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Cerliponase alfa

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Cerliponase alfa (Brineura™) **may be considered medically necessary** to slow the loss of ambulation in pediatric patients with a diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Cerliponase alfa (Brineura™) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Neuronal ceroid lipofuscinosis type 2 (CLN2) disease is an ultra-rare and rapidly progressive pediatric brain disorder and one of the most common forms of neuronal ceroid lipofuscinosis, a group of inherited disorders collectively known as Batten disease. (2, 3) In early stages, CLN2 disease is challenging to recognize, and diagnosis is often delayed until after the disease has progressed significantly. The initial features usually include recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects motor skills, such as sitting and walking, and speech development. This condition also causes the loss of previously acquired skills (developmental regression), intellectual disability that gradually gets worse, and behavioral problems. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens. (4)

CLN2 disease is autosomal recessive, meaning both parents of an affected child have a specific mutation on their tripeptidyl peptidase 1 (TPP1) gene. Parents are usually asymptomatic carriers. If both parents carry the mutation, there is a 25 percent chance that their child will have CLN2 disease. (2)

Children with CLN2 disease produce deficient levels of the enzyme TPP1. Without this enzyme, children are genetically unable to dispose of wastes normally metabolized in a cell's lysosomes. The waste accumulates in organs, particularly the brain and retina, contributing to the loss of cognitive, motor, and visual functions. (2)

Laboratory tests to diagnose CLN2 disease are well established. TPP1 enzyme activity can be assessed in several sample types: leukocytes, dried blood spots (DBS), fibroblasts, and saliva. The gold standard for laboratory diagnosis is demonstration of deficient TPP1 enzyme activity (in conjunction with normal activity of a control enzyme such as palmitoyl-protein thioesterase 1 [PPT1] and/or β-galactosidase) followed by molecular analysis that detects one pathogenic mutation on each parental allele of TPP1/CLN2. (3)

Cerliponase alfa (Brineura™)

Cerliponase alfa (Brineura™) has been approved by the U.S. Food and Drug Administration (FDA) to treat CLN2 disease, a specific form of Batten Disease, which is a rare set of genetic disorders that typically begin in childhood between ages 2 and 4. Brineura is the first treatment approved to treat children with CLN2 disease. Brineura is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. The active substance is a recombinant human tripeptidyl peptidase-1 (rhTPP1), a lysosomal exopeptidase. The primary activity of the mature enzyme is the cleavage of N-terminal tripeptides from a broad range of protein substrates. Cerliponase alfa contains 544 amino acids with an average molecular mass of 59 kDa. The mature enzyme is 368 amino acids in length. There are 5 consensus N-glycosylation sites on rhTPP1 that contain high mannose, phosphorylated high mannose and complex glycosylation structures. Cerliponase alfa is available as Brineura 150 mg/5 mL (30 mg/mL) solution for intraventricular infusion. It is packaged as two single-dose vials along with intraventricular electrolytes injection 5 mL in a single-dose vial. (1, 5)

Brineura™ is administered into the cerebrospinal fluid by infusion via a specific surgically implanted intraventricular access device in the head under the supervision of a physician experienced in intraventricular administration, including hypersensitivity reactions. Brineura is administered first followed by the infusion of intraventricular electrolytes which takes approximately 2 to 4.5 hours to administer. Brineura is not recommended in individuals less than 37 weeks post-menstrual age or those weighing less than 2.5 kg. (1, 3)

Regulatory Status

On April 27, 2017, Brineura (BioMarin Pharmaceutical Inc.) received FDA approval for the treatment of CLN2 (a specific form of Batten Disease) to slow loss of walking ability (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. (6)

In July 2024, the FDA approved the supplemental Biologics License Application (sBLA) for Brineura to slow the loss of ambulation in children of all ages with CLN2 disease. This expanded indication now includes children of all ages with CLN2 disease, regardless of whether they are symptomatic or presymptomatic. (1)

Per the FDA label, Brineura is not recommended for use in patients less than 37 weeks post-menstrual age (gestational age at birth plus post-natal age) or those weighing less than 2.5 kg due to physiologic immaturity which may increase risk of serious and clinically significant

adverse reactions observed with Brineura. Patients less than 3 years of age may be at increased risk for developing hypersensitivity reactions with Brineura use compared to patients 3 years of age and older.

