

## SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

### 1 NAME OF THE MEDICINAL PRODUCT

Brineura 150 mg solution for infusion

### 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 infusion contains 30 mg of cerliponase alfa.

\* Produced in mammalian Chinese Hamster Ovary cells.

Excipient with known effect:

Each vial contains 17.4 mg of sodium in 5 ml of solution.

For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Solution for infusion.

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 Posology and method of administration

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

Posology

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*

Treatment of Brineura was initiated in children 1 to 9 years of age in clinical studies. There is no clinical data available in children below 1 year of age (see section 5.1). 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.

The posology selected for patients is based on age at time of treatment and should be adjusted accordingly (see Table 1).

**Table 1: Dose and volume of Brineura**

<b>Age groups</b>	<b>Total dose administered every other week (mg)</b>	<b>Volume of Brineura solution (ml)</b>
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.

#### *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 only.

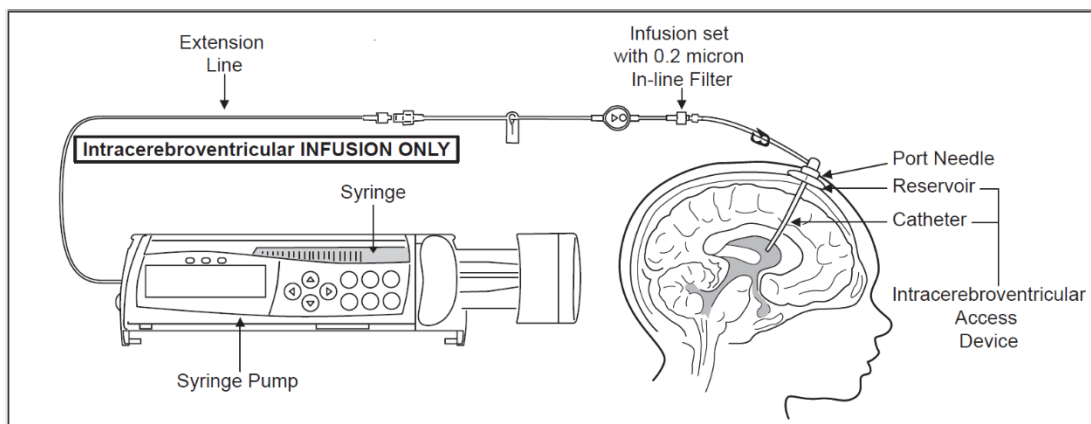
Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intracerebroventricular access device). The intracerebroventricular access device must be implanted prior to the first infusion. The implanted intracerebroventricular access device 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 the medicinal product and to maintain patency of the intracerebroventricular access device (see section 6.6). Brineura and flushing solution vials should be thawed prior to administration. The infusion rate for the medicinal product and the flushing solution is 2.5 ml/hour. The complete infusion time, including the medicinal product and the required flushing solution, is approximately 2 to 4.5 hours, depending on the dose and volume administered.

### *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 sections 4.3 and 4.4).
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).
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 section 6.6).
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.

For instructions on preparation of Brineura and flushing solution before administration, see section 6.6.

## **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).

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 sections 4.2 and 4.4).

## **4.4 Special warnings and precautions for use**

### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

### Device-related complications

Brineura must be administered using aseptic technique to reduce the risk of infection. Intracerebroventricular access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura (see section 4.8). 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.

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

intracerebroventricular access device. However, these signs may also occur in the context of device-related infections.

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 sections 4.2 and 4.3). 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 according to preliminary results of benchtop testing and as observed in clinical trials with approximately 4 years of use. In two clinical cases, the intracerebroventricular access devices did not show signs of failure at the time of infusion; however, after removal, material degradation of the devices were apparent and consistent with data from benchtop testing of intracerebroventricular access devices. The access devices were replaced and patients resumed treatment with Brineura.

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.

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).

