Brineura® (cerliponase alfa) dosing and administration guide

Brineura® (cerliponase alfa) injection for intraventricular use is indicated to slow the loss of ambulation in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2 disease), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

- **Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy.**
- **Initiate Brineura in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment.**
- **If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue Brineura and immediately initiate appropriate medical treatment, including use of epinephrine.**

The steps within this guide are suggested practice for Brineura administration. For further questions or detailed guidance, refer to your institution's policies and procedures. You also may want to consult with a neurosurgeon or other physicians within your institution who are experienced with intraventricular drug delivery.

Brineura® (cerliponase alfa)

Please see accompanying Important Safety Information, including Boxed Warning for risk of anaphylaxis, and full Prescribing Information.

INTRODUCTION TO BRINEURA® (CERLIPONASE ALFA)

Brineura® (cerliponase alfa) is indicated to slow the loss of ambulation in pediatric patients with CLN2 disease.[1]

- Brineura is the first and only treatment addressing the underlying cause of CLN2 disease
- Brineura is an enzyme replacement therapy (ERT)—it helps replace deficient TPP1 enzyme in children with CLN2 disease

Brineura is delivered via intraventricular infusion.[1] Intraventricular drug delivery is an established method with clinical experience in other disease areas, including oncology. Intraventricular infusion has been used in clinical settings for more than 50 years in both adults and children, and is established as a well-tolerated approach for delivery of drugs to a ventricle in the brain.[2] The use of intraventricular infusion ensures Brineura is delivered directly into the central nervous system. Before the first intraventricular infusion, patients will require a pediatric neurosurgical procedure to place the intraventricular access device.[1]

The information within this brochure can help you successfully administer Brineura and minimize the risk of complications.

This brochure contains guidance on the following:

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

DOSAGE AND ADMINISTRATION

Dosage[1]

- The recommended dosage of Brineura® (cerliponase alfa) in pediatric patients is provided in Table 1. The dose is administered once every other week by intraventricular infusion.
- The complete Brineura infusion, including the required infusion of Intraventricular Electrolytes, is approximately 2 to 4.5 hours, depending on the dose and volume administered. See Table 1 for the appropriate volume and infusion rate. Pretreatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion
- Monitor vital signs before infusion starts, periodically during infusion, and post-infusion

Table 1: BRINEURA Dose, Volume, and Infusion Rate by Age

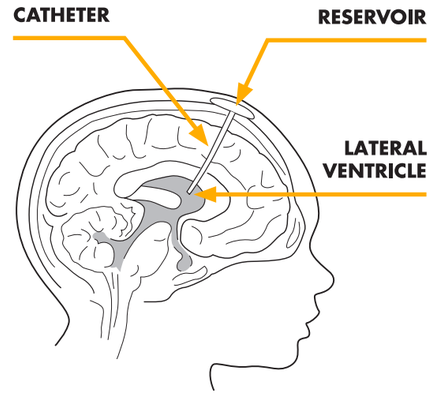
Age groups	BRINEURA dose administered every other week	Volume of BRINEURA solution	Infusion rate
Birth to < 6 months	100 mg	3.3 mL	1.25 mL/hr
6 months to < 1 year	150 mg	5 mL	2.5 mL/hr
1 year to < 2 years	200 mg (first 4 doses) 300 mg (subsequent doses)	6.7 mL (first 4 doses) 10 mL (subsequent doses)	2.5 mL/hr
2 years and older	300 mg	10 mL	2.5 mL/hr

- Brineura is not recommended 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

Important preparation and administration information[1]

Aseptic technique must be strictly observed during preparation and administration.

- Brineura should be initiated in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment.
- Administration of Brineura should be supervised by a healthcare provider knowledgeable in the management of interventricular administration as well as hypersensitivity reactions including anaphylaxis.
- Brineura and the Intraventricular Electrolytes must only be administered by the intraventricular route, using the provided Administration Kit for use with Brineura
  - Each vial of Brineura and the Intraventricular Electrolytes is intended for a single dose only



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Brineura® (cerliponase alfa)

DOSAGE AND ADMINISTRATION (CONTINUED)

