BRINEURA® ▼ (cerliponase alfa)

IMPORTANT INFORMATION ON DOSING & ADMINISTRATION FOR HEALTH CARE PROFESSIONALS

PLEASE READ PRIOR TO ADMINISTRATION OF CERLIPONASE ALFA

▼ This medicinal product is subject to additional monitoring, special reporting is required in relation to adverse reactions.

Version 2.0 Date of latest revision of the text 09 June 2025
EUCAN-BRIN-00167

DOSING & ADMINISTRATION GUIDE

Getting ready to administer BRINEURA[1]

BRINEURA is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency.

The following steps are recommended for the dosing and administration of BRINEURA and are based on the Summary of Product Characteristics. Please refer to the full Summary of Product Characteristics (provided with this pack), your physician's instructions and your institution's policies and procedures for additional information and guidance.

BRINEURA must only be administered via the intracerebroventricular route. BRINEURA must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.

Special warnings and precautions for use[1]

Device-related complications

BRINEURA must be administered using aseptic technique to **reduce the risk of infection**.

In clinical studies, events of intracerebroventricular access device-related infections were observed. In these cases, antibiotics were administered, the intracerebroventricular access device was replaced and BRINEURA treatment was continued.

Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. CSF samples should routinely be sent for testing to detect subclinical device infections. In clinical studies, antibiotics were administered, the intracerebroventricular access device was replaced, and BRINEURA treatment was continued.

Degradation of ICV device

Material degradation of the intracerebroventricular access device reservoir occurs after long periods of use according to bench-top testing and as observed in clinical trials with **approximately 4 years of use.**

Access device replacement should be considered prior to 4 years of regular administration of BRINEURA. However, it must always be ensured, that the intracerebroventricular access device is used in accordance with the provisions of the respective medical device manufacturer.

Prior to initiation of BRINEURA infusion healthcare professionals should:

- Implant an intracerebroventricular access device that is appropriate for accessing the cerebral ventricles for therapeutic administration. This should be done five to seven days before the first infusion in order to allow for healing.
- Inspect the scalp for skin integrity to ensure the intracerebroventricular access device is not compromised prior to each infusion.
- Inspect the infusion site.
- A patency check should be performed to detect intracerebroventricular access device leakage and/or failure.

If a problem is identified with the intracerebroventricular access device:

- Do not administer BRINEURA treatment.
- Prior to subsequent infusions, replacement of the access device may be required.
- In case of intracerebroventricular access device leakage, breakage, malfunction, or failure refer to the manufacturer's labelling for further instruction.
- Confirmation of the integrity of the device may require a consultation with a neurosurgeon.

Caution should be taken in subjects prone to complications from intracerebroventricular medicinal product administration, including patients with obstructive hydrocephalus.

Clinical and laboratory monitoring

Vital signs should be monitored before infusion starts, periodically during infusion, and post-infusion, in a healthcare setting. Upon completion of the infusion, the patient status should be clinically assessed and observation may be necessary for longer periods if clinically indicated, particularly in patients <3 years of age.

Electrocardiogram (ECG) monitoring during infusion should be performed in patients with a history of bradycardia, conduction disorder, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease. In cardiac normal patients, regular 12-lead ECG evaluations should be performed every 6 months.

Cerebrospinal fluid (CSF) samples should routinely be sent for testing to detect subclinical device infections.

Paediatric population

There are limited data in patients with advanced disease progression at treatment initiation who were included in clinical trials and no clinical data are available in children less than 1 year of age. New-borns may have decreased integrity of the blood-brain barrier. In children less than 3 years, increased medicinal product exposure on the periphery was not associated with a clear change in the safety profile.

Anaphylactic reactions

Anaphylactic reactions have been reported with BRINEURA. As a precautionary measure, appropriate medical support should be readily available when BRINEURA is administered. If anaphylactic reactions occur, the infusion should be immediately discontinued, and appropriate medical treatment should be initiated. Patients should be observed closely during and after the infusion. If anaphylaxis occurs, caution should be exercised upon re-administration.

Sodium and potassium content

This medicinal product contains 17.4 mg sodium per vial of BRINEURA and flushing solution, equivalent to 0.87% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This medicinal product contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially 'potassium-free'.

Recommended dose[1]

BRINEURA 150 mg solution for infusion is available in single-use vials, each containing 5 ml of solution. Each ml of solution for infusion contains 30 mg of cerliponase alfa.

