▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – CERLIPONASE ALFA (BRINEURA) 30 MG/ML SOLUTION FOR INJECTION

1. NAME OF THE MEDICINE

cerliponase alfa

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Brineura contains 150 mg of cerliponase alfa* in 5 mL of solution.

Each mL of solution for injection contains 30 mg of cerliponase alfa.

*Cerliponase alfa is produced in mammalian Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent and colourless to pale yellow solution, that may occasionally contain thin translucent fibres or opaque particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.

Dose

The recommended dose is 300 mg cerliponase alfa administered once every other week by intracerebroventricular infusion.

In patients less than 2 years of age, lower doses are recommended, see *Paediatric population* section.

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

Continuation of long-term treatment should be subject to regular clinical evaluation whether the benefits are considered to outweigh the potential risks to individual patients.

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 below 3 years of age.

Paediatric population

The safety and efficacy of Brineura in children less than 3 years of age has not yet been established. Limited data are available for children aged 2 years and no clinical data is available in children below 2 years of age (see section 5.1 Pharmacodynamic properties). The posology proposed in children below 2 years has been estimated based on brain mass.

Treatment of Brineura was initiated in children 2 to 8 years of age in clinical studies. There is limited data in patients older than 8 years of age. Treatment should be based on the benefits and risks to the individual patient as assessed by the physician.

The posology selected for patients is based on age at time of treatment and should be adjusted accordingly (see Table 1). In patients less than 3 years of age the recommended dose is in accordance with the posology used in the ongoing clinical study 190-203, see section 5.1 Pharmacodynamic properties.

Table 1: Dose and volume of Brineura

Age groups	**Total dose administered every other week (mg)**	**Volume of Brineura solution (mL)**
Birth to < 6 months	100	3.3
6 months to < 1 year	150	5
1 year to < 2 years	200 (first 4 doses) 300 (subsequent doses)	6.7 (first 4 doses) 10 (subsequent doses)
2 years and older	300	10

Method of administration

Intracerebroventricular use.

It is recommended that the first dose be administered at least 5 to 7 days after device implantation.

Precautions to be taken before handling or administering the medicinal product

Aseptic technique must be strictly observed during preparation and administration.

Brineura and the flushing solution must only be administered by the intracerebroventricular route. Each vial of Brineura and flushing solution are intended for single use in one patient only. Discard any residue.

Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intracerebroventricular access device). The intracerebroventricular access device must be implanted prior to the first infusion. The implanted intracerebroventricular access device should be appropriate for accessing the cerebral ventricles for therapeutic administration.

Following Brineura infusion, a calculated amount of flushing solution must be used to flush the infusion components including the intracerebroventricular access device in order to fully administer Brineura and to maintain patency of the intracerebroventricular access device (see section 6.6 Special precautions for disposal). Brineura and flushing solution vials should be thawed prior to administration. The infusion rate for Brineura and the flushing solution is 2.5 mL/hour. The complete infusion time, including Brineura and the required flushing solution, is approximately 2 to 4.5 hours, depending on the dose and volume administered.

Device compatibility

Brineura should be administered with infusion components shown to be chemically and physically compatible with administration of Brineura and flushing solution. CE marked intracerebroventricular access devices, and disposable components listed below or equivalent should be used to deliver Brineura.

Intracerebroventricular access devices shown to be compatible with Brineura and flushing solution and used in Brineura clinical studies include Codman HOLTER RICKHAM and HOLTER SALMON-RICKHAM Reservoirs, Codman Ventricular Catheter, and Medtronic CSF-Ventricular Reservoir (with catheter).

Brineura is compatible with disposable infusion components made of PVC, PVC (non-DEHP) polyethylene, polyethersulfone (PES), polypropylene (PP), and PTFE. The following CE marked disposable infusion components were used in Brineura clinical trials:

- Syringe: Braun and BD Luer-Lok™ Extension Set: Fresenius Injectomat® line, Alaris™ CC Extension set, Vygon Lectro-Cath Extension tube
- Extension Set with 0.2 micron filter: Impromediform GmbH
- Port needle: Deltec® GRIPPER® Needles

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

Preparation for administration of Brineura and flushing solution

The following components (not supplied) are required for proper administration of Brineura and flushing solution (see Figure 1). All infusion components must be sterile. Brineura and flushing solution are supplied and stored frozen (see section 6.4 Special precautions for storage).