Refer to <https://www.fda.gov> for current FDA guidance on dosage, volume, infusion rate, contraindications, warnings, and precautions.

Rationale

This policy is based upon the U.S. Food and Drug Administration (FDA) labeled indication for cerliponase alfa (Brineura™).

Brineura™ (cerliponase alfa) (1)
The efficacy of Brineura was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by tripeptidyl peptidase 1 (TPP1) deficiency. Brineura-treated patients were compared to untreated patients from a natural history cohort (an independent historical control group). The Motor domain of a CLN2 Clinical Rating Scale was used to assess disease progression. Scores ranged from 3 (grossly normal) to 0 (profoundly impaired) with unit decrements representing milestone events in the loss of motor function (ability to walk or crawl). Due to the inability to establish comparability for the CLN2 Language domain ratings between the clinical study with extension and the natural history cohort, efficacy of Brineura for the language domain cannot be established.

Twenty-four patients aged 3 to 8 years were enrolled in the Brineura single-arm clinical study (Trial 1, NCT01907087). Sixty-three percent of patients were female and 37% were male. Ninety-six percent of patients were White and 4% were Asian; for ethnicity, 4% identified as Hispanic/Latino, 96% as non-Hispanic/Latino. One patient withdrew after week 1 due to inability to continue with study procedures; 23 patients were treated with Brineura 300 mg every other week by intraventricular infusion for 48 weeks, and continued treatment during the 240-week extension period, Trial 2 (NCT02485899), for a total duration of 288 weeks, plus a 24-week safety follow-up.

In the clinical study with extension, patients were assessed for decline in the Motor domain of the CLN2 Clinical Rating Scale at 48, 72, and 96 weeks. Decline was defined as having an unreversed (sustained) 2-category decline or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale. Patients' responses to Brineura treatment were evaluated if at screening a combined Motor plus Language CLN2 score of less than 6 was recorded. Two patients with a combined Motor plus Language CLN2 score of 6 were excluded from the analyses; they maintained that score throughout the study period. The patient who terminated early was analyzed as having a decline at the time of termination. Data used in the analyses from the natural history cohort began at 36 months of age or greater and at the first time a Motor plus Language CLN2 score less than 6 was recorded.

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. The results of logistic modeling with covariates (screening age, screening motor score, genotype: 0 key mutations [yes/no]), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio [95% confidence interval]: 13.1 [1.2, 146.9]).

Descriptive Non-Randomized Comparison

In an unadjusted non-randomized comparison, 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 in the Motor domain of the CLN2 Clinical Rating Scale. Results from the natural history cohort demonstrated progressive decline in motor function; of the 42 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.

Given the non-randomized study design, a Cox Proportional Hazards Model adjusted for age, initial motor score, and genotype was used to evaluate time to unreversed 2-category decline or unreversed score of 0 in the Motor domain. This model showed a lesser decrease in motor function in the Brineura-treated patients when compared to the natural history cohort.

Motor Domain Scores: Matched Patients Only

To further assess efficacy, the 22 patients from the Brineura clinical study with a baseline combined Motor plus Language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. Patients were matched based on the following covariates: baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening.

Using the Motor domain of the CLN2 Clinical Rating Scale, decline was defined as having an unreversed 2-category decline or an unreversed score of 0. At 96 weeks, the matched analysis based on 17 pairs demonstrated fewer declines in the Motor domain for Brineura-treated patients compared to untreated patients in the natural history cohort.

Trial 3 (NCT02678689) was a Phase 2, open label clinical study designed to enroll symptomatic and presymptomatic CLN2 patients less than 18 years of age. The trial enrolled 14 patients ranging in age from 1 to 6 years at baseline, including 8 patients less than 3 years of age, with a median age was 2.7 years. Patients received Brineura at the recommended dose every 2 weeks by intraventricular infusion for 144 weeks (1 patient withdrew to receive treatment commercially). Fifty-seven percent of patients were female and 43% were male. All patients were White; for ethnicity, 14% identified as Hispanic/Latino, 86% as non-Hispanic/Latino. The mean baseline CLN2 Motor score was 2.3 (standard deviation [SD] 0.83) with a range from 1 to 3.

