Subject: Brineura (cerliponase alfa)	**Original Effective Date:** 08/15/2017
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members. Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Table of Contents

SUMMARY OF EVIDENCE/POSITION

This policy addresses **Brineura (cerliponase alfa)**, a recombinant human tripeptidyl peptidase 1 enzyme replacement therapy in the treatment of **late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)** when appropriate criteria are met. Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

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 disease: seizures, sleep-related problems, malnutrition, gastroesophageal reflux, pneumonia, hypersalivation, hyperactivity and behavior problems, psychosis, anxiety, spasticity, Parkinsonian 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.

<u>Cerliponase alfa (Brineura)</u>

- 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 8 years 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 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.
    - 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.*

FDA Indications

- **Late-infantile Neuronal Ceroid Lipofuscinosis, Type 2** Delay the loss of ambulation in symptomatic pediatric patients 3 years and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as TPP1-deficiency.

Available as: 150 mg/5 mL for intraventricular infusion (administration kit containing syringes, needles, an extension line, an infusion set with micron inline filter, and a port needle)

FDA Approved: April 27, 2017
Orphan Drug designation for cerliponase alfa for the treatment of CLN2 granted in 2013

Black Box Warnings/REMS: *None at the time of this writing*

**FDA-approved indication does not, in itself, dictate coverage. Molina coverage Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare. The covered FDA-approved indications are conditions that are considered medically necessary; however, it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria.*

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Brineura (cerliponase alfa) may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ 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). Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

  AND
- ❒ Requested drug will be administered in a healthcare facility by a board-certified physician who is knowledgeable in intraventricular administration

2. Diagnosis/Indication [ALL]

Documentation of ALL the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis

- ❒ Diagnosis of **late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)** [also known as tripeptidyl peptidase 1 (TPP1) deficiency]

  AND
- ❒ Diagnosis confirmed by based on TPP1 enzyme activity and CLN2 genotype analysis: [BOTH]

  - ❍ **Tripeptidyl peptidase 1 (TPPI) enzyme activity test indicates:** TPP1 deficiency in leukocytes *together with* normal activity of an appropriate control enzyme such as PPT1 and/or β-galactosidase
    - *Given the availability of reliable enzyme activity assays for both TPP1 and PPT1, together with the higher prevalence of the neuronal ceroid lipofuscinoses (NCLs) disorders for which TPP1 or PPT1 activity is lost (CLN2 disease and CLN1 disease, respectively), it is recommended that the activity of each enzyme be assayed early in any individual suspected of having an NCL disorder (Fietz M, et al. 2016). TTP1 levels can be measured in leukocytes, cultured fibroblasts, dried blood spots, and saliva. Fibroblast TTP1 activity is*

approximately 17,000 micromoles of amino acids produced per hour per mg of protein. The TTP1 activity in CLN2 NCL is less than 4% of normal.

AND

- ❍ **TPP1/CLN2 molecular test identifying:** TWO (2) pathogenic variants/mutations in *trans* in the TPP1/CLN2 gene (one pathogenic mutation on each parental allele of *TPP1*/*CLN2* gene)

MOLINA REVIEWER: 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 this 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 REVIEW REQUIRED]**

Informational Note: *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). However, when it is not feasible to perform both analyses, either deficient TPP1 enzyme activity in leukocytes or fibroblasts or the detection of two pathogenic mutations in trans alone can be diagnostic for CLN2 disease. (Fietz M, et al. 2016)*

AND

- ❒ Symptoms of late infantile CLN2 documented [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

- ❒ 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: [ALL]

  - ❍ Combined score of 3 to 6 in the motor and language domains

    **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*

  - ❍ Score of at least 1 in the motor domain

  - ❍ Score of at least 1 in the language domain

*****Refer to CLN2 Clinical Rating Scale in Appendix.

AND

- ❒ Baseline documentation of pre-treatment motor function/milestones, including but not limited to, the following validated scale: Motor and Language CLN2 score
  - *A Clinical Scoring System for Late Infantile Neuronal Ceroid Lipofuscinoses has been developed as a method for quantitative description of clinical courses over time (Steinfeld R, Heim P)*

