ANNEX I

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
The safety and efficacy of Brineura in children less than 3 years of age have 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). 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).

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.

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.

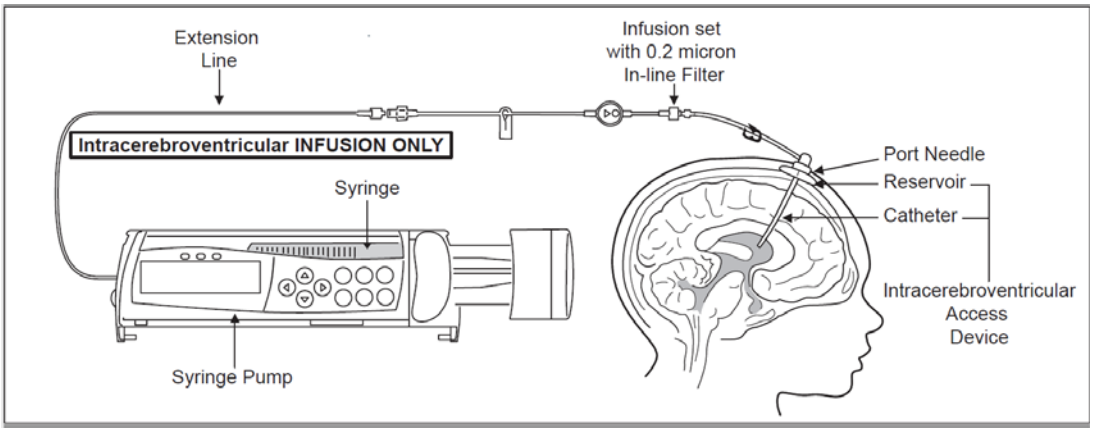


Figure 1: Infusion system set up

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 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.

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 24 patients with CLN2 disease who received at least one dose of Brineura in clinical studies of up to 141 weeks or in post-marketing experience. 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 reactions

Adverse reactions observed are listed below, by system organ class and frequency, following the MedDRA frequency convention defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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

MedDRA System organ class	**MedDRA Preferred term**	**Frequency**
Infections and infestations	Upper respiratory tract infection	Very common
	Conjunctivitis	Common
	Device-related infection[a]	Common
	Meningitis	Not known
Immune system disorders	Hypersensitivity	Very common
	Anaphylactic reaction	Common
Psychiatric disorders	Irritability	Very common
Nervous system disorders	Convulsion events[b]	Very common
	Headache	Very common
	CSF Pleocytosis	Very common
	Dropped head syndrome	Common
Cardiac disorders	Bradycardia	Common
Gastrointestinal disorders	Vomiting	Very common
	Abdominal pain	Common
	Oral mucosal blistering	Common
	Tongue blistering	Common
	Gastrointestinal disorder	Common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria	Common
General disorders and administration site conditions	Pyrexia[c]	Very common
	Feeling jittery	Common
	Pain	Common
Investigations	CSF protein increased	Very common
	ECG abnormalities	Very common
	CSF protein decreased	Very common
Product issues	Device issue:	
	Device leakage	Common
	Device occlusion[d]	Common
	Device dislocation[e]	Not known
	Needle issue[f]	Very common

[a] *Propionibacterium acnes, Staphylococcus epidermis*
[b] Atonic seizures, clonic convulsion, drop attacks, epilepsy, generalised tonic-clonic seizure, myoclonic epilepsy, partial seizures, petit mal epilepsy, seizure, seizure cluster, and status epilepticus
[c] Pyrexia includes combined preferred terms “Pyrexia” and “Increased body temperature”
[d] Catheter flow obstruction
[e] Device dislocation did not occur in clinical trials
[f] Dislodgement of infusion needle

Description of selected adverse reactions

Convulsions
Convulsions are a common manifestation of CLN2 disease and are expected to occur in this population. Overall, 23 (96%) subjects who received cerliponase alfa experienced an event that mapped to the Convulsions Standardised MedDRA Query. The most commonly reported convulsion events include seizure, epilepsy and generalised tonic-clonic seizure. Total convulsion events with a temporal relationship to cerliponase alfa administration was 17% and were mild to moderate, grade 1 to 2 in severity. Overall, 6% 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 14 out of 24 patients (58%) 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 21%, respectively, of patients treated with cerliponase alfa for up to 107 weeks. Drug-specific neutralising 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). 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.

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 in Appendix V.

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.

Clinical efficacy and safety

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 recognisably 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 as observed 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.

