

INTRODUCTION

- Neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of inherited, childhood lysosomal storage disorders (LSDs) characterized by the intracellular accumulation of storage material (lipopigment) leading to severe neurodegeneration (*FDA Summary Review 2017*). NCLs are collectively referred to as Batten disease (*Brineura Formulary Submission Dossier 2017, Batten Disease Fact Sheet*).
- Neuronal ceroid lipofuscinosis Type 2 (CLN2) is the second most common form of NCL and is due to a deficiency of the lysosomal enzyme tripeptidyl peptidase-1 (TPP1) (*FDA Summary Review 2017*). The disease follows a relatively predictable phenotype, with onset between 2 and 4 years of age followed by a progressive, steady deterioration resulting in profound neurological deficits by 6 years of age and death in adolescence (*FDA Summary Review 2017*).
 - CLN2 classically manifests with the onset of seizures, typically in combination with a history of early language delay (*Brineura Formulary Submission Dossier 2017*). Disease progression includes a loss of language and walking ability; movement disorders (eg, myoclonus, dystonia, chorea, pain, progressive dementia); and the eventual loss of vision (*Brineura Formulary Submission Dossier 2017*). Most children with CLN2 disease die between the ages of 8 years and early adolescence (*Brineura Formulary Submission Dossier 2017*).
 - Despite rapid disease progression, a definitive diagnosis of CLN2 disease (made by measurement of TPP1 enzymatic activity or CLN2 genotyping), is often delayed due to the lack of symptom specificity early in the disease and a general, low clinical awareness of CLN2 disease (*Brineura Formulary Submission Dossier 2017*).
 - CLN2 is very rare, with an estimated incidence between 0.56 and 4 patients per 100,000 live births in the United States and Europe (*FDA Summary Review 2017*).
- As there is no cure for CLN2, the current standard of care relies on a multidisciplinary approach including seizure management; physical, occupational, and speech therapy to optimize residual motor function; nutritional management; the general treatment of complications related to the loss of mobility and swallowing; management of sleep disturbances and behavior symptoms; and social and educational interventions (*FDA Summary Review 2017*).
- On April 27, 2017, the Food and Drug Administration (FDA) announced the approval of BioMarin's Brineura (cerliponase alfa), to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile CLN2, also known as TPP1 deficiency (*FDA Web site*). Cerliponase alfa underwent a priority review and was granted breakthrough therapy and orphan drug designations by the FDA; it is the first approved pharmacological treatment (ie, enzyme replacement therapy [ERT]) for CLN2 (*FDA News Release 2017*).
 - Under the same trade name, cerliponase alfa was also approved by the European Commission, but with an expanded age indication for the treatment of CLN2 in patients of all ages from birth (*European Medicines Agency [EMA] 2017, Markham 2017*).
- Cerliponase alfa is a recombinant form of human TPP1 (rhTPP1), the enzyme deficient in patients with CLN2.
 - After infusion, the cerliponase alfa proenzyme enters target cells in the central nervous system (CNS) where it is then transported into lysosomes via the cation-independent, mannose-6-phosphate receptor (*Markham 2017*). The drug is then activated in the lysosome to a proteolytic form of rhTPP1, which functions to cleave tripeptides from the N-terminus of proteins (*Markham 2017*).
 - Because cerliponase alfa cannot cross the blood-brain barrier, the drug is administered directly into the intracerebroventricular space via a specific surgically implanted reservoir and catheter in the head (intraventricular access device) (*FDA Summary Review 2017*).
- Medispan Class: Endocrine and Metabolic Agents – Misc; Metabolic Modifiers; Tripeptidyl Peptidase 1 Deficiency Treatment - Agents

INDICATIONS

- Cerliponase alfa is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile CLN2, also known as TPP1 deficiency (*Brineura prescribing information 2017*).

