Original Effective Date: 08/15/2017
Current Effective Date: 09/25/2024
Last P&T Approval/Version: 07/31/2024
Next Review Due By: 07/2025
Policy Number: C11526-A

Brineura (cerliponase alfa)

PRODUCTS AFFECTED

Brineura (cerliponase alfa)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2):
   1. Documented diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) [also known as tripeptidyl peptidase 1 (TPP1) deficiency]
      AND

2. Documentation diagnosis confirmed by BOTH of the following [DOCUMENTATION REQUIRED]:
   i. Tripeptidyl peptidase 1 (TPP1) enzyme deficiency in leukocytes or fibroblasts (Recommended together with normal activity of an appropriate control enzyme such as PPT1 and/or β-galactosidase.)
   AND
   ii. Molecular genetic test identifying TWO pathogenic variants/mutations in trans in the TPP1/CLN2 gene (one pathogenic mutation on each parental allele of TPP1/CLN2 gene)

   MOLINA REVIEWER NOTE: BOTH diagnostic tests above are the recommended gold standard for definitive diagnosis of CLN2 disease and must be submitted. In exceptional cases, where there may be laboratory accessibility concerns in the member's geographical area, Molina to confirm nearest testing center to support meeting this diagnostic criterion. If accessibility is determined by Molina Medical Reviewer as unreasonable for member, Prescriber may submit ONE of the two tests indicated above. Additional documentation and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff. [MEDICAL DIRECTOR/PHARMACIST REVIEW REQUIRED]
   AND
3. Documentation member has symptoms of late infantile CLN2 [may include but not limited to: language delay, unprovoked seizure, ataxia, movement disorders, motor deterioration, dementia, blindness, prominent truncal and peripheral ataxia, behavioral disturbances, and other developmental delays)] (Williams R.E.et al 2017)
   AND
4. Documentation of Mild to moderate disease documented by a two-domain score of 3-6 on *Motor and Language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains on the Clinical Scoring System for late infantile CLN2:
   i. Combined score of 3 to 6 in the motor and language domains
   ii. Score of at least 1 in the motor domain
   iii. Score of at least 1 in the language domain

   AND
5. Documentation of baseline/pre-treatment motor function/milestones, including but not limited to, the following validated scale: Motor and Language CLN2 score
   AND
6. Prescriber attests that member does not have, has not had, and does not require, ANY of the following:
   i. Score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale
   ii. Inherited neurologic disease (e.g., other forms of CLN or seizures unrelated to CLN2), another neurological illness that may have caused cognitive decline (e.g., trauma, meningitis, hemorrhage), or contraindications to neurosurgery (e.g., congenital heart disease, severe respiratory impairment, or clotting abnormalities)
   iii. Generalized motor status epilepticus or severe infection (e.g., pneumonia, pyelonephritis, or meningitis) within 4 weeks of initiation treatment (when the first dose is to be administered)
   iv. Stem cell, gene therapy, or enzyme replacement therapy in the past for CLN2
   v. Ventilation support (except for noninvasive support at night)
   vi. Prone to complications from intraventricular drug administration, including individuals with hydrocephalus or ventricular shunts

   AND
7. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Brineura (cerliponase alfa) include: Any sign or symptom of acute or unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or suspected or confirmed CNS infection (e.g., cloudy CSF or positive CSF gram stain, or meningitis), Any acute intraventricular access device-

related complication (e.g., leakage, extravasation of fluid, or device failure), Patients with ventriculoperitoneal shunts]

CONTINUATION OF THERAPY:

A. LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2):

1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity from Brineura (cerliponase alfa) or device- related complications (e.g., severe hypersensitivity reaction, severe cardiovascular reactions, severe hypotension; other intraventricular access device-related infections)
   AND
2. Prescriber attests to (or the clinical reviewer has found that) the member continues to not have any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Brineura (cerliponase alfa) include: Any sign or symptom of acute or unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or suspected or confirmed CNS infection (e.g., cloudy CSF or positive CSF gram stain, or meningitis), Any acute intraventricular access device-related complication (e.g., leakage, extravasation of fluid, or device failure), Patients with ventriculoperitoneal shunts]
   AND
3. Documentation of response to therapy compared to pretreatment baseline with disease stability or lack of decline in motor function, including but not limited to, the following:
   a. No decline* in the CLN2 Clinical Rating Scale [*decline is defined as an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale (normal: 3, clumsy/falls: 2, non-walking: 1, immobile: 0)]
   b. Loss of ambulation slowed
   c. Visual acuity has stabilized

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified neurologist, pediatric neurologist, pediatric epileptologist, or specialist with expertise in the diagnosis and treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

3 years of age to 18 years of age

QUANTITY:

300 mg (10 mL) intraventricularly once every other week; following cerliponase alfa infusion, administer 2 mL intraventricular electrolytes (included in administration kit)

Maximum Quantity Limits – 1 kit every 14 days, Up to 26 infusions per year

PLACE OF ADMINISTRATION:

The recommendation is that infused medications in this policy will be for medical benefit coverage administered in a place of service that is a non-hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intraventricular

