

# Brineura® (cerliponase alfa) dosing and administration guide

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.



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.



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

## INTRODUCTION TO BRINEURA® (CERLIPONASE ALFA)

Brineura® (cerliponase alfa) is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with CLN2 disease.<sup>1</sup>

- 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>1</sup>

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

This brochure contains guidance on the following:

- Dosage and administration overview (page 3)
- Brineura storage (page 4)
- Infusion supplies (page 5)
- Preparation and administration steps (page 6)
- Safety considerations (page 14)
- Tips for caregivers (page 18)
- Tips for healthcare professionals (page 20)

**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

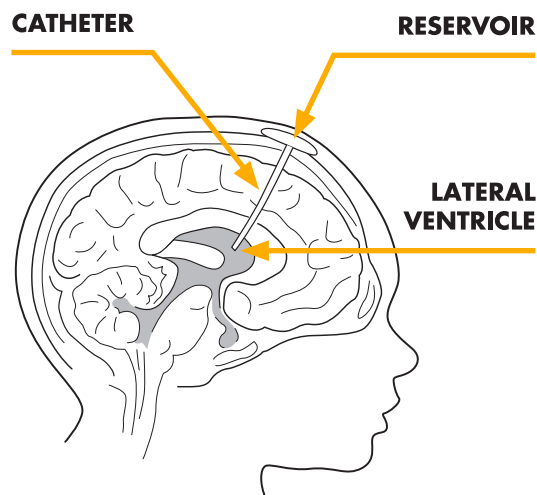
### Dosage<sup>1</sup>

- The recommended dosage of Brineura® (cerliponase alfa) in pediatric patients 3 years of age and older is 300 mg administered once every other week by intraventricular infusion
- The complete Brineura infusion, including the required infusion of Intraventricular Electrolytes, is approximately 4.5 hours. 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

### Important preparation and administration information<sup>1</sup>

**Aseptic technique must be strictly observed during preparation and administration.**

- Brineura should be administered by, or under the direction of, a physician knowledgeable in intraventricular administration
- 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
- 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 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.

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

 **Brineura**<sup>®</sup>  
(cerliponase alfa)

## 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<sup>1</sup>

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.

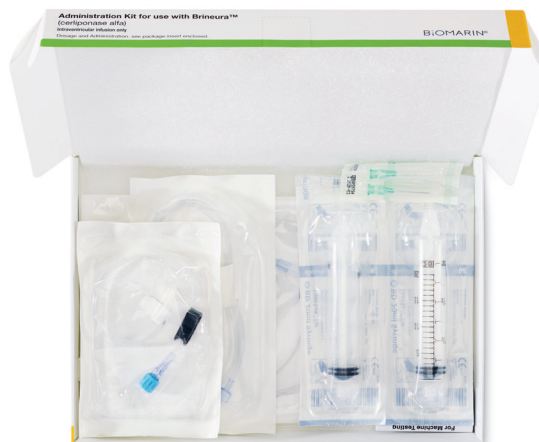


### Package 2 of 2: Administration Kit for use with Brineura<sup>1</sup>

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<sup>1</sup>:

- 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 2.5 mL/hr with delivery accuracy of  $\pm 1$  mL/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  $\leq 281$  mm Hg
- One sterile single-use luer lock syringe no larger than 3 mL (to check for patency and collect CSF as needed for testing) (not supplied). Larger syringes risk collapsing the catheter due to negative pressure and might be misinterpreted as an occlusion



B Braun Perfusor® Space Infusion Pump System

### Materials for aseptic technique<sup>1-3</sup>:

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

The brands listed are the registered trademarks of their respective owners and are not trademarks of BioMarin Pharmaceutical Inc.