- 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.
- Two single-use 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 is required. 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 CSF to check patency).

Thaw Brineura and flushing solution

Thaw Brineura vials and flushing solution vial at room temperature for approximately 60 minutes. **Do not** thaw or warm vials any other way. **Do not** shake vials. Condensation will occur during thawing period. Thawing the vials outside the carton is recommended.

Brineura and flushing solution must be completely thawed and used immediately (see section

6.3 Shelf life**).**

Do not re-freeze vials or freeze syringes containing Brineura or flushing solution.

Inspect thawed Brineura and flushing solution vials

Inspect the vials to ensure they are fully thawed. Brineura should be clear to slightly opalescent and colourless to pale yellow. 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. The flushing solution should be clear and colorless.

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 the green flip-off caps from both Brineura vials. Using aseptic technique, withdraw the volume of Brineura solution per required dose (see Table 1 in section 4.2) into the sterile syringe labelled “Brineura”. Do not dilute Brineura. Do not mix Brineura with any other medicinal product. Discard the 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 the needle and the vial with the remaining solution per local requirements.

Intracerebroventricular Infusion of Brineura

Administer Brineura **before** the 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.
3. Prime the infusion components with Brineura.
4. Inspect the scalp for signs of intracerebroventricular access device leakage or failure and for potential infections. Do not administer Brineura if there are signs and symptoms of acute intracerebroventricular access device leakage, device failure, or device-related infection (see section 4.3 Contraindications and 4.4 Special warnings and precautions for use).
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 (see section 4.4 Special warnings and precautions for use).
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 program the pump to deliver at an infusion rate of 2.5 mL per hour.

- Program 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.
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.

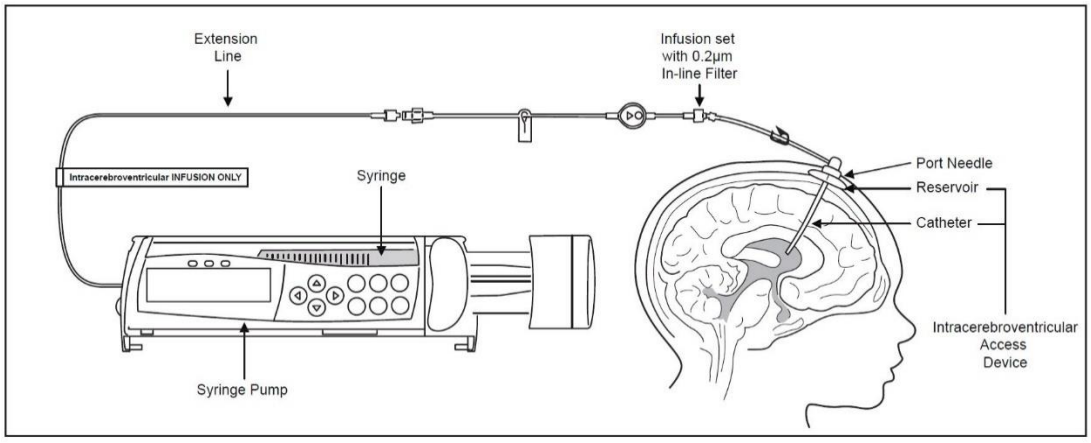


Figure 1: Infusion System Set Up

Intracerebroventricular infusion of the flushing solution

Administer the flushing solution provided **after** the Brineura infusion is complete.

1. Attach the syringe containing the calculated volume of flushing solution to the infusion components (see 6.6 Special precautions for disposal).
2. Place the syringe containing the flushing solution into the syringe pump and program the pump to deliver an infusion rate of 2.5 mL per hour.
   - Program 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 the 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.

4.3 Contraindications

Life-threatening anaphylactic reaction to the active substance or to any of the excipients listed in section 6.1, if re-challenge is unsuccessful (see section 4.4 Special warnings and precautions for use).

CLN2 patients with ventriculo-peritoneal shunts.