The recommended dose is 300 mg (10 ml total from 2 vials) administered once every other week by intracerebroventricular infusion. In patients <2 years of age, lower doses are recommended.

Pre-treatment of patients with antihistamines, with or without antipyretics, is recommended 30 to 60 minutes prior to the start of infusion.

Paediatric population

Treatment of BRINEURA in children 1 to 9 years of age in clinical studies. There is no clinical data available in children below 1 year of age. The posology proposed in children below 2 years has been estimated based on brain mass. Treatment should be based on the benefits and risks to the individual patient as assessed by the physician. It is important to initiate treatment in patients as early as possible.

DOSING & ADMINISTRATION GUIDE

BRINEURA should be administered according to the following recommended dose once every other week:

- Birth to <6 months: 100 mg
- 6 months to <1 year: 150 mg
- 1 year to <2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Dose adjustments

Consideration of dose adjustments may be necessary for patients who may not tolerate the infusion. The dose may be reduced by 50% and/or the infusion rate decreased to a slower rate. If the infusion is interrupted due to a hypersensitivity reaction, it should be restarted at approximately one-half the initial infusion rate at which the hypersensitivity reaction occurred.

The infusion should be interrupted and/or the rate slowed in patients who, in the judgement of the treating physician, have a possible increase in intracranial pressure during the infusion as suggested by symptoms such as headache, nausea, vomiting or decreased mental state. These precautions are of particular importance in patients <3 years of age.

Storage and care[1]

One carton of BRINEURA contains three vials (two vials of BRINEURA and one vial of flushing solution). Each vial of BRINEURA and flushing solution is intended for single use only:

- Store upright in a freezer (–25°C to –15°C).
- Store in the original package in order to protect from light.
- Unopened frozen vials have a shelf life of up to 2 years, see expiry date on the carton.

Before use:

- Vials should be thawed at room temperature for approximately 60 minutes.
- It is recommended to thaw vials outside the carton. Condensation will occur during the thaw period. Do not thaw or warm vials any other way.
- Do not shake vials.
- BRINEURA and flushing solution must be completely thawed and used immediately. Product should only be withdrawn from the unopened vials immediately prior to use. If immediate use is not possible, unopened vials of BRINEURA or flushing solution should be stored at 2–8°C and used within 24 hours.
- If open vials or product held in syringes are not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
- Do not dilute BRINEURA or mix with any other medications. Do not re-freeze vials or freeze syringes containing BRINEURA or flushing solution.

Prior to administration

Aseptic technique must be strictly observed during preparation and administration.

- BRINEURA and the flushing solution must only be administered via the intracerebroventricular route.
- Surgical implantation of an intracerebroventricular access device (reservoir and catheter) must take place prior to the first infusion.
- The implanted intracerebroventricular access device should be appropriate for accessing the cerebral ventricles for therapeutic administration.

A number of infusion components are required (but not supplied) – all must be sterile and compatible with BRINEURA and the flushing solution:

- Refer to BRINEURA Summary of Product Characteristics section 6.6 for the list of compatible infusion components.

Confirm you have the following sterile components before preparing to administer BRINEURA:

- A programmable syringe pump with appropriate delivery range, delivery rate accuracy and alarms for incorrect delivery or occlusion. The pump must be programmable to deliver the medicinal product at a constant rate of 2.5 ml/hr. The complete infusion time, including BRINEURA and the required flushing solution, is administered over approximately 2 to 4.5 hours, depending on the dose and volume administered.
- Two single-use drug syringes compatible with the pump equipment. A syringe volume of 10 to 20 ml is recommended.
- Two single-use hypodermic syringe needles (21 G, 25.4 mm).
- One single-use infusion set. An extension line may be added if needed. A length of 150 to 206 cm (not to exceed 400 cm) and an inner diameter of 0.1 cm is recommended.
- A 0.2 µm inline filter. The inline filter may be integral to the infusion set. The inline filter should be placed as close as practically possible to the port needle.
- A non-coring port needle with a gauge of 22 or smaller and a suggested length of 16 mm. Refer to the intracerebroventricular access device manufacturer's recommendation for the port needle.
- One empty sterile single-use syringe (for collection of cerebrospinal fluid (CSF) to check patency).

