Medical Policy Bulletin

Title:
Cerliponase alfa (Brineura®)
Policy #:
MA08.089d

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

MEDICALLY NECESSARY

INITIAL THERAPY
Cerliponase alfa (Brineura®) is considered medically necessary and, therefore, covered for pediatric individuals when all of the following criteria are met, including the dosing and frequency requirements listed in Dosing Requirements Section:

- Diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease confirmed by either of the following:
  - TPP1 enzyme activity test indicating deficient activity in leukocytes or fibroblasts
  - Genetic test validating homozygous pathogenic variation for *TPP1*
- Individual is symptomatic (i.e., seizures, ataxia, language delay, vision loss, or symptoms characteristic of CLN2)
- Score of at least 1 in the motor domain on the CLN2 Clinical Rating Scale

CONTINUATION THERAPY
Cerliponase alfa (Brineura) is considered medically necessary and, therefore, covered for continuation therapy when the pediatric individual meets all of the following criteria:

- Individual is symptomatic (i.e., seizures, ataxia, language delay, vision loss, or symptoms characteristic of CLN2)
- Score of at least 1 in the motor domain on the CLN2 Clinical Rating Scale

EXPERIMENTAL/INVESTIGATIONAL

For all other uses, cerliponase alfa (Brineura) is considered experimental/investigational and, therefore, not covered because its safety and/or effectiveness cannot be established by review of the available published peer-reviewed literature.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of Cerliponase alfa (Brineura®). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of Cerliponase alfa (Brineura®) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for cerliponase alfa (Brineura®).

Age Groups	BRINEURA Dose (Every Other Week)	Volume of BRINEURA Solution	Infusion Rate
Birth to < 6 months	100 mg	3.3 mL	1.25 mL/hr
6 months to < 1 year	150 mg	5 mL	2.5 mL/hr
1 year to < 2 years	200 mg (first 4 doses) 300 mg (subsequent doses)	6.7 mL (first 4 doses) 10 mL (subsequent doses)	2.5 mL/hr
2 years and older	300 mg	10 mL	2.5 mL/hr

The FDA does not recommend dosing in pediatric individuals less than 37 weeks post-menstrual age (gestational age plus post-natal age) or those weighing less than 2.5kg.

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of cerliponase alfa (Brineura). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of cerliponase alfa (Brineura) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member’s dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for cerliponase alfa (Brineura).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of cerliponase alfa (Brineura) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

BILLING REQUIREMENTS

If there is no specific Healthcare Common Procedure Coding System (HCPCS) code available for the drug administered, the drug must be reported with the most appropriate unlisted code along with the corresponding National Drug Code (NDC).

Guidelines

BENEFIT APPLICATION

There is no Medicare coverage determination addressing erliponase alfa (Brineura®) therefore, the Company policy is applicable.

Subject to the terms and conditions of the applicable Evidence of Coverage, cerliponase alfa (Brineura®) is covered under the medical benefits of the Company's Medical Advantage products when the medical necessity criteria and dosing and frequency requirements listed in this medical policy are met.

The CLN2 Disease Clinical Rating Scale assesses disease progression in the following functional areas: motor, language, vision, and seizures. The motor and language domains were designated as primary endpoint of the Brineura® studies. Each functional area is scored on a scale of 3 (normal function) to 0 (total loss of function), with the highest possible score being 6, with a decline of 1 point indicating a significant loss in function.

Motor Function	Language Function
3- Grossly normal gait; no prominent ataxia; no pathologic falls	**3-** Apparently normal language; intelligible and grossly age-appropriate; no decline noted yet
2- Independent gait, as defined by ability to walk without support for 10 steps; will have obvious instability, and may have intermittent falls	**2-** Language has become recognizably abnormal; some intelligible words; may form short sentences to convey concepts, requests, or needs; this score signifies a decline from a previous level of ability (from the individual maximum reached)
1- Requires assistance to walk, or can crawl only	**1-** Hardly understandable; few intelligible words
0- Can no longer walk or crawl	**0-** No intelligible words or vocalizations

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Cerliponase alfa (Brineura®) was approved by the FDA on April 27, 2017 to slow the loss of ambulation in symptomatic pediatric individuals 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2).

On July 24, 2024, the FDA approved Cerliponase alfa (Brineura®) to slow the loss of ambulation in symptomatic pediatric individuals younger than 18 years of age with CLN2.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, cerliponase alfa (Brineura®) is covered under the medical benefits of the Company's Medical Advantage products when the medical necessity criteria and dosing and frequency requirements listed in this medical policy are met.