Brineura must not be administered as long as there are signs of acute intracerebroventricular access device leakage, device failure, or device-related infection (see section 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Device-related complications

Brineura must be administered using aseptic technique to reduce the risk of infection. Intracerebroventricular access device-related infections, including sub-clinical and meningitis, have been observed in patients treated with Brineura. Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. In clinical studies, antibiotics were administered, the intracerebroventricular access device was replaced, and Brineura treatment was continued.

Healthcare professionals should inspect the scalp for skin integrity to ensure the intracerebroventricular access device is not compromised prior to each infusion. Common signs of device leakage and device failure include swelling, erythema of the scalp, extravasation of fluid, or bulging of the scalp around or above the intraventricular access device.

Inspection of the infusion site and a patency check must be performed to detect intracerebroventricular access device leakage and/or failure prior to initiation of Brineura infusion (see section 4.2 Dose and method of administration and 4.3 Contraindications). The signs and symptoms of device-related infections may not be apparent, therefore, CSF samples should routinely be sent for testing to detect subclinical device infections. Consultation with a neurosurgeon may be needed to confirm the integrity of the device. Brineura treatment should be interrupted in cases of device failure and may require replacement of the access device prior to subsequent infusions.

Material degradation of the intracerebroventricular access device reservoir occurs after long periods of use as confirmed in benchtop testing and 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.

In case of intracerebroventricular access device-related complications, refer to the manufacturer’s labelling for further instruction.

Caution should be taken in patients 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 less than 3 years.

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.

CSF samples should routinely be sent for testing to detect subclinical device infections (see section 4.2 Dose and method of administration).

Anaphylactic reactions

Anaphylactic reactions have been reported with Brineura use during clinical trials and during postmarketing use. Healthcare professionals should be aware of the possible symptoms of anaphylaxis such as: generalized hives, pruritus or flushing, swollen lips, tongue, and/or uvula, dyspnoea, bronchospasm, stridor, hypoxemia, hypotonia, syncope, diarrhoea or incontinence. As a precautionary measure, appropriate medical support should be readily available when Brineura is administered. If anaphylactic reactions occur, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion. If an anaphylactic reaction occurs, caution should be exercised upon re-administration.

Sodium content

This medicinal product contains 17.42 mg sodium per vial of Brineura and flushing solution. This should be taken into consideration for patients on a controlled sodium diet.

Use in the elderly

No data available.

Paediatric use

There were no patients with advanced disease progression at treatment initiation who were included in clinical trials and no clinical data is available in children < 2 years. Patients with advanced CLN2 disease and newborns may have decreased integrity of the blood-brain barrier. Effects of the potentially increased medicinal product exposure on the periphery are unknown.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interactions

No interaction studies have been performed. Cerliponase alfa is a zymogen that undergoes activation in lysosomes and has limited systemic exposure due to intracerebroventricular administration. Accordingly, interactions between cerliponase alfa and other medicinal products are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No fertility studies with cerliponase alfa have been conducted in animals or humans.

Use in pregnancy

Pregnancy Category B2

There are no data on the use of Brineura in pregnant women. Animal reproduction studies have not been conducted with cerliponase alfa. It is not known whether cerliponase alfa can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Brineura should be given to a pregnant woman only if clearly needed.

Use in lactation

There are no data on the presence of cerliponase alfa in human milk, the effects of cerliponase alfa on the breastfed child, or the effects of cerliponase alfa on milk production. Breastfeeding should be discontinued during treatment with Brineura.

4.7 Effects on ability to drive and use machines

No studies on the effect of Brineura on the ability to drive or use machines have been performed.

4.8 Adverse effects (Undesirable effects)

Summary of the safety profile

The adverse reactions described in this section were evaluated in 24 patients with CLN2 disease who received at least one dose of Brineura in clinical studies of up to 161 weeks. The most frequent (>20%) adverse reactions observed during Brineura clinical trials include pyrexia, low CSF protein, ECG abnormalities, vomiting, upper respiratory tract infections, and hypersensitivity. No patients had to have their treatment discontinued due to adverse events.

Tabulated list of adverse events reported in the pivotal clinical studies

The adverse events reported in ≥4% of patients in the pivotal studies, regardless of causality, are listed in Table 2.