#### 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'.

### Paediatric population

There are limited data in patients with advanced disease progression at treatment initiation and no clinical data is available in children less than 1 year of age. Newborns may have decreased integrity of the blood-brain barrier. In children less than 3 years, increased medicinal product exposure in the periphery was not associated with a clear change in the safety profile (see sections 4.8, 5.2).

## **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed. Cerliponase alfa is a recombinant human protein and systemic exposure is limited due to intracerebroventricular administration, therefore interactions between cerliponase alfa and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

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

### Breast-feeding

There is insufficient information on the excretion of cerliponase alfa/metabolites in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Brineura.

### Fertility

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

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

### Summary of the safety profile

The adverse reactions described in this section were evaluated in 38 patients with CLN2 disease who received at least one dose of Brineura in clinical studies of up to 309 weeks or in post-marketing experience. The most frequent (>20%) adverse reactions observed during Brineura clinical trials include pyrexia, convulsions, low CSF protein, ECG abnormalities, vomiting, needle issues, device related infections, and hypersensitivity. No patients had to have their treatment discontinued due to adverse events.

### Tabulated list of adverse reactions

Adverse reactions observed are listed below, by system organ class and frequency, following the MedDRA frequency convention defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

**Table 2: Frequency of adverse reactions with Brineura**

<b>MedDRA System organ class</b>	<b>MedDRA Preferred term</b>	<b>Frequency</b>
Infections and infestations	Device-related infection <sup>a</sup> Meningitis	Very common Not known
Immune system disorders	Hypersensitivity Anaphylactic reaction	Very common Common
Psychiatric disorders	Irritability	Very common
Nervous system disorders	Convulsion events <sup>b</sup> Headache CSF Pleocytosis	Very common Very common Very common
Cardiac disorders	Bradycardia	Common
Gastrointestinal disorders	Vomiting Gastrointestinal disorder	Very common Common
Skin and subcutaneous tissue disorders	Rash Urticaria	Common Common
General disorders and administration site conditions	Pyrexia <sup>c</sup> Feeling jittery Medical device site irritation	Very common Common Common
Investigations	CSF protein increased ECG abnormalities CSF protein decreased	Very common Very common Very common
Product issues	Device issue: Device leakage Needle issue <sup>d</sup> Device malfunction Device occlusion <sup>e</sup> Device breakage Device dislocation <sup>f</sup>	Very common Very common Very common Common Common Not known

<sup>a</sup> *Propionibacterium acnes*, *Staphylococcus epidermis*

<sup>b</sup> Atonic seizures, clonic convulsion, drop attacks, epilepsy, generalised tonic-clonic seizure, myoclonic epilepsy, partial seizures, petit mal epilepsy, seizure, seizure cluster, and status epilepticus

<sup>c</sup> Pyrexia includes combined preferred terms “Pyrexia” and “Increased body temperature”

<sup>d</sup> Dislodgement of infusion needle

<sup>e</sup> Catheter flow obstruction

<sup>f</sup> 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. In clinical studies, 31 of 38 (82%) patients 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. Overall, 4% 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 19 of 38 patients (50%) treated with Brineura. Severe (Common Terminology Criteria for Adverse Events (CTCAE) grade 3) hypersensitivity reactions occurred in 6 patients and no patients discontinued treatment. Hypersensitivity reactions were reported in 5 of 8 (63) patients < 3 years of age compared with 14 of 30 (47%) patients ≥ 3 years of age. 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.

## 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 via the national reporting system listed below:

### **United Kingdom**

Yellow Card Scheme

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store

## **4.9 Overdose**

No information is available.

# **5 PHARMACOLOGICAL PROPERTIES**

## **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: other alimentary tract and metabolism products, enzymes, ATC code: A16AB17.