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The cerliponase alfa clinical program included an interventional clinical study (Study 190-201) with an extension (Study 190-202) and comparison to an historical, untreated cohort (Study 190-901) (*Brineura Formulary Submission Dossier 2017, ClinicalTrials.gov Web site, FDA Statistical and Summary Reviews 2017*). The results of Studies 190-201/202 and 190-901 are currently unpublished.
 - Study 190-201 was a 48-week, Phase 1/2, single-arm, open-label (OL), clinical trial that enrolled 24 patients \geq 3 years of age with symptomatic CLN2 disease. Twenty-three patients entered the currently ongoing, 5-year extension phase (Study 190-202). Cerliponase alfa-treated patients were compared with an independent historical control group with similar, but not identical baseline characteristics (N = 42 untreated patients; Study 190-901).
 - Efficacy assessments were based on a clinician-reported outcome (ClinRo) known as the CLN2 Clinical Rating Scale that typically consists of 4 domains: Motor, Language, Visual, and Seizures. In studies of cerliponase alfa, only the Motor and Language domains were assessed; efficacy conclusions were based on multiple analyses of the best matched patients in the 2 cohorts and accounted for several confounding factors (age, genotype, screening motor score).
 - Motor function (walking or crawling ability) was assessed using the Motor domain of the CLN2 Clinical Rating Scale, which could range from a score of 3 (normal) to a score of zero (profoundly impaired).
 - Treatment with cerliponase alfa was associated with a slowing in progression of motor deterioration relative to a reasonably matched control cohort. There was a progressively larger difference with time between the treated and historical groups: 18%, 29%, and 59% at 48, 72, and 96 weeks, respectively. Of note, at Week 96, the 95% confidence interval (CI) for the odds ratio (OR) excluded 1 (ie, OR = 11; 95% CI: 1.6 to 500), which was not observed with shorter exposure to treatment.
 - In its analysis, the FDA noted that a longer duration of treatment was necessary to identify a treatment difference. The initial efficacy comparisons at 48 weeks were inconclusive, as were comparisons after 72 weeks of treatment (although an efficacy trend was observed at both time points, and more clearly at 72 weeks compared to 48 weeks). The 96-week time point ultimately provided adequate evidence of effectiveness.
 - Due to the inability to establish comparability for the CLN2 Language domain ratings between the clinical study with extension and the natural history cohort, the efficacy of cerliponase alfa for the Language domain could not be established.

CLINICAL GUIDELINES

Note: No CLN2 management guidelines exist and there is a paucity of published disease-specific evidence to inform clinical practice, which currently draws upon experience from the field of childhood neuro-disability (*Williams et al 2017*). A group of 24 disease experts were surveyed on CLN2 disease management and a subset met to discuss current practice; their recommendations (see below) were generally consistent and guided by the principles of pediatric palliative care (*Williams et al 2017*).

- **Management strategies for CLN2 disease** (*Williams et al 2017*)
 - Early diagnosis of CLN2 disease is critical to ensure optimal care for patients and families, but is challenging primarily due to a lack of disease awareness and the non-specificity of initial presenting symptoms. Most patients are diagnosed around 5 years of age when substantial loss of function has already occurred.
 - Once clinical suspicion of CLN2 disease or an NCL disorder has been established, the patient should undergo biochemical testing. The recommended gold standard for definitive diagnosis of CLN2 disease is the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots), together with the detection of pathogenic mutations in each allele of the TPP1 gene (also known as the CLN2 gene).
 - Management of CLN2 disease should be guided by the principles of pediatric palliative care, a holistic approach to caring for children with complex medical needs. Optimizing the quality of life for patients and their families requires a multidisciplinary team of health care professionals, including physicians, nurses, therapists (ie, physical, occupational, and speech), dietitians, psychologists, social workers, and counselors, working collaboratively to manage symptoms, minimize pain and suffering, and provide psychosocial and spiritual support. A supervising clinician (neurologist, palliative care specialist, or general pediatric specialist) typically oversees the coordination of care.