- Brineura is administered into the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device)
  - Brineura is intended to be administered via the Codman® HOLTER RICKHAM Reservoirs, part numbers 82-1625, 82-1621, and 82-1616, and with the Codman® Ventricular Catheter, part number 82-1650
  - The intraventricular access device must be implanted prior to the first infusion
  - It is recommended that the first dose be administered at least 5 to 7 days after device implantation
  - The intraventricular access device should be replaced prior to 4 years of single-puncture administrations, which equates to approximately 105 administrations of Brineura
  - Inspect the scalp for signs of intraventricular access device leakage, failure or potential infection

Each infusion consists of 3.3 to 10 mL of Brineura followed by 2 mL of Intraventricular Electrolytes. The complete infusion must be administered using an infusion set with a 0.2 micron inline filter. The Intraventricular Electrolytes are used to flush the infusion line, port needle, and intraventricular access device in order to fully administer Brineura and to maintain patency of the intraventricular access device.

HOW BRINEURA® (CERLIPONASE ALFA) IS SUPPLIED AND STORED

Brineura® (cerliponase alfa) and the Administration Kit for use with Brineura are supplied in 2 packages.

Package 1 of 2: Brineura Injection and Intraventricular Electrolytes Injection[1]

This package includes 2 vials of Brineura Injection and 1 vial of Intraventricular Electrolytes Injection.

- Each Brineura Injection vial has a green flip-off cap (plastic), and contains 150 mg cerliponase alfa per 5 mL (30 mg/mL)
- Each Intraventricular Electrolytes Injection vial has a yellow flip-off cap (plastic), and contains 5 mL of solution

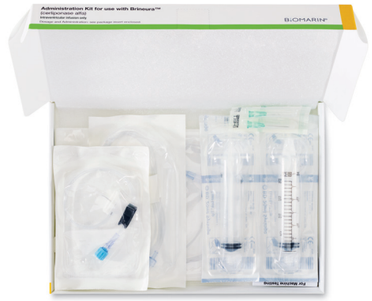
Brineura Injection and Intraventricular Electrolytes Injection should be stored upright in a freezer (–25°C to –15°C) in original carton to protect from light.

Package 2 of 2: Administration Kit for use with Brineura[1]

The Administration Kit for use with Brineura is supplied separately and contains the following single-use, sterile infusion components:

- Two 20-mL syringes (Becton Dickinson)
- Two syringe needles (21 G, 25.4 mm) (Becton Dickinson)
- One extension line (Smiths Medical)
- One infusion set with 0.2 micron inline filter (Smiths Medical)
- One port needle (22 G, 16 mm) (Smiths Medical)

Store the Administration Kit for use with Brineura in original carton separately from Brineura. Do not freeze.



SUPPLIES NEEDED FOR INFUSION

Gather supplies[1]:

- Brineura® (cerliponase alfa) and Intraventricular Electrolytes Injection vials (package 1 of 2)
- Administration Kit for use with Brineura (package 2 of 2)
- Syringe pump (not supplied)
  - Brineura is intended to be administered with the B Braun Perfusor® Space Infusion Pump System (Product Code: 8713030U). If an alternative pump must be used, the essential performance requirements for this syringe pump used to deliver Brineura are as follows:
    - Delivery rate of 1.25 or 2.5 mL per hr with delivery accuracy of +/- 1 mL per hr
    - Compatible with 20 mL syringes provided in the Administration Kit for use with Brineura
    - Cleared for intraventricular route of administration
    - Occlusion alarm setting to ≤281 mm Hg
- Connect a separate empty sterile single-use luer lock syringe, no larger than 3 mL (not provided) to the port needle.

B Braun Perfusor® Space Infusion Pump System

Materials for aseptic technique[1-3]:

Aseptic technique must be strictly observed during preparation and administration. Follow your institution's standard of care.

- Personal protective equipment
- Extra pair of sterile gloves for changing lines
- Skin antiseptic solution (eg, Betadine®-based, chlorhexidine)
- Gauze or another material to wrap head with during and after infusion process
- Sterile patch or gauze for the infusion site post-administration

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Brineura® (cerliponase alfa)

THAWING BRINEURA® (CERLIPONASE ALFA) AND INTRAVENTRICULAR ELECTROLYTES INJECTION

The following may be completed by the pharmacy. Before thawing and withdrawing Brineura® (cerliponase alfa), ensure patient is able to undergo infusion. Aseptic technique must be strictly observed during preparation.