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



## 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<sup>1</sup>:

- 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<sup>1</sup>:

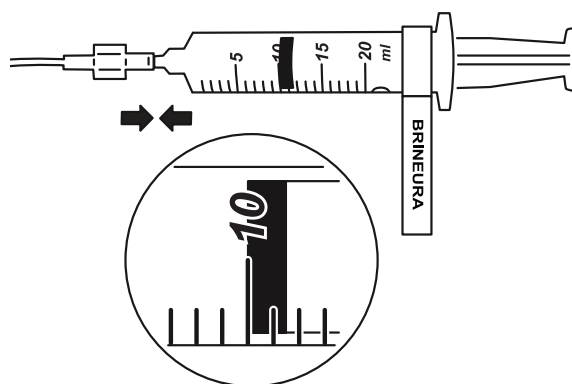
- Brineura is a clear to slightly opalescent and colorless to pale yellow solution. Intraventricular Electrolytes are a clear to colorless solution
- **Do not use** if the solutions are discolored or if there is other foreign particulate matter in the solutions
- Brineura vials may occasionally contain 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.

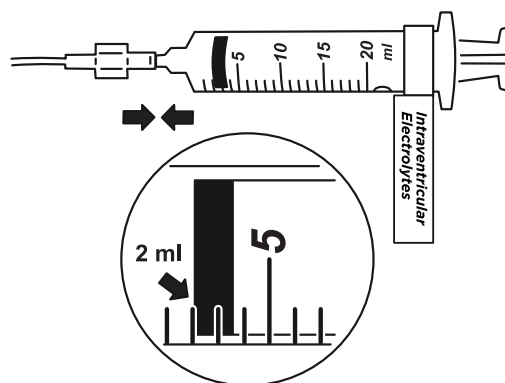
### Withdraw Brineura<sup>1</sup>:

- Use aseptic technique when preparing the Brineura syringe for infusion. Label 1 sterile syringe "Brineura" and attach the syringe needle
- Remove the green flip-off caps from the 2 Brineura vials
- Use the "Brineura" labeled syringe to withdraw a total of 10 mL from the Brineura vials
- **Do not** dilute Brineura
- **Do not** mix Brineura with any other drug