3. Age/Gender/Restrictions [ALL]

- ❒ 3 years of age and younger than 18 years of age
  - *Brineura (cerliponase alfa) is not indicated for use in adults.*
  - *Safety and efficacy not established in patients younger than 3 years of age*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Member does **not** have (or have had), nor does **not** require, **ANY** of the following: [ANY]
  - ❍ Score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale
  - ❍ 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)
  - ❍ 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)
  - ❍ Stem cell, gene therapy, or enzyme replacement therapy in the past for CLN2
  - ❍ Ventilation support (except for noninvasive support at night)
  - ❍ Prone to complications from intraventricular drug administration, including individuals with hydrocephalus or ventricular shunts

5. Contraindications*/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Severe hypersensitivity to Brineura (cerliponase alfa) or any of its components
  - *Hypersensitivity reactions, including pyrexia, vomiting, pleocytosis and irritability, have been reported in patients, during and up to 24 hours after completion of cerliponase alfa infusion. Pre-treat with antihistamines with or without antipyretics or corticosteroids 30 to 60 minutes prior to start of infusion*
- ❒ Acute intraventricular access device complications (e.g., leakage, device failure, or device-related infection)
- ❒ Ventriculoperitoneal shunts

Exclusions [ANY]

- ❒ Younger than 3 years of age or older than 18 years of age
- ❒ Score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale
- ❒ 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)
- ❒ 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)
- ❒ Stem cell, gene therapy, or enzyme replacement therapy in the past for CLN2
- ❒ Ventilation support (except for noninvasive support at night)
- ❒ Prone to complications from intraventricular drug administration, including individuals with hydrocephalus or ventricular shunts

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Brineura (cerliponase alfa) may be authorized for continuation of therapy if meet **ALL** the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❒ Member continues to meet applicable initial coverage criteria
- ❒ An office visit and re-assessment **at least once annually** to determine if continuation of treatment is medically necessary. Chart notes or consultation notes (if applicable) must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Restrictions/Clinical Tolerance [ALL]

- ❒ Member does not have ventriculoperitoneal shunts
- ❒ Absence of unacceptable toxicity from Brineura (cerliponase alfa) or device-related complications, including: severe hypersensitivity reaction, severe cardiovascular reactions, severe hypotension; other intraventricular access device-related infections
- ❒ No sign or symptom of acute, unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or a suspected or confirmed CNS infection;

MOLINA MEDICAL/PHARMACY REVIEWER: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized.

3. Labs/Reports/Documentation required [ALL APPLICABLE]
Continuation of treatment may be authorized with evidence of disease stabilization or improvement: [ALL]

- ❒ **<u>After 12 months of Brineura (cerliponase alfa) therapy</u>**
  Response to therapy compared to pretreatment baseline with disease stability or lack of decline in motor function, including but not limited to, the following: [ALL APPLICABLE]
  - ❍ 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)][Labeling]
  - ❍ Loss of ambulation slowed
  - ❍ Visual acuity has stabilized

Informational Note

- *In the clinical study with extension, patients were assessed for decline in the motor domain of the CLN2 Clinical Rating Scale. The scale measures performance of mobility, with normal function being a score of 3 and no function being a score of 0. Decline was defined Evaluation was completed at 48, 72, and 96 weeks.*
- *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.]*

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications to therapy

  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Severe hypersensitivity to Brineura (cerliponase alfa) or any of its components

    Hypersensitivity reactions, including pyrexia, vomiting, pleocytosis and irritability, have been reported in patients, during and up to 24 hours after completion of cerliponase alfa infusion. Pretreat with antihistamines with or without antipyretics or corticosteroids 30 to 60 minutes prior to start of infusion
  - ❍ Acute intraventricular access device complications (e.g., leakage, device failure, or device-related infection)
  - ❍ Ventriculoperitoneal shunts
- ❒ Exclusions [ANY]
  - ❍ Younger than 3 years of age or older than 18 years of age
  - ❍ Score of 0 points on the combined motor and language components of the Hamburg CLN2 rating scale
  - ❍ 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)
  - ❍ 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)
  - ❍ Stem cell, gene therapy, or enzyme replacement therapy in the past for CLN2
  - ❍ Ventilation support (with the exception of noninvasive support at night)
  - ❍ Prone to complications from intraventricular drug administration, including individuals with hydrocephalus or ventricular shunts

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

- ❒ Pediatric 3 years and older: 300 mg (10 mL) intraventricularly once every other week; following cerliponase alfa infusion, administer 2 mL intraventricular electrolytes (included in administration kit)

- ❒ Younger than 3 years: Safety and efficacy have not been established.
  - *Brineura (cerliponase alfa) is not indicated for use in adults*

2. Authorization Limit [ALL]

- ❒ Quantity limit: [ALL]

  - ❍ 300 mg every 14 days; 600 mg every 28 days
    *Brineura 150 mg/5 mL single dose vial: 2 vials every 14 days

  - ❍ Up to 26 infusions per year

- ❒ Duration of initial authorization: **6 months**

- ❒ Continuation of treatment: The first continuation of treatment is limited to **6 months,** then re-authorization for continuation of treatment is required every **12 months** thereafter to determine continued need based on documented positive clinical response.