Before use[1]:

- Thaw Brineura and Intraventricular Electrolytes Injection vials at room temperature for approximately 60 minutes
  - — Condensation will occur during thawing period
- **Do not** thaw or warm vials any other way
- **Do not** shake vials
- **Do not** refreeze vials or freeze syringes containing Brineura or Intraventricular Electrolytes

Storage of thawed product:

- Use thawed Brineura and Intraventricular Electrolytes immediately. If not used immediately, store unopened vials in the refrigerator at 2°C to 8°C and use within 24 hours

Storage of product in syringes:

- Use product held in labeled syringes immediately. If not used immediately, store product held in labeled syringes in the refrigerator at 2°C to 8°C up to 4 hours prior to infusion

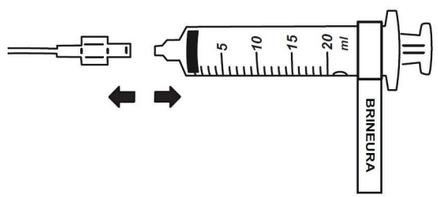
Inspect fully thawed vials before use[1]:

- Brineura is a clear to slightly opalescent and colorless to pale yellow solution. Intraventricular Electrolytes are a clear to colorless solution
- **Do not use** if the solutions are discolored or if there is other foreign particulate matter in the solutions
- Brineura vials may occasionally contain thin translucent fibers or opaque particles
  - — These naturally occurring particles are cerliponase alfa
  - — These particles are removed via the 0.2 micron inline filter without having a detectable effect on the purity or strength of Brineura
- Intraventricular Electrolytes may contain particles, which appear during the thaw period; however, they dissolve when the solution reaches room temperature

WITHDRAWING BRINEURA® (CERLIPONASE ALFA) AND INTRAVENTRICULAR ELECTROLYTES INJECTION

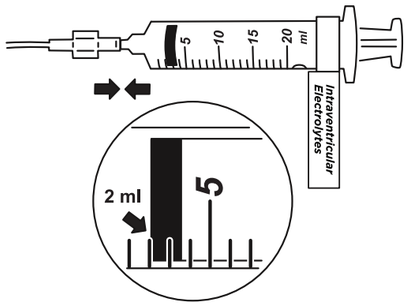
The following may be completed by the pharmacy. Before thawing and withdrawing Brineura® (cerliponase alfa), ensure patient is able to undergo infusion. Aseptic technique must be strictly observed during preparation.

Withdraw Brineura[1]:



- Use aseptic technique when preparing the Brineura syringe for infusion. Label 1 sterile syringe "Brineura" and attach the syringe needle
- Confirm required dose and volume based on patient age per Table 1. Remove the green flip-off caps from one or both Brineura vials. Each Brineura vial contains 150 mg or 5 mL
- Each Brineura vial contains 150 mg or 5 mL. Use the "Brineura" labeled syringe to withdraw the volume of Brineura solution from the vial per the required dose (see Table 1)
- Intermediate volumes that fall between 1 mL increments should be drawn up in the syringe to the nearest whole number, specifically 3.3 mL to 4 mL and 6.7 mL to 7 mL
- **Do not** dilute Brineura
- **Do not** mix Brineura with any other drug
- Discard any unused portion left in the vial

Withdraw Intraventricular Electrolytes[1]:



- Use aseptic technique when preparing the Intraventricular Electrolytes syringe for infusion. Label 1 sterile syringe "Intraventricular Electrolytes" and attach the syringe needle
- Remove the yellow flip-off cap from the Intraventricular Electrolytes Injection vial
- Withdraw 2 mL of Intraventricular Electrolytes
- Discard the remaining unused portion

Aseptic technique must be strictly observed during preparation and administration[1,3]