### Withdraw Intraventricular Electrolytes<sup>1</sup>:

- 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

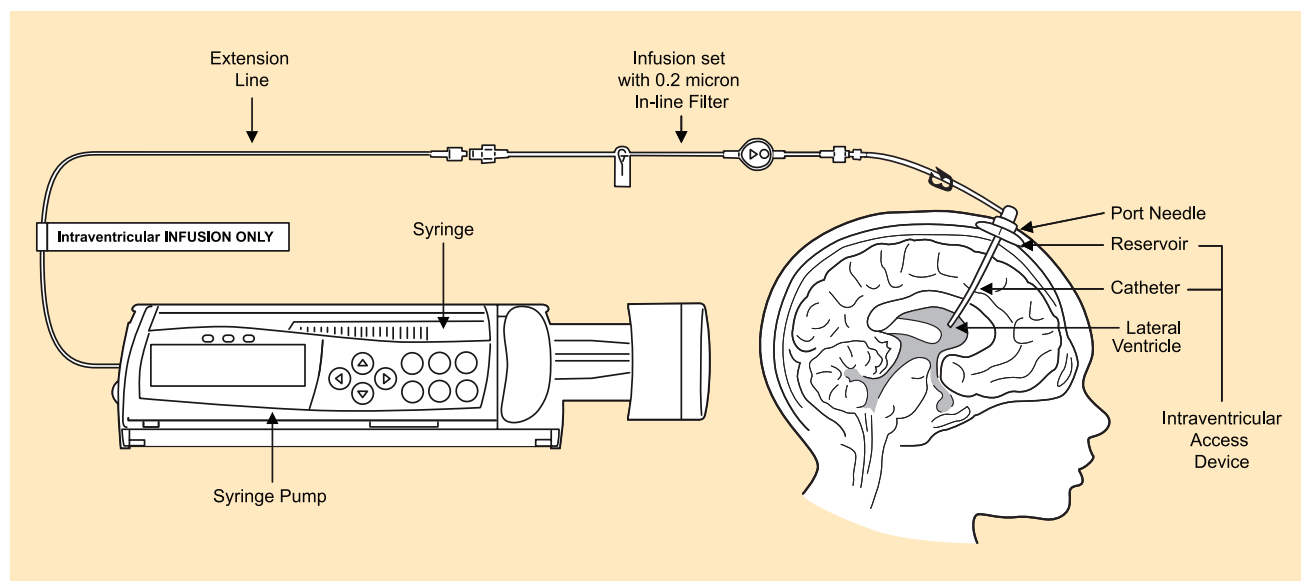


**Aseptic technique must be strictly observed during preparation and administration<sup>3</sup>**

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

**Brineura®**  
(cerliponase alfa)

## ADMINISTERING BRINEURA® (CERLIPONASE ALFA)<sup>1</sup>



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 the 2 vials, and the labeled syringe has been used to withdraw a total of 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<sup>3</sup>**



## ADMINISTERING BRINEURA® (CERLIPONASE ALFA) (CONTINUED)<sup>1</sup>



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.

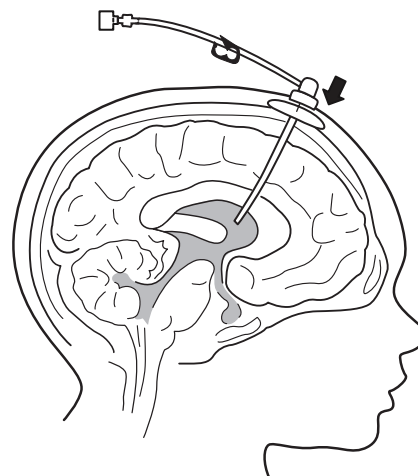
Please see Important Safety Information throughout, and accompanying full Prescribing Information.

 **Brineura**®  
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ADMINISTERING BRINEURA® (CERLIPONASE ALFA) (CONTINUED)<sup>1</sup>

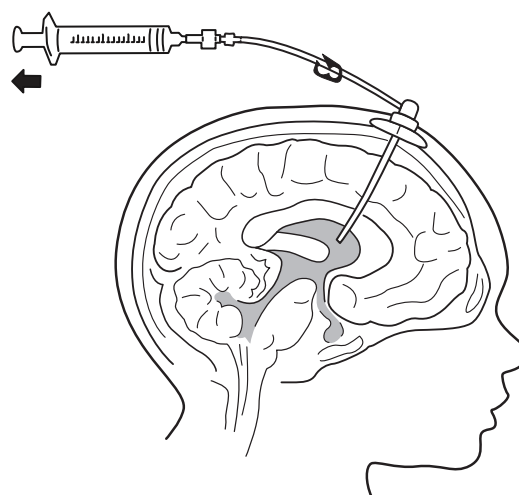
**7.** Insert the port needle into the intraventricular access device.

- Position the needle so that the line is running toward the back of the head
- If you do not successfully insert the port needle into the intraventricular access device on your first attempt, restart the procedure from the beginning (including rescrub, new sterile gloves, new port needle, etc)
- When puncturing, avoid rotating the needle if possible
- Do not force the needle—if it does not go in smoothly, check the reservoir position/usage



**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.

- Remove CSF slowly. If CSF cannot be withdrawn or other issues are encountered, consult with neurosurgeon
- **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
  - CSF may be sent for culture, glucose, protein, and cell count. Some sites also recommend sending CSF for s16/s18 PCR. It is recommended to send the first sample for culture, and with a separate syringe, collect a second sample for glucose, protein, cell count, and, if included, s16/s18 PCR



## ADMINISTERING BRINEURA® (CERLIPONASE ALFA) (CONTINUED)<sup>1</sup>

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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 pump to deliver at an infusion rate of 2.5 mL per hour. Set the occlusion alarm setting to alert at pressure  $\leq 281$  mm Hg. See syringe pump operating manual for details. **Do not deliver as a bolus or manually.**
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 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<sup>3</sup>**

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and accompanying full Prescribing Information.**



## ADMINISTERING INTRAVENTRICULAR ELECTROLYTES<sup>1</sup>

### 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 2.5 mL per hour. Set the occlusion alarm setting to alert at pressure  $\leq 281$  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<sup>1</sup>

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<sup>®</sup> gauze), then use a dry gauze to cover it for another 24 hours<sup>3</sup>**