- As the disease evolves beyond the initial presentation and the symptom burden increases, maintenance of function (particularly ambulation and communication) for as long as possible is the main goal of management. In the late stage, maintenance of the quality of life and the prevention of complications secondary to immobility and functional loss (eg, decubitus ulcers, muscle atrophy, aspiration pneumonia) are the priorities of care.
- Optimal management of patients requires ongoing assessments and modification of treatment plans as needed. The frequency of clinic visits/assessments should be tailored to meet the individual needs of each child/family.

SAFETY SUMMARY

- **Contraindications**
 - Patients with acute intraventricular access device-related complications (eg, leakage, device failure, or device-related infection).
 - Patients with ventriculoperitoneal shunts.
- **Warnings/precautions**
 - Intraventricular access device-related complications
 - The scalp should be inspected for skin integrity and for signs of intraventricular access device leakage; cerliponase alfa should not be administered if there are signs of device leakage or infection. Cerebrospinal fluid (CSF) samples should routinely be sent for testing to detect subclinical device-related infections.
 - Cardiovascular adverse reactions
 - Vital signs should be monitored before, during, and post-infusion. Electrocardiograms (ECGs) should be monitored in patients with a history of bradycardia, conduction disorder, or with structural heart disease, during the infusion. In patients without cardiac abnormalities, regular 12-lead ECG evaluations should be performed every 6 months.
 - Hypersensitivity reactions
 - Patients should be observed during and after the infusion. If a severe hypersensitivity reaction occurs, the infusion should be stopped immediately and appropriate treatment initiated.
- **Adverse effects**
 - The most common adverse reactions ($\geq 8\%$) reported in Studies 190-201/202 at Week 96 were: pyrexia (17/24 [71%]), ECG abnormalities (17 [71%]), decreased CSF protein (17 [71%]), vomiting (15 [63%]), seizures (12 [50%]), hypersensitivity (11 [46%]), increased CSF protein (5 [21%]), hematoma (5 [21%]), headache (4 [17%]), irritability (4 [17%]), pleocytosis (4 [17%]), device-related infection (2 [8%]), bradycardia (2 [8%]), feeling jittery (2 [8%]), and hypotension (2 [8%]).
 - Pyrexia includes: pyrexia and increased body temperature
 - ECG abnormalities include: non-specific repolarization abnormality, notched QRS, ST segment elevation, biphasic T wave abnormality, supraventricular extrasystoles, bradycardia, sinus tachycardia, and intraventricular conduction delay
 - Seizure types reported included atonic, generalized tonic-clonic, focal, and absence. Seizures were managed with standard anti-convulsive therapies and did not result in discontinuation of cerliponase alfa treatment.
 - Hypersensitivity includes: immune reactions and signs and symptoms observed concomitantly with hypersensitivity reactions including pyrexia, vomiting, pleocytosis or irritability
 - Device-related infections include: *Propionibacterium acnes* and *Staphylococcus epidermidis*
 - As with all therapeutic proteins, there is a potential for immunogenicity.
 - The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cerliponase alfa in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
 - Anti-drug antibodies (ADAs) to cerliponase alfa were detected in both serum and CSF in 79% and 33%, respectively, of patients treated with cerliponase alfa for up to 161 weeks. Patients who experienced hypersensitivity adverse reactions were tested for drug-specific IgE and found to be negative, including 3 patients for whom grade 3 (severe) hypersensitivity adverse reactions were reported.

- No association was found between serum or CSF ADA titers and incidence or severity of hypersensitivity. Drug-specific neutralizing antibodies have not been evaluated.