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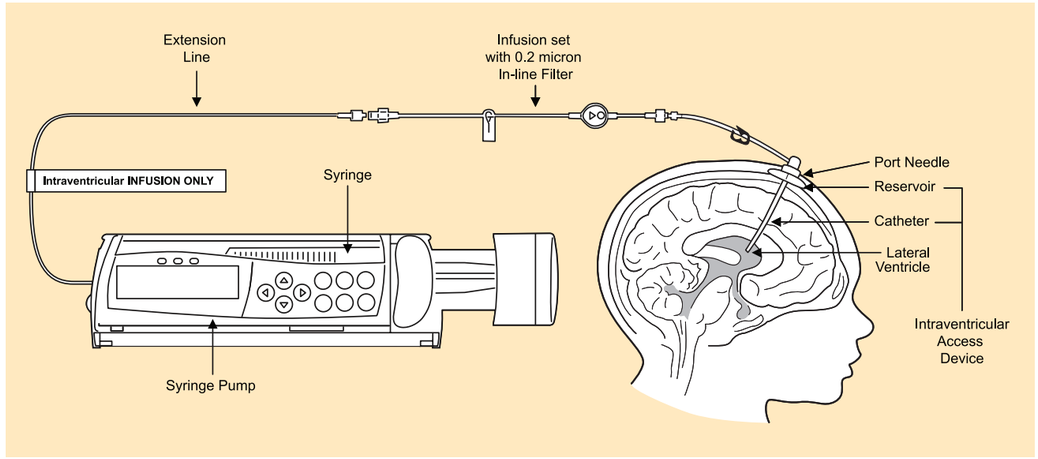
Brineura® (cerliponase alfa)

ADMINISTERING BRINEURA® (CERLIPONASE ALFA)[1]



This figure represents the intraventricular infusion system setup. Use aseptic technique during the Brineura® (cerliponase alfa) infusion. Follow the steps below to proceed with the intraventricular infusion.

1. As completed on page 7, one sterile syringe has been labeled "Brineura" and attached to the syringe needle. The green flip-off caps have been removed from one or both Brineura vials, and the labeled syringe has been used to withdraw up to 10 mL from the Brineura vials.

2. Label the infusion line "intraventricular infusion only."

3. Attach the syringe containing Brineura to the extension line. Then connect the extension line to the infusion set with a 0.2 micron inline filter.

4. Prime the infusion components with Brineura.

Consider wrapping the line connections with sterile gauze; while recommended, there is no evidence this practice reduces the risk of infection[3]

ADMINISTERING BRINEURA® (CERLIPONASE ALFA) (CONTINUED)[1]

5. Inspect scalp for signs of intraventricular access device leakage or failure and for potential infections.
   - **Do not** administer Brineura® (cerliponase alfa) in patients with acute intraventricular access device–related complications (eg, leakage, device failure, or signs of device-related infection such as swelling, erythema of the scalp, extravasation of fluid, or bulging around or above the intraventricular access device). Please consult with your neurosurgeon or infectious disease specialist should these complications occur

6. Prepare the scalp for intraventricular infusion per your institution's standard of care.

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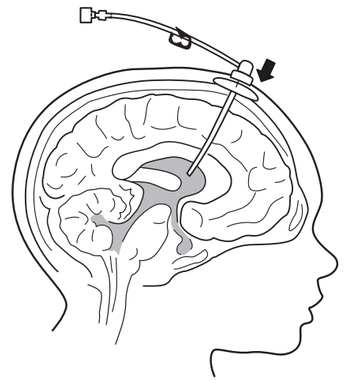
Brineura® (cerliponase alfa)

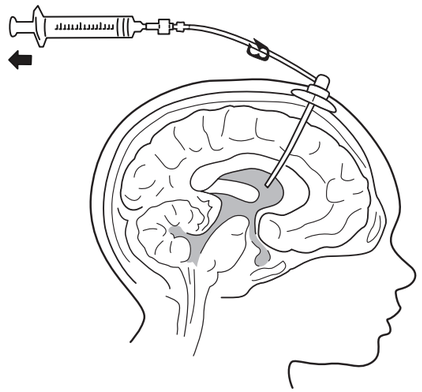
ADMINISTERING BRINEURA® (CERLIPONASE ALFA) (CONTINUED)[1]

7. Insert the port needle into the intraventricular access device reservoir.



8. Connect a separate empty sterile single-use luer lock syringe no larger than 3 mL (not provided) to the port needle. Withdraw 0.5 mL to 1 mL of CSF to check patency of intraventricular access device and send specimen for culture.