Description

Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) is one of a group of inherited, neurodegenerative, lysosomal storage disorders collectively referred to as Batten disease. It is a rare autosomal recessive disease caused by a deficiency of tripeptidyl peptidase 1 (TPP1) enzyme, due to a mutation in the TPP1 gene. It is

characterized by seizures, ataxia, language delays, blindness, and early death. Language delay and seizures are typically the initial symptoms and usually present between 2 and 4 years of age. Visual impairment may begin as early as 4 years, leading to blindness by age 7 to 10 years. Children generally succumb to the disease by the mid-teenage years.

The TPP1 gene provides instructions for making TPP1 enzyme, which is an inactive enzyme. This enzyme, found in the cells' lysosomes, breaks down peptides into amino acids. A deficiency of this enzyme decreases the breakdown of peptides and thereby causes peptide accumulation in the lysosomes. These accumulations cause cell damage and eventually cell death, particularly in the nerve cells. The progressive death of nerve cells in the brain leads to the signs and symptoms of CLN2 disease.

Cerliponase alfa (Brineura) was approved on April 27, 2017, to slow the loss of ambulation in symptomatic individuals 3 years of age and older with CLN2. On July 24, 2024, the FDA expanded cerliponase alfa (Brineura) to all pediatric individuals younger than 18 years of age with CLN2. It is a proenzyme, taken up by target cells in the central nervous system (CNS), and translocated to the lysosomes where it is activated. The activated form then cleaves the proteins, preventing the accumulation of lysosomal storage materials.

Cerliponase alfa (Brineura) is administered to the cerebrospinal fluid by intraventricular infusion at varying doses depending on age.

CLINICAL TRIALS

Schulz et al. (2018) conducted a nonrandomized, single-arm, dose-escalation study with extension consisting of 24 pediatric individuals with symptomatic CLN2, confirmed by TPP1 deficiency, treated with cerliponase alfa (Brineura) studied over 96 weeks. The efficacy population analysis consisted of 23 individuals with a mean age of 5 years at enrollment, excluding one individual who discontinued treatment due to an unwillingness to continue study visits, though will be included in the safety analysis. Results of the cerliponase alfa (Brineura)-treated group were compared to the scores of untreated individuals from an independent natural history cohort (n=42). The matched efficacy population consisted of 21 treated individuals matched to an untreated individual. A matched comparison was also conducted using natural historical controls (NHC), which resulted in 17 match pairs for analysis based on baseline age, genotype, and motor CLN2 score. Assessments for decline in the motor domain of the CLN2 Clinical Rating Scale were done at 48, 72, and 96 weeks. Primary outcome of interest was time until the first unreversed two-point decline measured using the combined CLN2 Clinic Rating Scale Motor-Language Domain. Each functional area is scored on a scale of 3 (normal function) to 0 (total loss of function), with the highest possible score being 6. The treatment group were significantly less likely than NHCs to have an unreversed two-point decline in the combined motor-language score (hazard ratio [HR] 0.08, 95% confidence interval [CI], 0.02–0.23; $P<0.001$), as well as in the motor score alone (HR, 0.04; 95% CI, 0.00–0.29; $P=0.002$) and the language score alone (HR, 0.15; 95% CI, 0.04–0.52; $P=0.003$). Nine percent of treated individuals had a decline of two points at 345 days (49.2 weeks). In the 17 matched pairs after 96 weeks, the mean decrease in motor-language score was 0.50±0.71 points among the treated cohort versus 2.80±1.10 points in the NHCs. The most common adverse events among the safety population were convulsions (96%), fever (71%), vomiting (63%), hypersensitivity reactions (63%), upper respiratory tract infection (54%), and common cold (42%). Fifty-five serious adverse events were reported in 20 individuals (83%) determined to be related to either the drug or intraventricular device. Despite high adverse events, the direct intraventricular delivery of cerliponase alfa appear to sustain worsening motor and language function in pediatric individuals with CLN2. Decline was defined as having an unreversed two-point decline or an unreversed score of 0 in the motor domain of the CLN2 Clinical Rating Scale. The results showed that when compared to the natural cohort group at 96 weeks, 21 of 21 (100%) of the matched cerliponase alfa (Brineura)-treated individuals had an absence of two-point decline in motor language (ML) score compared with nine of 21 (43%) of the untreated individuals. Also, the majority (95%) of the cerliponase alfa (Brineura)-treated individuals demonstrated sustained ambulation, as evidenced by less than a two-point decline in the CLN2 motor domain score.