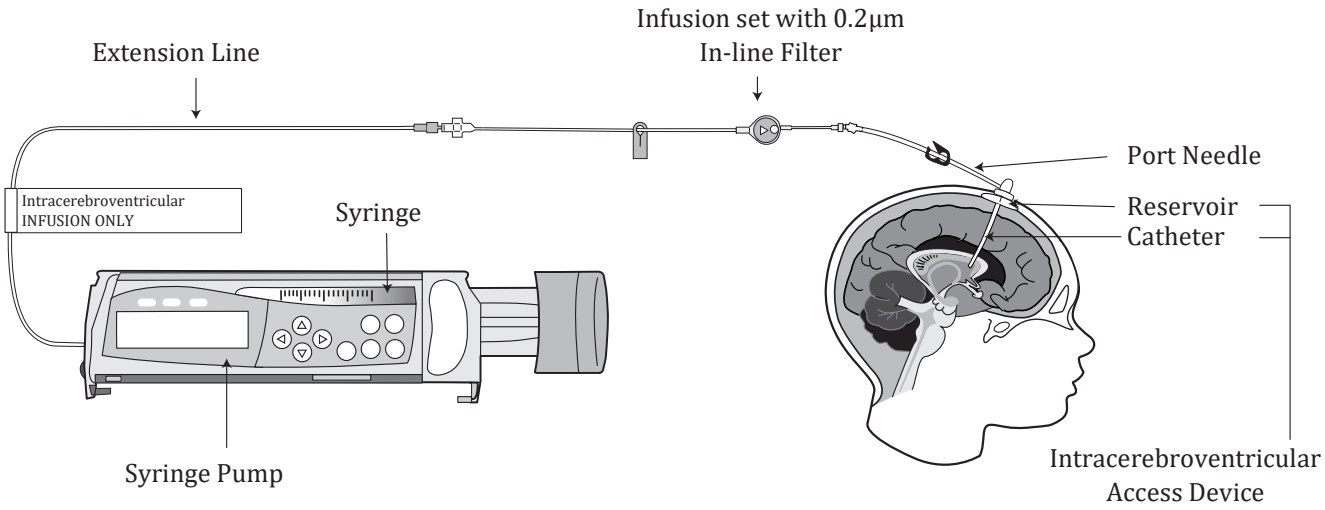

Figure 1: Infusion system set-up

Preparing BRINEURA and flushing solution

Remove the carton containing two vials of BRINEURA and one vial of flushing solution from the freezer:

- Vials should be thawed at room temperature for approximately 60 minutes.
- It is recommended to thaw vials outside the carton. Condensation will occur during the thaw period.
- Do not thaw or warm vials any other way.
- Do not shake vials.
- BRINEURA and flushing solution must be completely thawed and used immediately. Product should only be withdrawn from the unopened vials immediately prior to use. If immediate use is not possible, unopened vials of BRINEURA or flushing solution should be stored at 2–8°C and used within 24 hours.

Inspect all the thawed vials:

- BRINEURA solution should be clear to slightly opalescent and colourless to pale yellow. The flushing solution should be clear and colourless.
- BRINEURA vials may occasionally contain thin translucent fibres or opaque particles. These naturally occurring particles are cerliponase alfa. These particles are removed via the 0.2 µm inline filter without having a detectable effect on the purity or strength of BRINEURA. The flushing solution may contain particles that dissolve when the vial is fully thawed. Do not use if the solutions are discoloured or if there is other foreign particulate matter in the solutions.

WITHDRAW BRINEURA:

- Label one unused sterile syringe ‘BRINEURA’ and attach a syringe needle.
- Remove green flip-off caps from both BRINEURA vials.
- Using aseptic technique, withdraw the volume of BRINEURA solution per required dose into the sterile syringe labelled 'BRINEURA'.
- Do not dilute BRINEURA. Do not mix BRINEURA with any other medicinal product.
- Discard needle and empty vials per local requirements.