- **Do not return CSF to intraventricular access device**
- Obtain a sample of CSF for cell count and culture prior to each infusion and if clinically indicated[3]
  - Some sites also recommend sending CSF for s16/s18 PCR[3]



ADMINISTERING BRINEURA® (CERLIPONASE ALFA) (CONTINUED)[1]

9. Attach the infusion set with 0.2 micron inline filter to the port needle.

- Secure the components per your institution's standard of care

10. Place the syringe containing Brineura® (cerliponase alfa) into the syringe pump and program the pump to deliver at an infusion rate of 1.25 or 2.5 mL per hour. **Set the pump volume limit to deliver the exact volume that corresponds to the dose of Brineura solution appropriate for the patient's age.** Set the occlusion alarm setting to alert the pressure ≤ 281 mm Hg.

11. Administer premedication 30 to 60 minutes prior to the start of infusion.

12. Monitor vital signs (blood pressure, heart rate) prior to the start of infusion, periodically during infusion, and post-infusion.

13. Initiate infusion of Brineura at a rate of 1.25 or 2.5 mL per hour.

14. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure.

15. When the Brineura infusion is complete, detach and remove the empty syringe from the pump and disconnect from the tubing.

Wear sterile gloves when switching syringes[3]

Please see Important Safety Information throughout, and accompanying full Prescribing Information, with Boxed Warning for risk of anaphlyaxis or visit www.Brineura.com.

Brineura® (cerliponase alfa)

ADMINISTERING INTRAVENTRICULAR ELECTROLYTES[1]

Administer the Intraventricular Electrolytes provided after Brineura® (cerliponase alfa) infusion is complete.

The Intraventricular Electrolytes are used to flush the infusion line, port needle, and intraventricular access device in order to fully administer Brineura and to maintain patency of the intraventricular access device.

16. As covered on page 7, one sterile syringe has been labeled "Intraventricular Electrolytes" and attached to the syringe needle. The yellow flip-off cap has been removed from the vial, and the labeled syringe has been used to withdraw 2 mL of Intraventricular Electrolytes. Discard the remaining unused portion.

17. Attach the syringe to the extension line.

18. Place the syringe containing Intraventricular Electrolytes into the syringe pump and program pump to deliver at an infusion rate of 1.25 or 2.5 mL per hour. Set the pump volume limit to deliver 2 mL. Set the occlusion alarm setting to alert at pressure ≤ 281 mm Hg. See syringe pump operating manual for details. **Do not** deliver as a bolus or manually.

19. Initiate infusion of Intraventricular Electrolytes at a rate of 2.5 mL per hour.

COMPLETING THE INFUSION[1]

20. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure.

21. When the Intraventricular Electrolytes infusion is complete, detach and remove the empty syringe from the pump and disconnect from the infusion line.

22. Remove the port needle. Apply gentle pressure and bandage the infusion site per your institution's standard of care.

After covering the insertion site with sterile tissue and a bandage, you may want to instruct the caregiver to keep the infusion site covered for 24 hours (with Betadine® gauze), then use a dry gauze to cover it for another 24 hours[3]

Dispose of the infusion components, needles, unused solutions, and other waste materials in accordance with local requirements.

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ADVERSE REACTIONS[1]

Adverse reactions reported in ≥8% of symptomatic pediatric patients ≥ age 3 with CLN2 disease in the Brineura® (cerliponase alfa) single-arm clinical study with extension at week 96.

The most frequent adverse reactions reported in patients < 3 years treated with Brineura were similar to those observed in patients ≥ 3 years of age except for hypersensitivity reactions, which were reported in 5 of 8 (63%) in patients < 3 years at baseline compared with 0 of 6 in patients ≥ 3 years of age at baseline:

- Increased body temperature
- 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, and patients should be observed closely, during and after Brineura infusion. If anaphylaxis occurs, immediately discontinue infusion and initiate appropriate medical treatment. Inform patients/caregivers of the signs and symptoms of anaphylaxis and to seek immediate medical care should these occur. Consider the risks and benefits of readministration of Brineura following an anaphylactic reaction.

Remind caregivers to contact their healthcare professional immediately if they observe any adverse reactions.