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



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



## ADVERSE REACTIONS<sup>1</sup>

### Adverse reactions reported in $\geq 8\%$ of symptomatic pediatric patients with CLN2 disease in the Brineura<sup>®</sup> (cerliponase alfa) single-arm clinical study with extension at week 96:

- 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, 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)<sup>1</sup>

**To report suspected adverse reactions, contact:**

BioMarin Pharmaceutical Inc	FDA
Phone: 1-866-906-6100 Email: <a href="mailto:drugsafety@BMRN.com">drugsafety@BMRN.com</a>	Phone: 1-800-FDA-1088 Web: <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a>

**For medical information inquiries:**

- Email: [medinfo@BMRN.com](mailto: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](http://Brineura.com/HCP)**



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



## ADDITIONAL SAFETY INFORMATION<sup>1</sup>

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### 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

### Description of selected adverse reactions at 96 weeks

- Seizures were reported in 12 of 24 (50%) 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
- Hematoma adverse reactions were reported in 5 (21%) 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

### Device-related complications have been observed

- Brineura must only be administered via the intraventricular route using aseptic technique to reduce the risk of infection. Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage, failure or potential infection
- 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, 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 (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

## ADDITIONAL SAFETY INFORMATION (CONTINUED)<sup>1</sup>

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### Hypersensitivity reactions

- Hypersensitivity reactions have been reported in Brineura® (cerliponase alfa)-treated patients during the clinical studies. A total of 11 (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

### Other precautions and special populations

- 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 between serum or CSF ADA titers and incidence or severity of hypersensitivity
- Brineura has not been studied in pregnancy or lactation
- Safety and effectiveness in patients less than 3 years of age have not been established

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## PLANNING FOR INFUSION

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### 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<sup>1</sup>—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<sup>3</sup>
- 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<sup>1</sup>
  - 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<sup>3</sup>

### Post-infusion recommendations for caregivers and families:

- The dressing may be left in place for 24 to 48 hours
- 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
- Give caregivers instructions on when child may resume activities, and if there are any restrictions they should know about

### 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 unclear 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**



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



## PREPARING FOR INFUSION

Following aseptic technique is important for minimizing the risk of infection.<sup>1</sup>

### 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<sup>1</sup>
  - This allows for the wound to heal, the swelling to decrease, and prevents backward flow through the tract of the catheter<sup>3</sup>
- 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
- Reserve a private room or area for the intraventricular access portion of the procedure, preferably with a closed door/curtain to reduce foot traffic<sup>3,4</sup>
- 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<sup>3,4</sup>**



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<sup>1</sup>
- Apply numbing cream to the port area, allowing time for it to take effect<sup>3</sup>
  - 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
  - Have the child sit with a caregiver holding him or her gently from behind—child should be sitting up or positioned at a 45-degree angle<sup>3</sup>
  - 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
- Palpate the scalp to identify the intraventricular access device site<sup>3</sup>
- Disinfect the puncture site and surrounding area, following disinfectant instructions<sup>3</sup>



**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<sup>3</sup>**



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



## INDICATION AND IMPORTANT SAFETY INFORMATION

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### 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.

## INDICATION AND IMPORTANT SAFETY INFORMATION (CONTINUED)

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### 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 ( $\geq 8\%$ ) 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](http://www.fda.gov/medwatch).**

Please see accompanying full Prescribing Information, or visit [www.Brineura.com](http://www.Brineura.com).

## 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 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.



For any additional information about Brineura, please visit [Brineura.com/HCP](https://Brineura.com/HCP).

**References:** 1. Brineura [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2020. 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. Slavic I, Cohen-Pfeffer JL, Gururangan S, et al. Best practices for the use of intracerebroventricular drug delivery devices. *Mol Genet Metab*. 2018;124:184-188. 4. Peyrl A, Chocholous M, Azizi AA, et al. Safety of Ommaya reservoirs in children with brain tumors: a 20-year experience with 5472 intraventricular drug administrations in 98 patients. *J Neurooncol*. 2014;120:139-145.