Table 2: Frequency of Adverse Events with Brineura

MedDRA System Organ Class/Preferred Term	Overall (n = 24)	Frequency
Cardiac Disorders	4 (17%)	Very common
Bradycardia[a]	2 (8%)	Common
Gastrointestinal disorders	20 (83%)	Very common
Vomiting[a]	15 (63%)	Very common
Constipation	8 (33%)	Very common
Diarrhea	7 (29%)	Very common
Dysphagia	7 (29%)	Very common
Abdominal pain[a]	3 (13%)	Very common
Oral mucosal blistering[a]	1 (4%)	Common
Tongue blistering[a]	1 (4%)	Common
Gastrointestinal disorder[a]	1 (4%)	Common
General disorder and administration site conditions	19 (79%)	Very common
Pyrexia[a]	17 (71%)	Very common
Gait disturbance	7 (29%)	Very common
Feeling jittery[a]	2 (8%)	Common
Pain[a]	2 (8%)	Common
Immune system disorder	10 (42%)	Very common
Hypersensitivity[a]	9 (38%)	Very common
Infections and infestations	24 (100%)	Very common
Upper respiratory tract infection[a]	13 (54%)	Very common
Nasopharyngitis	10 (42%)	Very common
Rhinitis	10 (42%)	Very common
Viral infection	8 (33%)	Very common
Gastroenteritis	7 (29%)	Very common
Pharyngitis	7 (29%)	Very common
Viral upper respiratory tract infection	6 (25%)	Very common
Tonsillitis	5 (21%)	Very common
Conjunctivitis[a]	4 (17%)	Very Common
Device Related Infection[a]	2 (8%)	Common
Injury, poisoning, and procedural complications	19 (79%)	Very common
Fall	7 (29%)	Very common
Nervous system disorders	24 (100%)	Very common
Seizure[a]	14 (58%)	Very common
Epilepsy[a]	12 (50%)	Very common
Generalised tonic-clonic seizure[a]	12 (50%)	Very common
Myoclonus[a]	8 (33%)	Very common

MedDRA System Organ Class/Preferred Term	Overall (n = 24)	Frequency
Tremor	7 (29%)	Very common
Petit mal epilepsy[a]	7 (29%)	Very common
Dystonia	5 (21%)	Very common
Extensor plantar response	5 (21%)	Very common
Clonic convulsion[a]	1 (4%)	Common
Drop attacks[a]	2 (8%)	Common
Partial seizures[a]	2 (8%)	Common
Seizure cluster[a]	2 (8%)	Common
Status epilepticus[a]	1 (4%)	Common
Atonic Seizures[a]	2 (8%)	Common
Headache[a]	4 (17%)	Very common
CSF Pleocytosis[a]	4 (17%)	Very common
Dropped head syndrome[a]	2 (8%)	Common
Product issues	7 (29%)	Very Common
Needle issue[a,b]	5 (21%)	Very common
Device leakage[a]	2 (8%)	Common
Device occlusion[a,c]	1 (4%)	Common
Device dislocation[a,d]	N/A	Not known
Psychiatric disorders	14 (58%)	Very common
Insomnia	5 (21%)	Very common
Irritability[a]	4 (17%)	Very common
Respiratory, thoracic, and mediastinal disorders	12 (50%)	Very common
Cough	8 (33%)	Very common
Skin and subcutaneous tissue disorders	7 (29%)	Very common
Rash[a]	2 (8%)	Common
Urticaria[a]	2 (8%)	Common

[a] Adverse events that are also adverse reactions
[b] Dislodgement of infusion needle
[c] Catheter flow obstruction
[d] Device dislocation did not occur in clinical trials

Description of selected adverse reactions

Convulsions

Convulsions are a common manifestation of CLN2 disease and are expected to occur in this population. Convulsions include the following reported events: atonic seizures, clonic convulsion, drop attacks, epilepsy, generalised tonic-clonic seizure, myoclonic epilepsy, partial seizures, petit mal epilepsy, seizure, seizure cluster, and status epilepticus. Overall, 23 (96%) subjects who received cerliponase alfa experienced an event that mapped to the

Convulsions Standardized MedDRA Query. The most commonly reported convulsion events include seizure, epilepsy and generalized tonic-clonic seizure. Total convulsion events with a temporal relationship to cerliponase alfa administration was 15% and were mild to moderate, grade 1 to 2 in severity. Overall, 5% of all convulsion events were considered related to cerliponase alfa and ranged from mild to severe, CTCAE grade 1-4. Convulsions resolved with standard anti-convulsive therapies, and did not result in discontinuation of Brineura treatment.