ADVERSE REACTIONS (CONTINUED)[1]

To report suspected adverse reactions, contact:

BioMarin Pharmaceutical Inc	FDA
Phone: 1-866-906-6100 Email: drugsafety@BMRN.com	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® (cerliponase alfa), please visit Brineura.com/HCP

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ADDITIONAL SAFETY INFORMATION[1]

Contraindications

- Brineura® (cerliponase alfa) is contraindicated in patients with any sign of 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

Hypersensitivity reactions including anaphylaxis

- Life-threatening hypersensitivity reactions including anaphylaxis have been reported in patients treated with enzyme replacement therapies, including Brineura. Hypersensitivity reactions have been reported in Brineura treated patients during the clinical studies. A total of 11 of 24 (46%) patients experienced hypersensitivity reactions during the infusion or within 24 hours of completion of the infusions. The signs and symptoms observed concomitantly with hypersensitivity reactions included pyrexia, vomiting, pleocytosis or irritability. Patients were routinely premedicated with antihistamines with or without antipyretics or corticosteroids, prior to infusion of Brineura
- 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. Inform patients/caregivers of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur
- 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

Description of selected adverse reactions

- Seizures were reported in 12 of 24 (50%) patients. The seizure types reported include atonic, generalized tonic-clonic, focal, and absence. Seizures were managed with standard anticonvulsive therapies and did not result in discontinuation of Brineura treatment
- Hematoma adverse reactions were reported in 5 of 24 (21%) patients treated with Brineura and presented as hematoma, post procedural hematoma, traumatic hematoma and subdural hematoma. Hematomas did not require treatment and did not interfere with Brineura infusion

ADDITIONAL SAFETY INFORMATION (CONTINUED)[1]

Device-related complications have been observed

- Brineura must only be administered via the intraventricular route using aseptic technique to reduce the risk of infection.[1,3] Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage, failure or potential infection
- 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 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
- In clinical studies with Brineura, out of the 24 patients, 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

Cardiovascular adverse reactions

- Monitor vital signs before infusion starts, periodically during infusion, and post-infusion in a healthcare setting
- Perform 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
- In the clinical studies, hypotension was reported in 2 of 24 (8%) patients, which occurred 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

Other precautions and special populations

- In a pivotal trial anti-drug antibodies (ADAs) were detected in serum (79%) and CSF (33.3%) in patients treated with Brineura for up to 161 weeks. No association was found in between serum of CSF ADA titers and incidence or severity of hypersensitivity
- In a separate trial that involved patients < 3 years of age, 14 of 14 (100%) and 3 of 14 (21%) of patients treated with Brineura developed ADAs in serum and CSF, respectively
- 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 2.5kg[1]
- Brineura has not been studied in pregnancy or lactation

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Brineura® (cerliponase alfa)

PLANNING FOR INFUSION

Healthcare professionals can help the caregivers or family plan ahead by:

- Explaining the infusion process so families know what to expect
- Suggesting they bring comforting items for their child, like a favorite blanket or pillow
- Recommending they bring items to keep their child engaged and entertained for about 4.5 hours during the infusion[1]—tablets or similar devices, books, toys, snacks, music, games, or favorite items
- Instructing them to prepare the child's infusion site in advance of the infusion
  - This may include providing specific instructions on hair removal, washing hair with antibacterial shampoo, or applying numbing cream[3]
- Preparing them for post-infusion, including informing them about which activities the child can resume and when, how to care for the wound site, and what to do if they notice adverse reactions and/or signs of infection
- Informing them about hypersensitivity[1]
  - Advise caregivers that hypersensitivity reactions related to Brineura® (cerliponase alfa) treatment, including fever, vomiting, and irritability, may occur. Inform caregivers of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur

AFTER INFUSION[3]

Post-infusion recommendations for caregivers and families:

- The dressing may be left in place for 24 hours[3]
- Watch for signs of infection or complication, which may include swelling, pain, discharge, or fever
  - If any signs of infection are present, instruct caregivers to immediately contact their child's healthcare provider

Recommendations for caregivers on what to prevent:

- Direct trauma to the reservoir
- Head injury
- Touching and scratching the intraventricular access device

For the first few days after infusion, public pools and other areas that may bathe the reservoir area with unclean water should be avoided to reduce the risk of infection.

As a healthcare professional, you can help advise caregivers about which activities are appropriate and safe for a child after infusion, and when their child may be able to return to regular routines and activities

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PREPARING FOR INFUSION

Following aseptic technique is important for minimizing the risk of infection.[2,3]

Some suggestions for the healthcare team:

- It is recommended that the first dose be administered at least 5 to 7 days after intraventricular access device implantation[1]
- Ensure your team is prepared and knowledgeable of the access and infusion steps
  - This includes coordinating with the pharmacy/healthcare team who will be preparing the drug for the child after he or she has been evaluated and deemed able to receive infusion
- If possible, use a child life specialist to help prepare the child for the procedure

If a caregiver is holding the child, he or she should consider wearing a mask to ensure that the area above the child's head and the reservoir remain sterile[3,4]

The steps within this guide are suggested practice for Brineura® (cerliponase alfa) administration. For further questions or detailed guidance, refer to your institution's policies and procedures. You also may want to consult with a neurosurgeon or other physicians within your institution who are experienced with intraventricular drug delivery.