3. Route of Administration [ALL]

- ❒ Brineura (cerliponase alfa) is considered a **provider-administered** medication by, or under the direction of, a physician knowledgeable in **intraventricular administration** and aseptic technique must be strictly observed during preparation and administration.
  - *Cerliponase alfa is an infusion administered into the cerebrospinal fluid by way of a surgically implanted reservoir and catheter (an intraventricular access device).*
  - *The complete infusion, including the required infusion of intraventricular electrolytes, lasts approximately 4.5 hours. Pre-treatment of patients with antihistamines with or without antipyretics (drugs for prevention or treatment of fever) or corticosteroids is recommended 30 to 60 minutes prior to the start of the infusion*

- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

COVERAGE EXCLUSIONS

This policy only addresses the indication of **Neuronal Ceroid Lipofuscinosis Type 2** when appropriate criteria are met.

All other uses of Brineura (cerliponase alfa) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Cerliponase alfa (Brineura) has not been studied for any other indications, other than to slow the loss of ambulation in CLN2. Therefore, its use for any other condition is considered investigational.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

BACKGROUND/SUMMARY

Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)

- Rare, autosomal recessive, pediatric-onset, rapidly progressive neurodegenerative lysosomal storage disorder caused by tripeptidyl peptidase 1 (TPP1) enzyme deficiency (Williams R.E. et al 2017).
- CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), which may also be collectively referred to as Batten disease. CLN2 results from a functional reduction in an enzyme called tripeptidyl peptidase 1 which is an acid protease that degrades proteins. In the absence of tripeptidyl peptidase 1, the lysosomal storage materials that are normally metabolized by this enzyme accumulate in organs, particularly in the brain. The buildup of these storage materials in the brain can cause progressive neurodegeneration and loss of cognitive, motor and visual functions.
- The different NCLs are distinguished by their genetic cause. Each disease type is given the designation "CLN," meaning ceroid lipofuscinosis, neuronal, and then a number to indicate its subtype. Clinically, the diseases are subcategorized into infantile, late infantile, juvenile and adult forms based on their age of onset.

CLN2 Symptoms

- The first symptoms of CLN2 disease typically appear between age two and four years, usually starting with epilepsy. Early signs typically include loss of muscle coordination and drug-resistant seizures. This form progresses rapidly, and death usually occurs between 8 and 12 years of age. (National Institute of Neurological Disorders and Stroke, 2011).
- The most common initial symptoms are language delay and seizures, which typically begin to manifest between the ages of two to four years; often, language delay precedes the onset of seizures (Williams R.E. et al 2017).
- The classic late-infantile phenotype of CLN2 disease has a predictable clinical course marked by epilepsy and rapid psychomotor decline. Affected children most commonly present with an unprovoked seizure, although febrile seizures have also been reported. Generalized tonic-clonic seizures, absences, and partial-onset seizures may be observed. Myoclonus becomes prominent after the onset of seizures.

- Visual impairment may begin as early as age four years but is not usually apparent or troublesome until severe deterioration is evident, and children eventually become blind by age 7-10 years.
- Other initial symptoms include prominent truncal and peripheral ataxia, behavioral disturbances, and other developmental delays. Seizures may be polymorphic (e.g., generalized tonic-clonic, myoclonic, atonic) and often become drug resistant. Following the onset of seizures, a rapid deterioration in cognitive and motor functions ensues over two to three years, leading to loss of speech and loss of voluntary movement by age six years.
- Movement disorders, including myoclonus, dystonia, and spasticity, develop. Myoclonus (epileptic and non-epileptic) is a major feature that can be particularly difficult to treat and can disrupt rest and sleep.
- Children often have sleep disturbance and behavioral symptoms.
- Children lose the ability to swallow and become gastrostomy tube dependent. Hearing is typically spared. Death usually occurs by mid-adolescence. Atypical phenotypes associated with earlier or later symptom onset, varied symptoms, and/or slower disease progression have also been reported but still lead to neurodegeneration and premature death.