Hypersensitivity

Hypersensitivity reactions were reported in 15 out of 24 patients (63%) treated with Brineura. Severe (Common Terminology Criteria for Adverse Events (CTCAE) grade 3) hypersensitivity reactions occurred in three patients and no patients discontinued treatment. The most common manifestations included pyrexia with vomiting, pleocytosis, or irritability, which are inconsistent with classic immune mediated hypersensitivity. These adverse reactions were observed during or within 24 hours after completion of the Brineura infusion and did not interfere with treatment. Symptoms resolved over time or with administration of antipyretics, antihistamines and/or glucocorticosteroids.

Immunogenicity

Anti-drug antibodies (ADAs) were detected in both serum and CSF in 79% and 33%, respectively, of patients treated with cerliponase alfa for up to 161 weeks. Drug-specific neutralizing antibodies (NAb) capable of inhibiting receptor-mediated cellular uptake of cerliponase alfa were not detected in the CSF. No association was found between serum or CSF ADA titres and incidence or severity of hypersensitivity. Patients who experienced moderate hypersensitivity adverse events were tested for drug-specific IgE and found to be negative. No correlations were found between higher ADA titres and reductions in efficacy measurements. There was no apparent effect of serum or CSF ADA on the plasma or CSF pharmacokinetics, respectively.

Paediatric population

An ongoing study provides experience with two patients aged 2 years of age treated with Brineura at 300 mg every other week (see section 5.1 Pharmacodynamic properties). Both patients have received 8 infusions and the overall safety profile of Brineura in these younger patients appears consistent with the safety profile observed in older children. Currently no clinical experience of Brineura in children below 2 years of age is available.

Post-marketing experience

The following adverse reactions have been identified during post approval use of Brineura. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: Meningitis.
Immune system disorders: Anaphylactic reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

No information is available. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Cerliponase alfa is a recombinant form of human tripeptidyl peptidase-1 (rhTPP1). Cerliponase alfa is the inactive proenzyme (zymogen) form of a protease that is activated in the lysosome. Due to its attached mannose 6-phosphate residues, cerliponase alfa is bound by the cation-independent mannose-6-phosphate receptor (M6P, also known as the IGF2 receptor)on target cells and, following clathrin-mediated endocytosis of the complex, is translocated to lysosomes.

The activated proteolytic enzyme (rhTPP1) cleaves tripeptides from the N-terminus of the target protein with no known substrate specificity. Inadequate levels of TPP1 cause CLN2 disease, resulting in neurodegeneration, loss of neurological function and death during childhood.

Clinical trials

The safety and efficacy of Brineura were assessed in an open label, dose escalation clinical study (190-201) and an ongoing long term extension study (190-202) in patients with CLN2 disease compared to untreated patients with CLN2 disease from a natural history database (natural history control group). These studies used the aggregate of the motor and language domains of a disease-specific clinical rating scale (see Table 3) to assess disease progression. Each domain encompasses scores of 3 (grossly normal) to 0 (profoundly impaired), for a total possible score of 6, with unit decrements representing milestone events in the loss of previously attained functions of ambulation and speech.

Table 3: CLN2 Clinical Rating Scale

Domain	Score	Rating
Motor	3	Grossly normal gait. No prominent ataxia, no pathologic falls.
	2	Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability, and may have intermittent falls.
	1	Requires external assistance to walk, or can crawl only.
	0	Can no longer walk or crawl.
Language	3	Apparently normal language. Intelligible and grossly age-appropriate. No decline noted yet.
	2	Language has become recognizably abnormal: some intelligible words, may form short sentences to convey concepts, requests, or needs. This score signifies a decline from a previous level of ability (from the individual maximum reached by the child).
	1	Hardly understandable. Few intelligible words.
	0	No intelligible words or vocalizations.

A total of 24 patients, aged 3 to 8 years, were treated with Brineura 300 mg every other week. In study 190-201, 23 patients were treated for 48 weeks (1 patient withdrew after week 1 due to the inability to continue with study procedures). The mean baseline CLN2 score was 3.5 (standard deviation (SD) 1.20) with a range from 1 to 6; no patients with advanced disease progression were studied (inclusion criteria: mild to moderate progression of CLN2 disease). All 23 patients completed study 190-201 and continued to the ongoing extension study 190-202 treated with Brineura at 300 mg every other week to a maximum of 124 weeks.