Williams RE, Adams HR, Blohm M, al. cerliponase alfa (Brineura) was given to pediatric individuals between 1 and 6 years of age (n=14) with symptomatic and presymptomatic CLN2 primarily evaluating motor function over 169 weeks (3.25 years). This study was conducted to determine safety, efficacy, and dosing and frequency among those less than 3 years of age. Thirteen of the 14 treated were matched with up to three NHCs on the basis of age, CLN2 motor score, and genotype (i.e., 0, one, or two key mutations). By week 169, none of the individuals treated with cerliponase alfa (Brineura) had a two-point decline, or score of zero, on the CLN2 scale. Among the matched NHCs (n=31), 65% of individuals had unreversed two-point decline, or score of zero, by last assessment. The median time to decline for the matched NHCs was 133 weeks. Of the NHCs under 3 years of age (n=18), 61% had a two-point decline or score of zero in the CLN2 score by last visit. The phase II study appears to demonstrate some efficacy among all pediatric individuals in the treatment group compared to the matched pairs, including those under

age 3 years who were previously never evaluated prior to this clinical trial. The FDA label did not provide safety results specific to this study.

Several limitations exist among the evaluated studies. The phase II trial (NCT02678689) has not undergone the peer-review process, thereby omitting pertinent details regarding the eight individuals under 3 years of age such as participant characteristics, statistical analyses, and safety results. Further, due to the aggregation of motor and language scales, it is unclear which domain may have declined over another. Although the FDA indicates cerliponase alfa (Brineura) to slow the loss of ambulation alone, capturing language decline may be as essential as motor for a comprehensive understanding of disease progression when treated with cerliponase alfa (Brineura). Interestingly, a minimal clinically important difference on the CLN2 Clinical Rating Scale Motor-Language Domain (CLN2 scale) is typically defined as one point; however, the studies used a two-point decline to demarcate clinical importance, which may limit an understanding of the individual's true decline in motor-language function. Regardless, intraventricular administration of cerliponase alfa (Brineura) appears to demonstrate a slower or even halted rate of decline in motor and language function compared to that of historical controls in all pediatric ages. Further expansion on the current evidence will require awaiting the publication of peer-reviewed data from the phase II trial.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Brineura® (cerliponase alfa) drug label [FDA Web site]. 7/2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761052s014lbl.pdf. Accessed October 17, 2024.

Williams RE, Adams HR, Blohm M, et al. Management strategies for CLN2 disease. *Pediatr Neurol.* 2017;69:102-112.

Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E75.4 Neuronal ceroid lipofuscinosis

HCPCS Level II Code Number(s)
J0567 Injection, cerliponase alfa, 1 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.089d:

12/15/2025	This policy has been reissued in accordance with the Company's annual review process.
12/02/2024	This version of the policy will become effective 12/02/2024. The policy has been updated to communicate revised dosing and frequency requirements in for Cerliponase alfa (Brineura®) based on the current US Food and Drug Administration (FDA) label. Initial therapy and continuation therapy headers have been added for clarity. The following criterion has been **added** to this policy: • Under initial and continuation therapy: Score of at least 1 in the motor domain on the CLN2 Clinical Rating Scale The following policy criterion has been **revised**:

	FROM Individual is symptomatic (i.e., seizures, ataxia, language delay, vision loss) **TO** Individual is symptomatic (i.e., seizures, ataxia, language delay, vision loss, or symptoms characteristic of CLN2)

Revisions From MA08.089c:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
09/05/2023	This policy has been reissued in accordance with the Company's annual review process.
05/04/2022	This policy has been reissued in accordance with the Company's annual review process.
05/05/2021	This policy has been reissued in accordance with the Company's annual review process.
03/25/2020	This policy has been reissued in accordance with the Company's annual review process.
06/03/2019	This version of the policy will become effective 06/03/2019. This policy has been updated to communicate dosing and frequency requirements for Cerliponase alfa (Brineura®).).

Revisions From MA08.089b:

01/01/2019	This policy has been identified for the HCPCS code update, effective 01/01/2019. TThe following HCPCS code has been **added** to this policy: J0567 Injection, cerliponase alfa, 1 mg The following HCPCS codes have been **termed** from this policy: C9014 Injection, cerliponase alfa, 1 mg J3590 Unclassified biologics

Revisions From MA08.089a:

06/06/2018	This policy has been reissued in accordance with the Company's annual review process.
01/01/2018	This policy has been identified for the HCPCS code update, effective 01/01/2018. The following HCPCS code has been **added** to this policy: C9014 Injection, cerliponase alfa, 1 mg

Revisions From MA08.089:

09/08/2017	This version of the policy will become effective 09/08/2017. This new policy has been developed to communicate the Company’s coverage criteria for cerliponase alfa (Brineura®).

Version Effective Date:
12/16/2024
Version Issued Date:
12/16/2024
Version Reissued Date:
12/15/2025