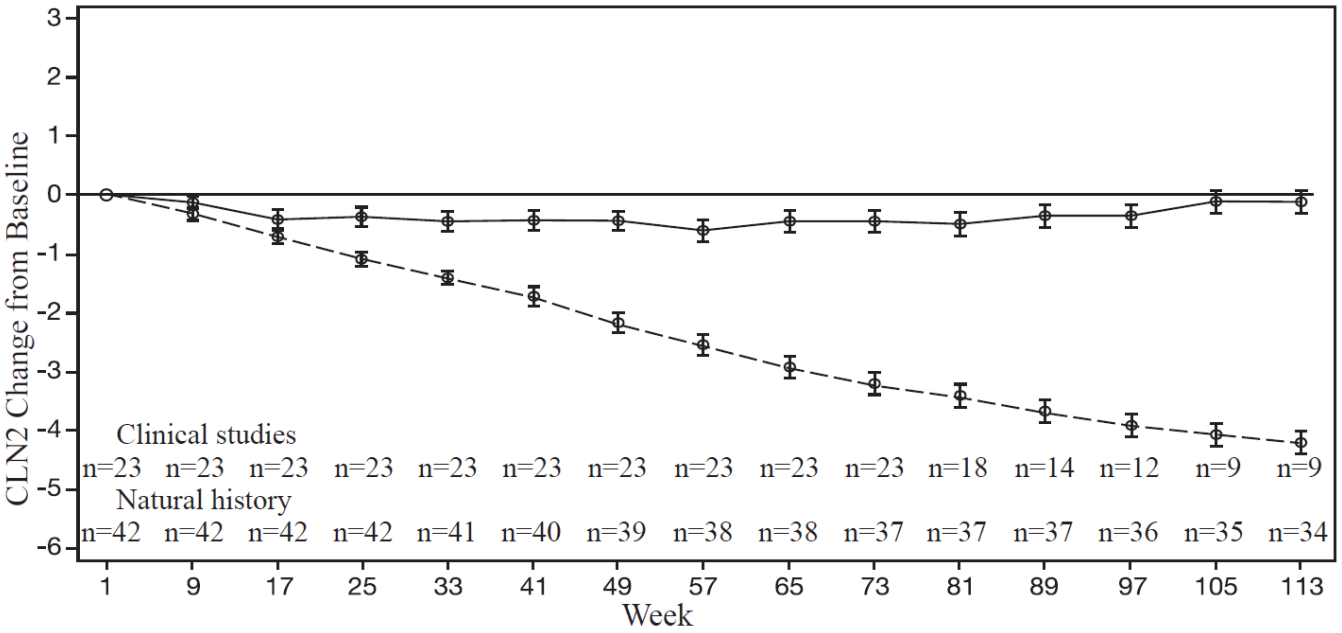
Table 4: 0 to 6 point motor-language CLN2 clinical rating scale: Rate of decline over 48 weeks (Intent to treat (ITT) population)

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

Vision and seizure scores when combined with CLN2 score (motor and language domains) remain stable. MRI volumetry measurements show attenuated rate of loss.

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).

The European Medicines Agency has deferred the obligation to submit the results of studies with Brineura in one or more subsets of the paediatric population in CLN2 (see section 4.2 for information on paediatric use).

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.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

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 µg/ml, and mean AUC_{0-t} of 24.1 µg-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_{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 localised 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.

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), 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:
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)

EU/1/17/1192/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 May 2017
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

BioMarin Pharmaceutical Inc.
Galli Drive Facility
46 Galli Drive, Novato
94949
United States

BioMarin International Limited
Shanbally
Ringaskiddy
Cork
Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release
BioMarin International Limited
Shanbally
Ringaskiddy
Cork
Co. Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Brineura in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).
The MAH shall ensure that in each MS where Brineura is marketed, all HCPs who are expected to handle/administer the product are provided with an educational programme (i.e. a dosing and administration guide), aiming at preventing and/or minimising the important identified risk of Device issues (infection/blockage/dislocation), containing information about:

- How to store Brineura;
- The device-related complications (i.e. infections, device's leakage and/or failure; the integrity of the device should be confirmed by a neurosurgeon);
- How to prepare Brineura and the flushing solution;
- A detailed step-by step description of Brineura intra-cerebro-ventricular infusion and the administration of the flushing solution (provided after Brineura infusion is complete)
- How to monitor the patients receiving Brineura.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): Study 190-504. In order to evaluate the long-term safety of cerliponase alfa, including the occurrence of serious hypersensitivity reactions and anaphylactic reactions, the MAH should submit the results of a study based on adequate source of data deriving from a registry of patients with neuronal ceroid lipfuscinosis Type 2 (CLN2).	Annual reports to be submitted as part of the annual re-assessment
Post-authorisation efficacy study (PAES): Study 190-203. In order to further evaluate the treatment effectiveness as a delay in progression of CLN2 motor-language clinical sale and to further evaluate the safety and tolerability of cerliponase alfa, the MAH will submit the results of study 190-203 including at least 5 patients below the age of 2 years.	February 2023

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Brineura 150 mg solution for infusion
cerliponase alfa

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of Brineura contains 150 mg cerliponase alfa in 5 ml of solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Brineura and flushing solution excipients:
Sodium phosphate dibasic heptahydrate;
Sodium dihydrogen phosphate monohydrate;
Sodium chloride;
Potassium chloride;
Magnesium chloride hexahydrate;
Calcium chloride dihydrate;
Water for injections.