DRUG CLASS:
Tripeptidyl Peptidase 1 Deficiency Treatment – Agents

FDA-APPROVED USES:
Indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
CLN2 Clinical Rating Scale: Scale used to calculate patient's degree of disease severity

Score	Functional Description	
	Motor Domain	Language Domain
3	Has grossly normal gait; no prominent ataxia, no pathologic falls	Has apparently normal language that is intelligible and grossly age-appropriate, with no decline noted
2	Has independent gait as defined by ability to walk without support for 10 steps; obvious instability and possibly intermittent falls	Has language that has recognizable abnormalities but includes some intelligible words; may form short sentences to convey concepts, requests, or needs
1	Requires external assistance to walk or can only crawl	Has language that is hard to understand with few intelligible words
0	Can no longer walk or crawl	Has no intelligible words or vocalizations

Reference: Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular cerliponase alfa forCLN2 disease. NEngl J Med. 2018; 378(20):1898-1907.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
CLN2 disease (neuronal ceroid lipofuscinosis type 2)

- An ultra-rare, autosomal recessive lysosomal storage disorder (LSD) Pediatric-onset; rapidly progressive neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency, and is characterized by language delay, seizures, rapid cognitive and motor decline, blindness, and early death
- One of the most common forms of neuronal ceroid lipofuscinosis (NCL)
- Estimated incidence of CLN2 is 0.5-1/100,000 live births per year and the U.S. prevalence is estimated to range from 400 to 500 patients (FDA, CDER)
- Most commonly presents as the late–infantile phenotype

Management of CLN2 disease
Historically, treatment has been limited to symptomatic and supportive care. Management of CLN2 is symptomatic and palliative. Treatment is directed at mitigating manifestations of the hypersalivation, hyperactivity and behavior problems, psychosis, anxiety, spasticity, Parkinsonian

disease: seizures, sleep-related problems, malnutrition, gastroesophageal reflux, pneumonia, symptoms, and dystonia.

- The goals of CLN2 disease care should evolve as the disease progresses. Experts have noted that reassessing the goals of care and management is important throughout the course of the disease. At the onset and earlier stages of the disease, the goal is to strive to maintain function for as long as possible.

As disease progresses, management goals evolve toward maintenance of quality of life and pain control as functions are lost. (Williams RE, 2016).

- There is no cure for CLN2 disease. Brineura (formerly BMN 190) is the first FDA-approved treatment for CLN2 disease. There are no other FDA-approved treatments for CLN2 disease; Brineura is the only enzyme replacement therapy for the treatment of CLN2 disease at this time. Cerliponase alfa (Brineura)
- A recombinant form of human TPP1 that provides enzyme replacement therapy (ERT). The enzyme results in a restored breakdown of the lysosomal storage materials that cause CLN2 disease and restore TPP1 enzyme activity.
- Indicated to slow loss of walking ability in symptomatic pediatric patients aged 3 years and older with late infantile neuronal ceroid lipofuscinosis CLN2
- For intraventricular administration only; ERT is delivered directly into the cerebrospinal fluid, through an intraventricular access device, surgically implanted reservoir, and catheter, in order to reach the cells of the brain and central nervous system.

The FDA approval was based on results of a phase I/II open-label dose-escalation study of intracerebroventricular Brineura in patients aged 3 to 8 years with CLN2 disease (NCT01907087).The FDA evaluated efficacy data in 22 patients and safety data in 24 patients.

- The efficacy of cerliponase alfa was evaluated in a prospective, non-randomized, open- label, single- arm clinical study with extension trial in symptomatic pediatric patients (N=23) aged 3 to 8years with CLN2 disease, confirmed by TPP1 deficiency.

A total of 24 participants were originally enrolled in the single-arm study. One participant withdrew after 1 week. The remaining 23 participants received cerliponase alfa every other week for 48 weeks and continued treatment during the extension period.

- The primary objectives were to evaluate the safety and tolerability of intracerebroventricular-administered Brineura and to evaluate effectiveness using a CLN2 disease-specific rating scale score in comparison with natural history data after 48 and 72 weeks of treatment.
- The primary endpoint was decline in motor domain of the CLN2 clinical rating scale. Decline was defined as having an unreversed 2 category decline or an unreversed score of 0 (normal: 3, clumsy/falls: 2, non-walking: 1, immobile: 0). Evaluation was completed at 48, 72, and 96 weeks.
- Fewer patients treated with cerliponase alfa (n=22) experienced a decline in the motor domain of the CLN2 Clinical Rating Scale compared with historical controls (n=42). A sustained 2-category decline or an unreversed score of 0 were defined as a decline.
- At week 96, only 1 of 22 patients receiving cerliponase alfa had declined in the motor domain of the CLN2 Clinical Rating Scale, while 50% of the 42 historical controls had declined. A matched analysis of 17 patients from each treatment group reported similar findings [Prescribing Information 2017]

Of the 22 patients treated with Brineura and evaluated for efficacy at week 96, 21 (95%) did not decline, and only the patient who terminated early was deemed to have a decline.

Results from the natural history cohort demonstrated progressive decline in motor function; of the42 patients in the natural history cohort, 21 (50%) experienced an unreversed (sustained) 2- category decline or unreversed score of 0 in the motor domain of the CLN2 Clinical Rating Scale over 96 weeks.