### Mechanism of action

Cerliponase alfa is a recombinant form of human tripeptidyl peptidase-1 (rhTPP1). Cerliponase alfa is a proteolytic inactive proenzyme (zymogen) that is activated in the lysosome. Cerliponase alfa is taken up by target cells and translocated to the lysosomes through the Cation Independent Mannose-6-Phosphate Receptor (CI-MPR, also known as M6P/IGF2 receptor). The glycosylation profile of cerliponase alfa results in consistent cellular uptake and lysosomal targeting for activation.

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.

### Immunogenicity

Anti-drug antibodies (ADA) in serum and CSF were very commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. However data are limited.

### Clinical efficacy and safety

The safety and efficacy of Brineura were assessed in three open-label clinical studies in a total of 38 patients with CLN2 disease, ages 1 to 9 years at baseline, 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 (referred to as the ML score of the CLN2 clinical rating scale. 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: Motor language score - 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.

In pivotal study 190-201, a total of 24 patients, ages 3 to 9 years at baseline, were treated with Brineura 300 mg every other week. Of these, 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 ML 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).

A total of 20 out of 23 (87%) patients receiving Brineura for 48 weeks did not have an unreversed 2 point decline compared to the 2 points per 48 weeks 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 ML 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.

All 23 patients completed study 190-201 and continued to the extension study 190-202 where they were treated with Brineura at 300 mg every other week for a total duration of 288 weeks. Efficacy results from studies 190-201 and 190-202 were pooled and compared with a natural history control group that included patients that satisfied the inclusion criteria for studies 190-201 and 190-202. The median time to an unreversed 2 point decline or ML score of 0 in patients treated with Brineura ( $N=23$ ) was 272 weeks compared with 49 weeks among the natural history control group ( $N=42$ ) (hazard ratio 0.14, 95% CI 0.06 to 0.33;  $p<0.0001$ ). The median time until a ML score of 0, marking loss of all ability to ambulate and communicate, was not reached in Brineura treated patients compared with 109 weeks among the natural history control group (hazard ratio, 0.01; 95% CI, 0.00 to 0.08;  $p<0.0001$ ).

An exploratory survival analysis showed the estimated median age of death for the natural history control group was 10.4 years; 95% CI, 9.5 to 12.5 years. No deaths occurred in the Brineura treated patients during the study, median (min, max) age at last assessment was 10.3 (7.8, 13.1) years ( $N=23$ ).

The mean rate of decline in patients treated with Brineura at 300 mg every other week was 0.38 points per 48 weeks. When compared to the estimated rate of decline in natural history of 2.13 points per 48 weeks, 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) <sup>a</sup>	190-201/202 participants Overall (n = 23)	Natural History Control Group (n=42)	p-value <sup>b</sup>
Mean (SD)	0.38 (0.499) <sup>c</sup>	2.13 (0.952) <sup>c</sup>	<0.0001
Median	0.30	2.08	
Min, Max	0.00, 2.18	0.45, 4.27	
95% CI Limits	0.16, 0.59	1.84, 2.43	