Findings from studies 190-201 and 190-202 were compared with a natural history control group that included patients that satisfied the inclusion criteria for studies 190-201 and 190-202. Results from the natural history control group demonstrate CLN2 disease is a rapidly progressive neurodegenerative disease with predictable decline in motor and language function with an estimated mean rate of decline in the CLN2 score of 2 points per 48 weeks.

Treatment effect in patients receiving Brineura was assessed using the CLN2 clinical rating scale, and results were compared to the 2 points per 48 weeks predicted decline in the natural history control group. In study 190-201, 20 out of 23 (87%) patients receiving Brineura for 48 weeks did not have an unreversed 2 point decline compared to the expected decline in the untreated patient population ($p=0.0002$, binomial test assuming $p_0= 0.50$). A total of 15 patients out of 23 (65%) had no overall decline in CLN2 score, irrespective of baseline score, and 2 of these 15 patients increased their score by one point during the treatment period. Five patients experienced a single point decrease, and 3 patients experienced a 2 point decrease.

In study 190-201, the mean rate of decline in patients treated with Brineura at 300 mg every other week was 0.40 points per 48 weeks. When compared to the expected rate of decline based on natural history, the study results are statistically significant ($p < 0.0001$)

(see Table 4). The observed treatment effect was considered clinically meaningful in light of the natural history of untreated CLN2 disease.

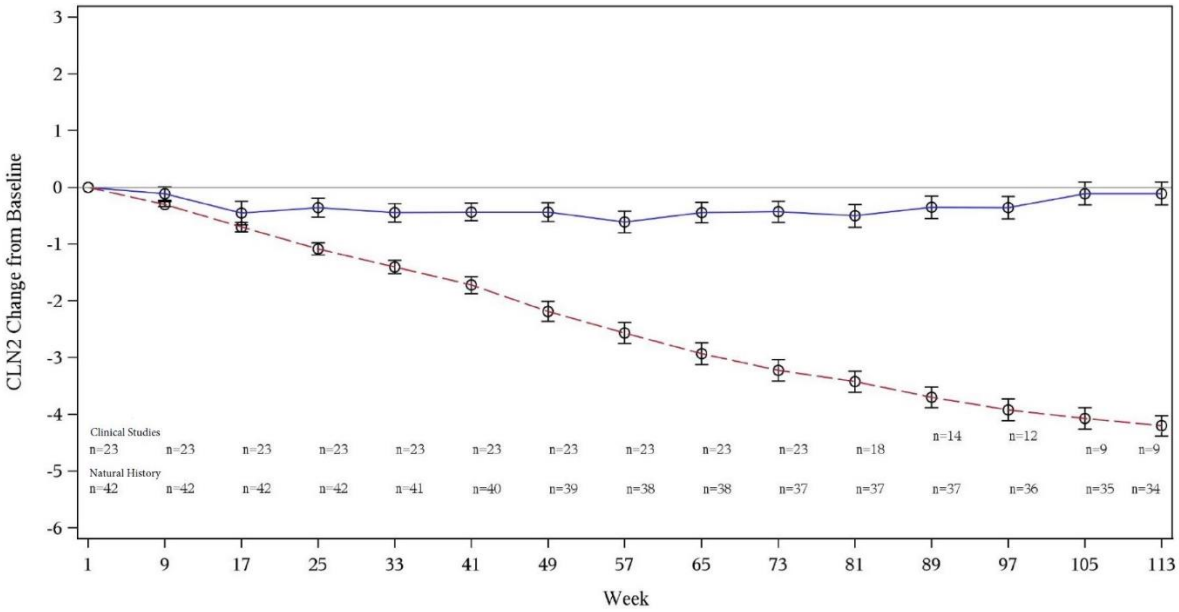
Table 4: 0 to 6 Point Motor-Language CLN2 Clinical Rating Scale: Rate of Decline over 48 weeks (Intent to Treat (ITT) population)

Rate of Decline (points/48 weeks)[a]	Overall (n = 23)	p-value[b]
Mean (SD)	0.40 (0.809)[c]	<0.0001
Median	0.00	
Min, Max	-0.88, 2.02	
95% CI Limits	0.05, 0.75	

[a] Patient rate of decline per 48 weeks: (baseline CLN2 score - last CLN2 score) / (time elapsed in units of 48 weeks)
[b] p-value based on 1-sample T-test comparing rate of decline to the value 2
[c] Positive estimates indicate clinical decline; negative estimates indicate clinical improvement

In the ongoing study 190-202 (as of 03 June 2016), the rate of decline in patients treated with Brineura compared to the natural history control group (N=42 patients) continues to show durability of the treatment effect (see Figure 2).