Thirteen of the 14 Brineura treated patients were matched with up to 3 natural history comparators on the basis of age within 3 months, equal CLN2 Motor score, and genotype (0, 1, or 2 key mutations). None of the Brineura treated patients (N=14) had a 2-point decline or score of zero in the Motor scale by Week 169. Among the matched natural history comparators (N=31), 20 subjects (65%) had an unreversed 2-point decline or score of zero by last assessment.

The median time to an unreversed 2-point decline in Motor score or score of 0 was 133 weeks among the natural history comparators and was not reached by last assessment (Week 169) in patients treated with Brineura.

In patients below 3 years of age, none (0%) of the Brineura treated patients (N=8) had a 2-point decline or score of zero in the Motor score by Week 169. Among the 8 treated patients, 7 were matched to 18 untreated patients from the natural history cohort. Among the matched natural history comparators (N=18), 11 subjects (61%) had an unreversed 2-point decline or score of zero in the Motor score by last assessment. All seven of the treated patients below 3 years of age with a motor score of 3 at baseline remained at a motor score of 3 at the last measured timepoint, which represents grossly normal gait. In this population Brineura treated patients showed a delay in disease onset.

Summary of Evidence

Cerliponase alfa (Brineura) is U.S. Food and Drug administration (FDA) approved to slow the loss of ambulation in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0567

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. FDA – Label Brineura™ (cerliponase alfa). Food and Drug Administration - Center for Devices and Radiologic Health (July 2024). Available at: <https://www.accessdata.fda.gov> (accessed August 26, 2025).

Other:

2. BioMarin: Our therapy areas. 2024. Available at: <https://biomartin.com> (accessed January 7, 2025).
3. Fietz M, AlSayed M, Burkeet D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab. Sep 2016; 119(1-2):160-167. PMID 27553878
4. MedlinePlus. CLN2 disease. National Library of Medicine. Nov 2016. Available at: <https://www.medlineplus.gov> (accessed January 7, 2025).
5. FDA News Release - FDA approves first treatment for a form of Batten disease. Food and Drug Administration. Center for Devices and Radiologic Health. April 26, 2017. Available at: <https://www.fda.gov> (accessed January 7, 2025).
6. FDA – BLA Approval Letter - Brineura™ (cerliponase alfa). Food and Drug Administration - Center for Devices and Radiologic Health (2017). Available at: <https://www.accessdata.fda.gov> (accessed January 7, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/01/2025	Document updated with literature review. The following changes were made to Coverage: 1) Removed “as determined by TPP1 enzyme activity (dried blood spot)” from the medical necessity criterion; and 2) Added “non-Food and Drug Administration approved” to experimental, investigational and/or unproven statement. No new references added; some removed.
03/01/2025	Document updated with literature review. The following change was made to Coverage 1) Removed “3 years of age and older” and “late infantile” to the existing medically necessary coverage statement. No new references, others updated and/or removed.

03/15/2024	Document updated with literature review. Updated “patients” to “individuals” although no change to intent. Added references 3, 7 and 8.
03/15/2023	Reviewed. No changes.
04/15/2022	Document updated with literature review. Coverage unchanged. No new references added; others updated.
02/15/2021	Reviewed. No changes.
04/15/2020	Document updated with literature review. The following change was made to Coverage: Modified language specific to age from “3 to 15 years of age” to “3 years of age and older”. Title changed from: “Brineura (cerliponase alfa)”.
11/15/2018	Reviewed. No changes.
11/01/2017	New medical document. Brineura™ (cerliponase alfa) may be considered medically necessary to slow the loss of ambulation in symptomatic pediatric patients 3 to 15 years of age with a diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, as determined by TPP1 enzyme activity (dried blood spot). Brineura™ (cerliponase alfa) is considered experimental, investigational and/or unproven for all other indications.