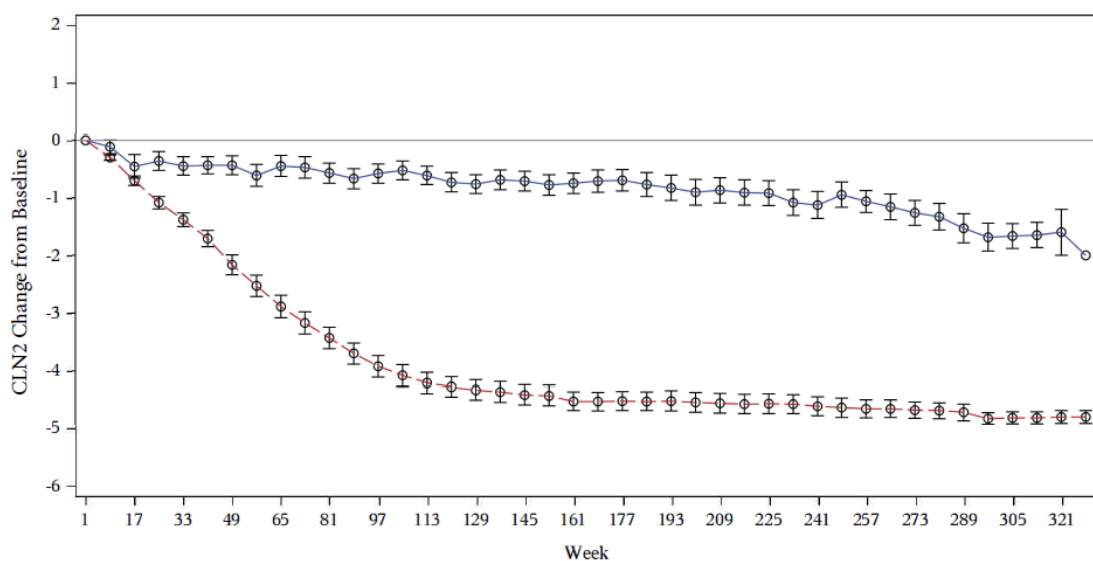
<sup>a</sup> Patient rate of decline per 48 weeks: (baseline CLN2 score - last CLN2 score) / (time elapsed in units of 48 weeks)

<sup>b</sup> p-value based on 1-sample T-test comparing rate of decline to the value 2

<sup>c</sup> Positive estimates indicate clinical decline; negative estimates indicate clinical improvement

The estimated mean change from baseline in patients treated with Brineura compared to the natural history control group (N=42 patients) showed attenuation of disease progression and durability of the treatment effect up to last assessment (Week 321) (see Figure 2).

**Figure 2: Mean change from baseline in 0-6 point motor-language score (Natural history control group vs Brineura treated patients, 300 mg every other week)**



190-201/202 N: 23 23 23 23 23 23 23 23 23 23 23 22 22 22 22 22 21 20 18 16 5 1  
 Natural History N: 42 42 42 40 39 37 36 34 34 32 30 29 26 25 23 22 20 19 17 15 14 14

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

MRI volumetry measurements show attenuated rate of loss.

In Study 190-203 a total of 14 patients with CLN2 disease, ages 1 to 6 years at baseline (8 of 14 less than 3 years of age) were treated with Brineura for up to 142.6 weeks (1 patient withdrew to receive treatment

commercially) and a safety follow-up for 24 weeks. The mean (SD) baseline ML score was 4.6 (1.69) with a range from 1 to 6.

Brineura treated patients were matched to natural history comparators on the basis of age, CLN2 motor language score and pooled genotype. The mean ( $\pm$ SD) rate of decline on the ML scale was 0.15 (0.243) points per 48 weeks for the matched Brineura treated patients (N=12) and 1.30 (0.857) points per 48 weeks for the matched natural history comparators (N=29). There was a mean difference of 1.15 points (SE 0.174), 95% CI 0.80, 1.50 points in the rate of decline between the groups;  $p < 0.0001$ .

The median time to an unreversed 2 point decline or score of 0 in patients treated with Brineura was not reached by last assessment (Week 169) compared with 103 weeks among the natural history comparators (hazard ratio 0.091; 95% CI, 0.021, 0.393;  $p < 0.0001$ ). The median time to a ML score of 0 was not reached in Brineura treated patients compared with 163 weeks among the matched natural history comparators (hazard ratio, 0.00; 95% CI, 0.00, 0.00;  $p = 0.0032$ ). A total of 10 of 12 (83%) treated patients had less than a 2 point decline on the ML scale from baseline to last assessment. Eight patients (67%) showed no clinical progression on the ML scale, two (17%) lost a single point and 2 (17%) lost 2 points. No treated patients reached an ML score of zero compared with 10 of 29 (34%) of the matched natural history comparators.