PRE-INFUSION STEPS

Before beginning the infusion, consider taking the following steps:

- Administer premedications, which may include antihistamines with or without antipyretics or corticosteroids 30 to 60 minutes prior to the start of infusion[1]
- Apply numbing cream to the port area, allowing time for it to take effect[3]
  - You may choose to have a parent or caregiver apply numbing cream in advance
- Encourage the caregiver to take an active role during the infusion process
  - A sitting position is recommended for the patient[3]
  - Caregiver may help keep the child distracted during the port access by showing a movie or TV show on a tablet, or reading a book—this will help minimize movement
  - Caregiver may also help the medical team hold the child's head to minimize movement
- Disinfect the puncture site and surrounding area, following disinfectant instructions[3]

5 swabs are recommended: Clinicians experienced in intraventricular infusion recommend beginning the disinfection process by wearing 2 pairs of gloves and using 3 swabs, then removing the top pair of gloves to complete disinfection with the remaining 2 swabs[3]

Please see Important Safety Information throughout, and accompanying full Prescribing Information, with Boxed Warning for risk of anaphlyaxis or visit www.Brineura.com.

Brineura® (cerliponase alfa)

INDICATION AND IMPORTANT SAFETY INFORMATION

Brineura® (cerliponase alfa) injection for intraventricular use is indicated to slow the loss of ambulation in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2 disease), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Patients treated with enzyme replacement therapies have experienced life-threatening hypersensitivity reactions, including anaphylaxis. These reactions have occurred during and up to 24 hours after completion of the Brineura infusion. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy.

Administration of Brineura should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. Initiate Brineura in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue Brineura and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur.

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.

Observe patients closely during and after the infusion. 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. Consider the risks and benefits of readministration of Brineura following an anaphylactic reaction. If the decision is made to readminister Brineura after the occurrence of anaphylaxis, ensure appropriately trained personnel and equipment for emergency resuscitation (including epinephrine and other emergency medicines) are readily available during infusion. Initiate subsequent infusion at approximately one-half the initial infusion rate at which the anaphylactic reaction occurred.

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

Recommendations Prior to Brineura Treatment

Premedication of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30–60 minutes prior to the start of infusion. 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. Replace the intraventricular access device reservoir prior to 4 years of single-puncture administrations.

Special Populations

Brineura is not recommended 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.

Brineura has not been studied in pregnancy or lactation.

INDICATION AND IMPORTANT SAFETY INFORMATION (CONTINUED)

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 supervision of, a physician experienced in intraventricular administration.

Intraventricular Access Device-Related Complications

During the clinical trials 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.

Infusion Associated Reactions (IAR) such as vomiting, seizure, rash, pyrexia, hypersensitivity, and anaphylactic reaction have been observed in patients treated with Brineura. If an IAR occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administering antihistamines and/or antipyretics may ameliorate the symptoms. Closely monitor patients who have experienced IARs when re-administering Brineura.

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

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**, with Boxed Warning for risk of anaphylaxis or visit **www.Brineura.com**.

Brineura®
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Brineura® (cerliponase alfa)—the first and only treatment addressing the underlying cause of CLN2 disease

Brineura® (cerliponase alfa) injection for intraventricular use is indicated to slow the loss of ambulation in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2 disease), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

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

References: 1. Brineura [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2024. **2.** Cohen-Pfeffer JL, Gururangan S, Lester T, et al. Intracerebroventricular delivery as a safe, long-term route of drug administration. *Pediatr Neurol.* 2017;67:23-35. **3.** Development of the "Hamburg Best Practice Guidelines for ICV-Enzyme Replacement therapy (ERT) in CLN2 Disease" Based on 6 Years Treatment Experience in 48 Patients. Schwering C et col. *J Child Neurol.* 2021 Jul;36(8):635-641.

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