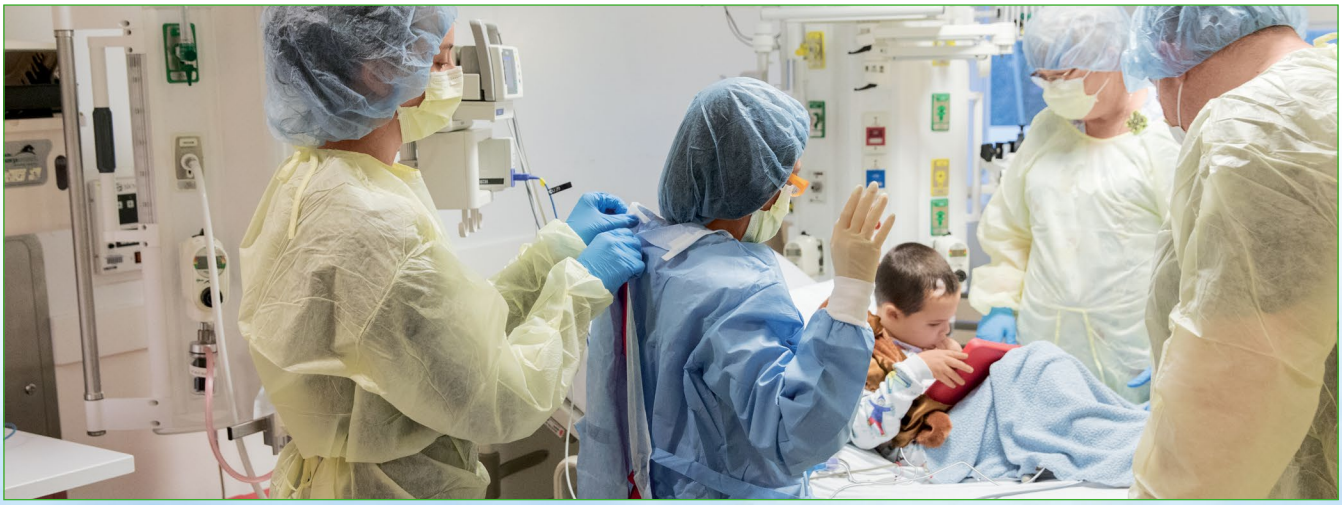
The most frequent adverse reactions reported in patients less than 3 years of age treated with BRINEURA were similar to those observed in patients 3 years of age and older except for hypersensitivity reactions, which were reported in 5 of 8 (63%) in patients less than 3 years of age at baseline compared with 0 of 6 in patients 3 years of age and older at baseline.

**These are not all of the possible side effects with Brineura. Talk to your child's doctor if they have any symptoms that bother them or that do not go away.**

## What to watch for after infusion

After Brineura infusion, it is very important to watch for signs of infection—such as swelling or reddening of the skin—or intraventricular access device leakage.[7]

Make sure that you have the emergency contact information for your healthcare team and keep it readily accessible at all times and in multiple places. Also be sure to provide this information to other family members and your child's day care or school.



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## Available support and resources throughout your journey

Brineura® (cerliponase alfa)

Caring for a child who has CLN2 disease can be emotionally and physically demanding. Connecting with other parents/caregivers and healthcare professionals can help make the disease easier to manage. Fortunately, there are support resources available to you and your family.

### Batten Disease Support & Research Association (BDSRA)

The BDSRA is committed to providing family support services and has experience coordinating travel logistics for CLN2 families. If you have a child with CLN2 disease, the BDSRA welcomes you and wants to answer your questions.

**Join the BDSRA community at bdsrafoundation.org or 1-800-448-4570.**

### Uncommon Support for Rare Disease

Beyond the therapeutic support provided to children with CLN2 disease, BioMarin is committed to supporting family members and caregivers. BioMarin RareConnections™ provides personalized support to coordinate additional services, including information about financial assistance programs.

**Visit biomarin-rareconnections.com or contact the BioMarin RareConnections team for more information by emailing support@biomarin-rareconnections.com or by calling 1-866-906-6100.**

*"Newly diagnosed parents should reach out to the BDSRA. They are there for just that, support. They can connect you to other families going through similar stories. They can just point you in the right direction. They're the best people to reach out to."*

*—Maria, Layla's mom*

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# Definitions

Brineura® (cerliponase alfa)

## Anaphylaxis[7]
A severe allergic reaction characterized by increased body temperature, respiratory distress, rapid heart rate, low blood pressure, diarrhea, and rash.