- The study did not include a control group. Instead, results of the treatment were compared to those of a study of the natural course of the disease. Findings indicated that Brineura slowed the loss of walking ability: Motor scores of the 22 Brineura-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study.
- Hypersensitivity reactions have been reported in 11 (46%) Brineura treated patients during the clinical studies. The most common adverse reactions (≥8%) are pyrexia, ECG abnormalities, decreased cerebrospinal fluid (CSF) protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension.

No practice guidelines or management consensus exist at the present time; however, management goals and strategies are generally consistent among experts and are guided by the principles of pediatric palliative care through a multidisciplinary approach to management. Experts have identified common management practices and taken significant steps toward the development of consensus- based management guidelines (Williams RE, 2016).

Pharmacologic Category: Enzyme replacement therapy (ERT); Hydrolytic Lysosomal N-terminal Tripeptidyl Peptidase *Enzyme replacement therapy: A treatment provided, usually via intravenous infusion, to provide enzymes in an individual unable to make sufficient amounts of that enzyme on their own.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Brineura (cerliponase alfa) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Brineura (cerliponase alfa) include: Any sign or symptom of acute or unresolved localized infection on or around the device insertion site (e.g., cellulitis or abscess); or suspected or confirmed CNS infection (e.g., cloudy CSF or positive CSF gram stain, or meningitis), Any acute intraventricular access device-related complication (e.g., leakage, extravasation of fluid, or device failure), Patients with ventriculoperitoneal shunts.

OTHER SPECIAL CONSIDERATIONS:
Brineura should be administered by, or under the direction of, a physician experienced in intraventricular administration.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0567	Injection, cerliponase alfa, 1 mg

AVAILABLE DOSAGE FORMS:
Brineura KIT 2 X 150MG/5ML

REFERENCES

1. Brineura (cerliponase alfa) [prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc; March 2020.
2. FDA.gov. FDA approves first treatment for a form of Batten disease.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm555613.htm . Accessed on May 2020.
3. FDA.gov. Center for Drug Evaluation and Research (CDER). April 25, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761052Orig1s000RiskR.pdf Accessed on May 2020.
4. BioMarin Announces Ongoing Study Demonstrates Durable Treatment Benefit from Brineura (cerliponase alfa) for 3 Years. BioMarin Published Feb. 07, 2019. Accessed July 2019.
5. ClinicalTrials.gov. A Phase ½ Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients With Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease. Available from: ClinicalTrials. Accessed May 2020. ClinicalTrials.gov. A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients With CLN2 Disease. Available from: ClinicalTrials Accessed May 2020.
6. Cherukuri A, Cahan H, Van Tuyl A, et al. Immunogenicity to cerliponase alfa, an enzyme replacement therapy for patients with CLN2 disease: results from a phase ½ study. Molecular Genetics and Metabolism. 2017 Jan 1;120(1):S35.
7. Cherukuri A, Cahan H, de Hart G, et al. Immunogenicity to cerliponase alfa intracerebroventricular enzyme replacement therapy for CLN2 disease: results from a Phase ½ study. Clin Immunol. 2018; 197:68-76.
8. Schulz A, Specchio N, Gissen P. Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: Results from a Phase ½, open-label, dose-escalation study. J Inherit Metab Dis. 2016;39(Suppl. 1):S51.
9. Schulz A, Specchio N, Gissen P, et al. Long-term safety and efficacy of intracerebroventricular enzyme replacement therapy with cerliponase alfa in children with CLN2 disease: interim results from an ongoing multicenter, multinational extension study. Molecular Genetics and Metabolism. 2017 Jan 1;120(1):S120.
10. Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular cerliponase alfa for CLN2 disease. N EnglJ Med. 2018; 378(20):1898-1907.
11. Fietz M, Al-Sayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab. 2016; 119:160-167. Available at: http://www.mgmjournal.com/article/S1096-7192(16)30155- X/fulltext#t0010 Accessed on May 2020.
12. Geraets RD, Koh SY, Hastings ML, et al. Moving towards effective therapeutic strategies for NeuronalCeroid Lipofuscinosis. Orphanet J Rare Dis. 2016; 11:40.
13. Williams RE, Adams HR, Blohm M, Cohen-Pfeffer JL, de Los Reyes E, Denecke J, et al. Management Strategies for CLN2 Disease. Pediatr Neurol. 2017 Apr;69:102- 112.
14. CLN2 disease. Genetics Home Reference. Available at: https://ghr.nlm.nih.gov/condition/cln2-disease. Accessed September 2019. Accessed on May 2020.
15. CADTH Canadian Drug Expert Committee Recommendation: Cerliponase Alfa (Brineura — Biomarin Pharmaceutical [Canada] Inc.): Indication: For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 May. Available from: https://www.ncbi.nlm.nih.gov/books/NBK543392/ Accessed on May 2020.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity FDA-Approved Uses Contraindications/Exclusions/Discontinuation Other Special Considerations References	Q3 2023
REVISION- Notable revisions: Required Medical Information	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file