Figure 2: CLN2 Score Mean Change from Baseline (Natural History Control Group vs Brineura treated patients, 300 mg every other week)



Vertical bars represent standard error of the mean
Solid line: 190-201 and 190-202 clinical studies
Dash line: 190-901 Natural history control group

Paediatric population

It is important to initiate treatment in children as young as possible, although patients less than 3 years of age were not included in the pivotal study.

Study 190-203 is an ongoing open label clinical study evaluating the safety and efficacy in patients from birth to 18 years of age. Posology was based upon analysis of differences in

brain mass values for children less than 3 years of age. So far safety results in younger patients appears consistent with the safety profile observed in older children. Currently no clinical experience of Brineura in children below 2 years of age is available (see section 4.8 Adverse effects (Undesirable effects)).

5.2 Pharmacokinetic properties

The pharmacokinetics of cerliponase alfa were evaluated in patients with CLN2 disease who received intracerebroventricular infusions of 300 mg over approximately 4.5 hours once every other week.

All pharmacokinetic parameters were similar following the initial infusion on Day 1 and following infusions at Week 5 and Week 13, indicating no apparent accumulation or time dependent PK of cerliponase alfa in CSF or plasma when administered at of dose of 300 mg once every other week. The pharmacokinetic parameters in CSF were assessed in 17 patients and are summarized in Table 5 below. Cerliponase alfa plasma pharmacokinetics were assessed in 13 patients, and a median T_{max} of 12.0 hours (since start of infusion), a mean C_{max} of 1.39 µg/mL, and mean AUC_{0-t} of 24.1 µg-hour/mL were characterized. There was no apparent effect of serum or CSF ADA on the plasma or CSF pharmacokinetics, respectively.

Table 5: Pharmacokinetic properties following first Intracerebroventricular infusion (approximately 4 hours in duration) of 300 mg cerliponase alfa in CSF

Parameter	CSF (N=17) Mean (SD)
T_{max}*, hr	4.50 [4.25, 5.75]
C_{max}, µg/mL	1490 (942)
AUC_{0-t}, µg-hr/ mL	9510 (4130)
Vz, mL	435 (412)
CL, mL/hr	38.7 (19.8)
$t_{1/2}$, hr	7.35 (2.90)

*T_{max} expressed as time since start of ~4 hour infusion and presented as median [min, max], and occurred at the first sampling timepoint post infusion

Distribution

The estimated volume of distribution of cerliponase alfa following intracerebroventricular infusion of 300 mg (V_z = 435 mL) exceeds the typical CSF volume (100 mL), suggesting distribution to tissues outside the CSF. The large CSF to plasma ratios in C_{max} and AUC_{0-t} (approximately 1000 and 400, respectively) suggest that the majority of administered cerliponase alfa remains localized within the CNS. Intracerebroventricular administration of cerliponase alfa is not expected to result in therapeutic concentrations in the eye due to the limited access from the CSF to the affected cells of the retina and the presence of the blood-retinal barrier.

Metabolism

Cerliponase alfa is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, impaired liver function is not expected to affect the pharmacokinetics of cerliponase alfa.

Excretion

Renal elimination of cerliponase alfa is considered a minor pathway for clearance.

5.3 Preclinical safety data

Limited preclinical safety data of cerliponase alfa were generated from single dose toxicity studies in monkeys and repeated-dose studies in a dachshund dog model of classic late infantile neuronal ceroid lipofuscinosis type 2. This disease model primarily served to investigate the pharmacodynamic and pharmacokinetic properties of cerliponase alfa, but also aimed to evaluate the toxicity of the substance. However, the results of these studies in dachshund dogs cannot reliably predict human safety, because the regimen of cerliponase alfa infusions was different and highly variable even within the same study due to difficulties with the indwelling catheter system and prominent hypersensitivity reactions. In addition, these investigations included very small animal numbers, mostly tested single dose groups and lacked appropriate controls. Thus, the non-clinical development is inconclusive with respect to the clinical safety of cerliponase alfa. Reproductive toxicity investigations have not been performed.