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Brineura (cerliponase alfa)	Injection	Intraventricular infusion	Every other week Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion.	<p>Must be administered under sterile conditions by, or under the direction of a physician knowledgeable in intraventricular administration.</p> <p>Following administration of cerliponase alfa, an infusion of intraventricular electrolytes must follow. The entire procedure takes approximately 4.5 hours.</p> <p>Cerliponase alfa is a drug-device combination product; it is co-packaged with the intraventricular electrolytes injection and with an administration kit containing syringes, needles, infusion set with filter, extension and a port needle.</p> <p>Cerliponase alfa is intended to be administered via the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman® Ventricular Catheter (Part Number: 82-1650). The pump to be used is the B Braun Perfusor® Space Infusion Pump System.</p>

See the current prescribing information for full details

CONCLUSION

- Brineura (cerliponase alfa) is indicated to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency.
- Cerliponase alfa is the first approved pharmacological treatment (ie, enzyme replacement therapy) for CLN2, a pediatric-onset, autosomal recessive, neurodegenerative, lysosomal storage disorder caused by the deficient activity of the enzyme TPP1. The data supporting the approval of cerliponase alfa are currently unpublished.
- Treatment with cerliponase alfa was associated with a slowing in progression of motor deterioration relative to a reasonably matched untreated cohort. There was a progressively larger difference with time between the treated and historical groups (N = 17 pairs): 18%, 29%, and 59% at 48, 72, and 96 weeks, respectively. Of note, at Week 96, the

95% confidence interval (CI) for the odds ratio (OR) excluded 1 (ie, OR = 11; 95% CI: 1.6 to 500), which was not observed with shorter exposure to treatment.

- Because cerliponase alfa cannot cross the blood-brain barrier, the drug is administered directly into the intracerebroventricular space via a specific surgically implanted reservoir and catheter in the head (intraventricular access device).
- Although the intraventricular infusions required to administer cerliponase alfa carry several inherent risks and must be performed under the supervision of knowledgeable healthcare providers, the approval of cerliponase alfa marked an important treatment milestone for patients with rare CLN2 disease. While the effects of cerliponase alfa on the language, visual, and seizure complications associated with CLN2 remain unknown, a significant slowing in the progression of motor deterioration in cerliponase alfa-treated patients relative to a reasonably matched, untreated cohort was demonstrated by 96 weeks.

REFERENCES

- Batten Disease Fact Sheet. National Institute of Neurological Disorders and Stroke (NINDS). NINDS Web site. <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Batten-Disease-Fact-Sheet>. Accessed August 31, 2017.
- Brineura [formulary submission dossier], Novato, CA: BioMarin Pharmaceutical Inc.; May 2017.
- Brineura [package insert], Novato, CA: BioMarin Pharmaceutical Inc.; April 2017.
- ClinicalTrials.gov Web site. <http://clinicaltrials.gov/>. Accessed August 31, 2017.
- European Medicines Agency. Cerliponase alfa (Brineura): summary of product characteristics 2017. http://ec.europa.eu/health/documents/community-register/2017/20170530137963/anx_137963_en.pdf. Accessed August 31, 2017.
- FDA Approves first treatment for a form of Batten disease. FDA News Release [April 27, 2017]. FDA Web site. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm555613.htm>. Accessed August 31, 2017.
- FDA/CDER resources page. Food and Drug Administration Web site. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed September 5, 2017.
- FDA Center for Drug Evaluation and Research. Medical Review [Application Number 761052Orig1s000]. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761052Orig1s000MedR.pdf. Accessed August 31, 2017.
- FDA Center for Drug Evaluation and Research. Statistical Review [Application Number 761052Orig1s000]. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761052Orig1s000StatR.pdf. Accessed August 31, 2017.
- FDA Center for Drug Evaluation and Research. Summary Review [Application Number 761052Orig1s000]. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761052Orig1s000SumR.pdf. Accessed August 31, 2017.
- Markham A. Cerliponase Alfa: First Global Approval. *Drugs*. 2017 Jul;77(11):1247-1249.
- Williams RE, Adams HR, Blohm M, et al. Management Strategies for CLN2 Disease. *Pediatr Neurol*. 2017;69:102-112.

Publication Date: September 06, 2017