In patients below 3 years of age, the mean (SD) rate of decline on the ML scale was 0.04 (0.101) points per 48 weeks for matched treated patients (N=8) compared with 1.09 (0.562) points per 48 weeks for matched natural history comparators (N=20) (difference 1.05 points;  $p < 0.0001$ ). Seven of the treated patients below 3 years of age with an ML score of 6 at baseline remained at an ML score of 6 at the last measured timepoint, which represents grossly normal gait and language. Three of these 7 patients remained with no other symptoms of CLN2 disease at week 145, as assessed by the CLN2 rating scale, brain imaging and adverse events, whereas all matched comparators had become symptomatic. In this population Brinerua treated patients showed a delay in disease onset.

#### Exceptional circumstances

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

## **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 pharmacokinetics 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 summarised in Table 5 below. Cerliponase alfa plasma pharmacokinetics were assessed in 13 patients, and a median  $T_{max}$  of 12 hours (since start of infusion), a mean  $C_{max}$  of 1.39  $\mu$ g/ml, and mean  $AUC_{0-t}$  of 24.1  $\mu$ g-hour/ml were characterised. 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 <sub>max</sub> <sup>*</sup> , hr	4.50 [4.25, 5.75]
C <sub>max</sub> , µg/ml	1490 (942)
AUC <sub>0-t</sub> , µg-hr/ml	9510 (4130)
V <sub>Z</sub> , ml	435 (412)
CL, ml/hr	38.7 (19.8)
t <sub>1/2</sub> , hr	7.35 (2.90)

\*T<sub>max</sub> 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<sub>Z</sub> = 435 ml) exceeds the typical CSF volume (100 ml), suggesting distribution to tissues outside the CSF. The large CSF to plasma ratios in C<sub>max</sub> and AUC<sub>0-t</sub> (approximately 1000 and 400, respectively) suggest that the majority of administered cerliponase alfa remains localized within the central nervous system. 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.

### Elimination

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.

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

### Paediatric population from 0 to 3 years

Paediatric CLN2 patients ages 1 to < 2 years (n=2) and 2 to < 3 years (n=6) were administered cerliponase alfa according to the recommended paediatric dosing regimen for up to 144 weeks. CSF exposure was within the range characterised to be safe and effective in the pivotal study. Plasma exposure in younger patients trended higher than the range characterised in the pivotal study however the greater plasma exposure was not associated with clear changes in the safety profile. There are no pharmacokinetic data in patients below 1 year of age.

## **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. Genotoxicity, carcinogenicity and reproductive toxicity investigations have not been performed.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Brineura solution for infusion and flushing solution

Sodium phosphate dibasic heptahydrate  
Sodium dihydrogen 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**

2 years

Thawed Brineura and flushing solution should be used immediately. The medicinal 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 in a refrigerator (2°C - 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°C - 25°C). From a microbiological point of view, open vials or medicinal product held in syringes should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

### **6.4 Special precautions for storage**

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

#### Transportation of vials

Transport and distribute frozen (-85°C to -15°C).

### **6.5 Nature and contents of container**

#### Brineura solution for infusion and flushing solution

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

#### Pack size

Each pack contains two vials, each containing 150 mg of cerliponase alfa in 5 ml of solution for infusion, and one vial containing 5 ml of flushing solution.

## 6.6 Special precautions for disposal and other handling

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.

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.

### 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 in section 4.2). All infusion components must be sterile. Brineura and flushing solution are supplied and stored frozen (see section 6.4).

- 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 cm 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).

**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 solution 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 colourless.

**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.

### Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7     MARKETING AUTHORISATION HOLDER**

BioMarin International Limited  
Shanbally, Ringaskiddy  
County Cork  
Ireland

## **8     MARKETING AUTHORISATION NUMBER(S)**

PLGB 45814/0001

## **9     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 01/01/2021

Date of latest renewal: 24/05/2022

## **10    DATE OF REVISION OF THE TEXT**

08/01/2024

Detailed information on this medicinal product is available on the website of the Medicines and Healthcare products Regulatory Agency <https://products.mhra.gov.uk>.