## Autosomal recessive disease[3]
A pattern of inheritance where 2 variant genes (one from each parent) are passed to their child, which then causes a certain disease.

## Batten disease[10,15]
A group of rare autosomal recessive, neurodegenerative diseases that typically begin in childhood. It is named for Dr. Batten, who discovered the disease.

## Cerebrospinal fluid (CSF)[16]
Body fluid surrounding the brain and spine.

## Cerliponase alfa[7,17]
A drug form of human TPP1, the enzyme that is absent or not working properly in patients with CLN2 disease. It is the generic name for Brineura® (cerliponase alfa).

## CLN2 disease[7,17]
Neuronal ceroid lipofuscinosis type 2, a rare autosomal recessive condition where lysosomes in the brain don't have enough of the TPP1 enzyme to break down materials in cells.

## CLN2 Clinical Rating Scale[17]
This scale was designed specifically for CLN2 disease and evaluates motor function, language, vision, and seizures. It can also help doctors determine how well treatment with Brineura is working.

## Enzyme[16]
Proteins that facilitate reactions to occur in cells.

## Enzyme replacement therapy (ERT)[3,16]
A treatment that helps replace missing or improperly working enzymes. In the case of CLN2 disease, treatment with ERT helps replace the TPP1 enzyme.

## Hypersensitivity[16]
A set of exaggerated or abnormal reactions produced by the immune system.

## Infusion[16]
A way in which drugs are delivered into the veins or ventricles.

## Intraventricular infusion[7,8]
A method in which a drug is infused directly into a ventricle in the brain. This is how Brineura is delivered in children with CLN2 disease.

## Lysosome[3]
Lysosomes are structures within cells that contain enzymes. One of their primary purposes is to recycle materials using enzymes.

## Lysosomal storage disorder (LSD)[18]
An inherited disease that is caused by an abnormal build-up of materials in lysosomes in the body's cells as a result of a reduced amount of a particular enzyme or enzymes. More than 70 types of LSD have been identified to date.

## Meningitis[16]
An inflammation, or swelling, of the protective membranes covering the brain and spinal cord.

## Motor function[10]
The ability to walk or crawl, which is one of the domains the CLN2 Clinical Rating Scale measures.

## Neuronal ceroid lipofuscinoses (NCLs)[1]
A group of rare, genetic, neurodegenerative disorders.

## Neurodegenerative[19]
Having a decline in brain function.

## Tripeptidyl peptidase 1 (TPP1)[3]
An enzyme that breaks down specific material within the lysosomes of cells. A reduced amount of this enzyme is what causes CLN2 disease.

## Lateral ventricle[20]
A hollow cavity. In the brain, this cavity contains CSF.

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**What is Brineura used for?**

Brineura® (cerliponase alfa) is a prescription medication used to slow loss of ability to walk or crawl (ambulation) in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2 disease), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

**What is the most important safety information I should know about Brineura?**

Severe and life-threatening allergic reactions, including anaphylaxis, can occur during Brineura infusions and up to 24 hours after infusion. These reactions can occur in people receiving Brineura for the first time or in people who have previously received Brineura without having an allergic reaction. Your child's doctor should ensure appropriately trained personnel and equipment for emergency resuscitation (including epinephrine and other emergency medicines) are readily available during your child's Brineura infusion.

Your child's doctor will tell you about the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and when to seek immediate medical care. Signs of anaphylaxis can include cough, rash, throat tightness, hives, flushing, changes in skin color, low blood pressure, shortness of breath, chest pain, and gastrointestinal symptoms such as nausea, abdominal pain, retching, and vomiting. If a severe allergic reaction (e.g., anaphylaxis) occurs during infusion, the infusion should be stopped immediately, and your child should receive medical attention. Contact your child's doctor or get medical help right away if your child develops any severe symptoms after infusion.

If anaphylaxis occurs, you and your child's healthcare providers should consider the risks and benefits of readministration of Brineura. If the decision is made to readminister Brineura after the occurrence of anaphylaxis, the healthcare providers should ensure appropriately trained personnel and equipment for emergency resuscitation (including epinephrine and other emergency medicines) are readily available during infusion.