See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
150 mg/5 ml
Two vials of 5 ml of Brineura solution for infusion
One vial of 5 ml of flushing solution

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Thaw at room temperature and use immediately.
Read the package leaflet before use.
Intracerebroventricular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Open vials or product in syringes should be used immediately. In-use storage times and conditions prior to use are the responsibility of the user.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1192/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (Brineura solution for infusion)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Brineura 150 mg solution for infusion
cerliponase alfa
Intracerebroventricular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg/5 ml

6. OTHER

Thaw before use.
Administer Brineura before flushing solution.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (flushing solution)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Flushing solution for Brineura
Intracerebroventricular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

Thaw before use.
Administer flushing solution after Brineura.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Brineura 150 mg solution for infusion
cerliponase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you or your child is given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you or your child get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Brineura is and what it is used for

Brineura contains the active substance cerliponase alfa, which belongs to a group of medicines known as enzyme replacement therapies. It is used to treat patients with neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency.

People with CLN2 disease do not have any enzyme called TPP1 or they have too little of it and this causes a build-up of substances called lysosomal storage materials. In people with CLN2 disease, these materials build-up in certain parts of the body, mainly the brain.

How Brineura works
This medicine replaces the missing enzyme, TPP1, which minimises the build-up of the lysosomal storage materials. This medicine works to slow the progression of the disease.

2. What you need to know before you or your child is given Brineura

You must not receive Brineura
- If you or your child has had life-threatening allergic reactions to cerliponase alfa or any of the other ingredients of this medicine (listed in section 6), and the reactions continue to happen when cerliponse alfa is given again.
- If you or your child has a device implanted to drain extra fluid from the brain.
- If you or your child currently has signs of a device infection or problems with the device. Your doctor may decide to continue treatment once the device infection or problems are resolved.

Warnings and precautions
Talk to your doctor before you or your child is given Brineura.
- You or your child may get problems with the implanted device used during treatment with Brineura (see section 4 “Possible side effects”), including infection or a fault in the device. Signs that you or your child may have an infection include fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. Signs of problems with the device

include swelling, redness of the scalp, fluid leaking from device and bulging of the scalp. Treatment may be interrupted if the device needs to be replaced or until the infection clears. Within 4 years of use, the access device may need to be replaced and will be determined by your doctor. Talk to your doctor if you have any questions about your device.
- Life-threatening allergic reactions (anaphylactic reactions) are possible with this medicine. Your doctor will monitor you or your child for symptoms of life threatening allergic reactions, such as hives, itching or flushing, swollen lips, tongue, and/or throat, chills, accelerated heart rhythm, shortness of breath, hoarseness, turning blue around finger tips or lips, low muscle tone, fainting, diarrhoea or incontinence. Seek immediate medical care should these symptoms occur.
- Your doctor will check your or your child's heart rate, blood pressure, respiratory rate, and temperature before, during, and after treatment. The doctor may decide on additional monitoring if it is needed.
- Your doctor will check for abnormal heart electrical activities (ECG) every 6 months. If you or your child has a history of heart problems, your doctor or nurse will monitor your heart activity during each infusion.
- Your doctor may send samples of brain fluid to check for signs of infection.
- This medicine has not been given to patients with advanced disease at the start of treatment or in children younger than 2 years of age. Your doctor will discuss whether Brineura treatment is right for you or your child.

Other medicines and Brineura
Tell your doctor if you or your child is taking, has recently taken, or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before treatment with this medicine.

You should not receive this medicine during pregnancy unless clearly necessary. It is not known if this medicine can harm your unborn baby.

You should not receive this medicine if you are breast-feeding. It is not known if this medicine passes into human breast milk.

It is not known if this medicine impacts human fertility.

Driving and using machines
It is not known if this medicine will impact the ability to drive or use machines. Please consult your doctor.

Brineura contains sodiumand potassium
This medicine contains 17.4 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.87% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains potassium, less than 1 mmol (39 mg) per vial, that is to say essentially 'potassium-free'.