WITHDRAW FLUSHING SOLUTION:

- Determine the volume of flushing solution needed to ensure complete delivery of BRINEURA to the cerebral ventricles. Calculate the flush volume by adding the priming volume of all infusion components, including the intracerebroventricular access device
- Label one unused sterile syringe ‘flushing solution’ and attach a syringe needle
- Remove the yellow flip-off cap from the flushing solution vial
- Using aseptic technique, withdraw the appropriate amount of flushing solution from the vial into the new sterile syringe labelled ‘flushing solution’
- Discard needle and vial with remaining solution

Administering BRINEURA

IMPORTANT INFORMATION ON COMPATABILITY OF INFUSION COMPONENTS:

1. BRINEURA should be administered with **infusion components** shown to be **chemically and physically compatible** with BRINEURA and flushing solution.
2. **CE marked intracerebroventricular access devices**, and disposable components listed below or equivalent **should be used** to deliver BRINEURA.
   - BRINEURA is compatible with intracerebroventricular access **devices made of a silicone dome with a stainless steel or polypropylene base that is attached to a silicone catheter**.
   - BRINEURA is compatible with **disposable infusion components made of PVC, PVC (non-DEHP) polyethylene, polyethersulfone (PES), polypropylene (PP), and PTFE**.

INTRACEREBROVENTRICULAR INFUSION OF BRINEURA:

Administer BRINEURA **before** flushing solution.

1. Label the infusion line for 'intracerebroventricular infusion only'.
2. Attach the syringe containing BRINEURA to the extension line, if used, otherwise connect the syringe to the infusion set. The infusion set must be equipped with a 0.2 µm inline filter. See Figure 1 on page 5.
3. Prime the infusion components with BRINEURA
4. Inspect the scalp for signs of intracerebroventricular access device leakage or failure and for potential infections (swelling, erythema of the scalp, extravasation of fluid or bulging of the scalp around or above the intracerebroventricular access device). Do not administer BRINEURA if there are signs and symptoms of acute intracerebroventricular access device leakage, device failure or device-related infection.
5. Prepare the scalp for intracerebroventricular infusion using aseptic technique per institution standard of care.
6. Insert the port needle into the intracerebroventricular access device.
7. Connect a separate empty sterile syringe (no larger than 3 ml) to the port needle. Withdraw 0.5 ml to 1 ml of CSF to check patency of the intracerebroventricular access device.
   - Do not return CSF to the intracerebroventricular access device. CSF samples should routinely be sent for infection monitoring.
8. Attach the infusion set to the port needle (see Figure 1)
   - Secure the components per institution standard of care.
9. Place the syringe containing BRINEURA into the syringe pump and programme the pump to deliver at an infusion rate of 2.5 ml per hour.
   - Programme the pump alarms to sound at the most sensitive settings for pressure, rate and volume limits. See the syringe pump manufacturer's operating manual for details.
   - **Do not deliver as a bolus or manually.**
10. Initiate infusion of BRINEURA at a rate of 2.5 ml per hour
    - Advise caregivers that movement of the child during the infusion should be kept to a minimum to avoid dislodgement of the needle.
11. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure.
12. Verify that the 'BRINEURA' syringe in the syringe pump is empty after the infusion is complete. Detach and remove the empty syringe from the pump and disconnect from the tubing. Discard the empty syringe in accordance with local requirements.

INTRACEREBROVENTRICULAR INFUSION OF FLUSHING SOLUTION:

Administer the flushing solution provided after BRINEURA infusion is complete.

1. Attach the syringe containing the calculated volume of flushing solution to the infusion components
2. Place the syringe containing flushing solution into the syringe pump and programme the pump to deliver at an infusion rate of 2.5 ml per hour
   - Programme the pump alarms to sound at the most sensitive settings for pressure, rate and volume limits. See the syringe pump manufacturer's operating manual for details
   - **Do not deliver as a bolus or manually.**
3. Initiate infusion of flushing solution at a rate of 2.5 ml per hour.
4. Periodically inspect the infusion components during the infusion for signs of leakage or delivery failure.
5. Verify that the 'flushing solution' syringe in the syringe pump is empty after the infusion is complete. Detach and remove the empty syringe from the pump and disconnect from the infusion line.
6. Remove the port needle. Apply gentle pressure and bandage the infusion site per institution standard of care.
7. Dispose of the infusion components, needles, unused solutions and other waste materials in accordance with local requirements.

TRACEABILITY

Please ensure you record the product name and batch number in the patient file.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt

Adverse events can also be reported directly to BioMarin via the following email address: drugsafety@bmrn.com

Reference: 1. BRINEURA® Summary of Product Characteristics.
Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/brineura#product-info and https://medicinesauthority.gov.mt/rmm

Developed and funded by BioMarin International Ltd.

Version 2.0 Date of latest revision of the text 09 June 2025
EUCAN-BRIN-00167