Genotoxicity

The genotoxic potential of cerliponase alfa has not been assessed. Based on its mechanism of action, cerliponase alfa is not expected to be genotoxic.

Carcinogenicity

The carcinogenic potential of cerliponase alfa has not been assessed. Based on its mechanism of action, cerliponase alfa is not expected to be tumorigenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Brineura and flushing solution
Dibasic sodium phosphate heptahydrate
Monobasic sodium phosphate monohydrate
Sodium chloride
Potassium chloride
Magnesium chloride hexahydrate
Calcium chloride dihydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store upright in a freezer (-25°C to -15°C).
Transport and distribute frozen (-85°C to -15°C).
Store in the original package in order to protect from light.

Thawed Brineura and flushing solution should be 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.

Chemical and physical in-use stability has been demonstrated for up to 12 hours at room temperature (19-25°C). From a microbiological point of view, open vials or medicinal product held in syringes should be used immediately.

6.5 Nature and contents of container

Vial (type I glass) with a stopper (butyl rubber), a flip-off cap (polypropylene) and crimp seal (aluminium). Brineura has a green flip-off cap and flushing solution has a yellow flip-off cap.

Pack size of three vials: two 10 mL vials, each containing 150 mg of cerliponase alfa in 5 mL of solution; and one 10 mL vial, containing 5 mL flushing solution.

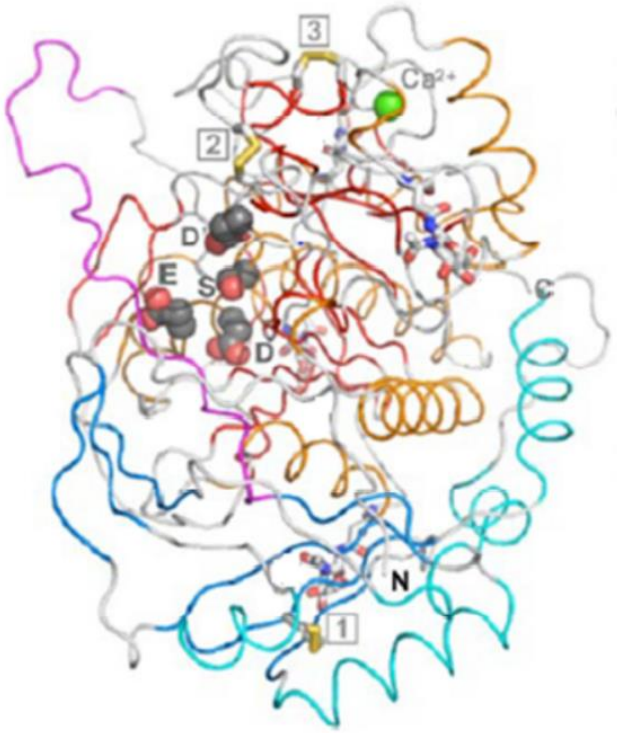
6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Unwanted medicines can be returned to local pharmacies involved in the Return Unwanted Medicines (RUM) Project.

6.7 Physicochemical properties

Chemical structure

Crystal structure of the pro-peptide



CAS number

151662-36-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8. SPONSOR

Brineura is supplied in Australia by:
BioMarin Pharmaceutical Australia Pty Ltd
119 Willoughby Road
Crows Nest, NSW 2065
Telephone (02) 8520 3255

For enquiries about Brineura, contact medinfoasia@bmrn.com or call BioMarin Australia on 1800 387 876.

To report adverse events, contact drugsafety@bmrn.com or call BioMarin Australia on 1800 387 876.

9. DATE OF FIRST APPROVAL

10 August 2018

10. DATE OF REVISION

18 October 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Clarify description of Brineura and flushing solution.
4.4	New information regarding anaphylactic reactions.
4.8	Addition of anaphylactic reactions to post-marketing experience.