3. How Brineura is given

You or your child will need to have surgery to implant the device for giving this medicine. The device helps the medicine to reach a specific part of the brain.

This medicine will be given by a doctor with knowledge of giving medicines by intracerebroventricular use (infusion into the fluid of the brain) in a hospital or clinic.

This medicine has not been given to patients younger than 2 years of age or older than 8 years of age (at the start of the clinical trial). There is limited experience in a few patients aged 2 years old.

The recommended dose of this medicine is based upon your or your child's age, and is given once every other week as follows:

- 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 (all other doses)
- ≥ 2 years: 300 mg

Your doctor may adjust you or your child's dose or the amount of time the medicine is given if the infusion is not tolerated, there is an allergic reaction or there is a possible increase of pressure in the brain.

The medicine is slowly pumped through the implanted device. After the medicine has been given, a shorter infusion of a solution is given to flush Brineura out of the infusion equipment so that the full dose reaches the brain. The medicine and solution will be given over about 2 to 4 hours and 30 minutes according to your or your child's dose. Your doctor may lower the dose or the speed of the infusion based on your response during the treatment.

Your doctor may give you or your child medicines, such as antipyretics to reduce fever or antihistamines to treat allergic reactions before each treatment with this medicine to reduce side effects that can occur during or shortly after treatment.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Talk to your doctor or nurse immediately if you experience any of the following:

Very common side effects (may affect more than 1 in 10 people):
- convulsions (seizures)
- reactions during or shortly after being given the medicine, such as hives, itching or flushing, swollen lips, tongue and/or throat, shortness of breath, hoarseness, turning blue around finger tips or lips, low muscle tone, fainting or incontinence.

Common side effects (may affect up to 1 in 10 people):
- device-related bacterial infections
- severe allergic reaction (anaphylactic reactions).

Not known (frequency cannot be estimated from the available data):
- inflammation of the brain (meningitis) due to device-related infection.

This medicine may cause other side effects:

Very common side effects (may affect more than 1 in 10 people):
- fever
- vomiting
- feeling irritable
- headache
- increased or decreased protein in the brain fluid detected by laboratory monitoring
- abnormal results of heart electrical activity (ECG)
- increased cells in the spinal fluid detected by laboratory monitoring
- infection of your nose or throat (cold)
- needle issue (infusion needle falls out of implanted device).

Common side effects (may affect up to 1 in 10 people):
- slower heart beat
- device does not function correctly due to a blockage detected during preparation for infusion
- pain
- rash
- hives
- head dropping (so that the chin drops towards the chest)
- stomach pain
- leakage of the device
- mouth or tongue blisters
- swelling or redness of the eyelid and the white part of the eye (conjunctivitis)
- feeling nervous
- disorder of the stomach or intestines.

Not known (frequency cannot be estimated from the available data):
- device is displaced and does not function correctly when preparing for infusion.

Reporting of side effects
If you or your child gets any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Brineura

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the vials and carton after EXP. The expiry date refers to the last day of that month.

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

Thawed Brineura and flushing solution should be used immediately. This medicine 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.

Your doctor or pharmacist is responsible for storing Brineura. They are also responsible for disposing of any unused Brineura properly.

6. Contents of the pack and other information

What Brineura contains

- The active substance is cerliponase alfa. 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.
- The other ingredients of Brineura solution for infusion and the flushing solution are: sodium phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate and water for injections (see section 2 “Brineura contains sodium and potassium”).

What Brineura looks like and contents of the pack

Brineura and the flushing solution are solutions for infusion. The Brineura solution for infusion is clear to slightly opalescent, colourless to pale yellow that may occasionally contain thin translucent fibres or opaque particles. The flushing solution is clear and colourless.

Pack size: Each pack contains two vials of Brineura solution for infusion and one vial of flushing solution, each containing 5 ml of solution.

Marketing Authorisation Holder and Manufacturer

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

ANNEX IV

GROUNDS FOR ONE ADDITIONAL RENEWAL

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Brineura remains positive, but considers that an additional renewal is required for the following reasons:

In the framework of the initial marketing authorisation under exceptional circumstances, a post-authorisation efficacy study (study 190-203) has been adopted as specific Obligation (SOP). An in-depth assessment of the totality of the data is needed at the time of submission of the final CSR, especially an in-depth assessment for efficacy and safety data for those patients <2 years of age. This will include the appropriateness of the current dosing recommendations with regard to efficacy and safety in younger children (below the age of 3 years), taking the available PK data into consideration.

A second renewal of the marketing authorisation is required due to unfulfilled SOB, i.e. an uncompleted post-authorisation efficacy study, study 190-203.