**Who should not take Brineura?**

- Patients with any sign or symptom of acute or unresolved localized infection around the device insertion site (eg, cellulitis or abscess) or suspected or confirmed central nervous system (CNS) infection (eg, cloudy cerebrospinal fluid [CSF] or positive CSF gram stain, or meningitis)
- Patients with active intraventricular access device-related complications (eg, leakage, device failure, or device-related infection, including meningitis)
- Patients with shunts used to drain extra fluid around the brain

**Administration:** Brineura is only given by infusion into the fluid of the brain (known as an intraventricular injection) and using sterile technique to reduce the risk of infection. An intraventricular access device or port must be in place at least 5 to 7 days prior to the first infusion.

- Prior to administration, it is important to discuss your child's medical history with their doctor
- Tell the doctor if your child is sick or taking any medication and if they are allergic to any medicines
- Brineura is not recommended for use in patients less than 37 weeks post-menstrual age (gestational at birth plus post-natal age) or those weighing less than 2.5kg.

**Meningitis and other device-related infections:** Intraventricular access device-related infections, including meningitis, were observed with Brineura treatment. Infections required treatment with antibiotics and removal of the access device. If any signs of infection or meningitis occur, contact your child's doctor immediately. The signs and symptoms of infections may not be readily apparent in patients with CLN2 disease.

- Your child's doctor should vigilantly be looking for signs and symptoms of infection, including meningitis, during treatment with Brineura
- Your child's doctor should inspect the scalp and collect samples of your child's CSF prior to each infusion of Brineura, to check for infections and that there is no device failure
- Signs of infection on or around the device insertion site may include redness, tenderness, or discharge

**Device-related complications** such as device leakage, device failure, leakage of CSF fluid, or bulging of the scalp around or above the intraventricular access device have occurred. In case of intraventricular access device-related complications, Brineura infusions may be discontinued. 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 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.

**Cardiovascular side effects:** Low blood pressure and/or slow heart rate may occur during and following the infusion of Brineura. Contact your child's healthcare provider immediately if these reactions occur. As part of the infusion, the healthcare provider will monitor vital signs (blood pressure, heart rate) before infusion starts, periodically during infusion, and post-infusion, and assess the patient's status after administration to determine if continued observation may be necessary. Additional monitoring is required for patients with a history of cardiac abnormalities. In patients without cardiac abnormalities, regular 12-lead electrocardiogram (ECG) evaluations should be performed every 6 months.

**Infusion Associated Reactions** (IAR) such as vomiting, seizure, rash, pyrexia, hypersensitivity, and anaphylactic reaction have been observed in patients treated with Brineura. Your child's doctor may prescribe medicines for your child to take 30 to 60 minutes prior to the start of infusion.

**The most common side effects reported** during Brineura infusions included:

- Fever, problems with the electrical activity of the heart, decreased or increased protein in the fluid of the brain, vomiting, seizures, device-related complications, hypersensitivity, collection of blood outside of blood vessels (hematoma), headache, irritability, increased white blood cell count in the fluid of the brain, device-related infection, slow heart rate, feeling jittery, and low blood pressure.
- The most frequent adverse reactions reported in patients less than 3 years of age treated with BRINEURA were similar to those observed in patients greater than 3 years of age except for hypersensitivity reactions, which were reported in 5 of 8 (63%) in patients less than 3 years of age at baseline compared with 0 of 6 in patients greater than 3 years of age at baseline. The most common manifestations of hypersensitivity were fever and vomiting. Such symptoms resolved over time or with administration of antipyretics, antihistamines and/or corticosteroids. Symptoms of severe hypersensitivity reactions (e.g., anaphylaxis) included rapid heartbeat, throat tightness, coughing, wheezing, trouble breathing, rash, diarrhea, hypotension, increased body temperature and vomiting.

**The risk information provided here is not comprehensive. Talk to your healthcare provider to learn more or for medical advice about any side effects.**

**You may report side effects to BioMarin at 1-866-906-6100.**

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1–800-FDA-1088.**

**Please click here for full Prescribing Information, with important warning for risk of anaphylaxis, or visit www.Brineura.com.**

**For more information on how to get started with Brineura, contact BioMarin RareConnections™ at 1-866-906-6100 or support@biomarin-rareconnections.com.**

Brineura® (cerliponase alfa)

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