PIVOTAL TRIAL

Cerliponase alfa (Brineura) received FDA approval based on a non-randomized, single-arm dose escalation study over 96 weeks. Clinical evidence for the safety and efficacy of cerliponase alfa for the treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) was demonstrated in a **prospective Phase 1/2 Open-Label Dose-Escalation Study and Extension (NCT01907087).** The objective of the study was to evaluate the safety and tolerability of cerliponase alfa administered to patients with CLN2 disease by intraventricular administration.

A total of 24 participants, children age 3 to 8 years of age, all had a diagnosis of CLN2 of mild to moderate disease documented by a two-domain score of 3-6 on motor and language domains of the Hamburg Scale.

- 1 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. During the study with extension, the participants were assessed for decline in the Motor domain of the CLN2 Clinical Rating Scale at 48, 72, and 96 weeks.
- 2 participants with a combined Motor plus Language CLN2 score of 6 were excluded from the analyses while the participant who dropped out of the study early was analyzed as having a decline at the time of termination.
- At week 96, when compared to the natural cohort group, of the 22 participants treated with cerliponase alfa, 21 of the participants did not decline while 21 participants in the natural cohort group showed a sustained decline. The most common side effects during the trial were fever, electrocardiogram abnormalities, and decreased cerebrospinal fluid protein.
- 22 patients were evaluated at week 96, 21 (95%) did not have a decline in the motor domain of the CLN2 clinical rating scale. Only the patient who terminated early was deemed to have a decline in the motor domain of the CLN2 clinical rating scale.
- Patients were treated with intraventricular infusion of cerliponase alfa with doses ranging from 30 to 300 mg every 14 days in the dose escalation study and were maintained at 300 mg every 14 days in the extension study.
- Disease progression was measured by the Motor domain of a CLN2 Clinical Rating Scale in which scores ranged from 3 (grossly normal) to 0 (profoundly impaired). Decline was defined as an unreversed (sustained) 2-category decline or an unreversed score of 0.

Primary Endpoint

The primary endpoint was response rate, defined as the absence of an unreversed two-point decline or score of zero in the CLN2 score at 48 weeks. 24 patients were enrolled, with 23 patients completing the study. By

motor/language CLN2 scores measured from baseline, 87% (20/23) of treated patients responded to treatment, defined as an absence of an unreversed two-point decline or score of zero by Week 48, compared to an expected response rate of 50% (P-value=0.0002).

Results

- 65% of treated patients experienced no progression in their CLN2 score.
- Of all points lost, approximately 80% occurred within four months of treatment initiation. The proportion of patients with a response to treatment was 87% at Week 48 and 63% at Week 965.
- Results were compared with untreated patients from a natural history cohort.
    - 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). 24 patients, aged 3 to 8 years were enrolled in the Brineura single-arm clinical study. 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 for 48 weeks, and continued treatment during the extension period.
- Common adverse effects include fever, ECG abnormalities such as slow heart rate, hypersensitivity, decrease or increase in CSF protein, vomiting, seizures, hematoma, headache, irritability, increased CSF white blood cell count, device-related infection, feeling jittery, and low blood pressure.
- 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.
    - 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. During the study with extension, the participants were assessed for decline in the Motor domain of the CLN2 Clinical Rating Scale at 48, 72, and 96 weeks.
    - 2 participants with a combined Motor plus Language CLN2 score of 6 were excluded from the analyses while the participant who dropped out of the study early was analyzed as having a decline at the time of termination.
    - At week 96, when compared to the natural cohort group, of the 22 participants treated with cerliponase alfa, 21 of the participants did not decline while 21 participants in the natural cohort group showed a sustained decline. The most common side effects during the trial were fever, electrocardiogram abnormalities, and decreased cerebrospinal fluid protein.
    - 22 patients were evaluated at week 96, 21 (95%) did not have a decline in the motor domain of the CLN2 clinical rating scale. Only the patient who terminated early was deemed to have a decline in the motor domain of the CLN2 clinical rating scale.

HAYES

A Technology assessment addressing Brineura (Cerliponase Alfa) was updated in Jul 22, 2019.

The report concluded there is insufficient published evidence to draw firm conclusions regarding the safety and efficacy of Brineura for the treatment of CLN2 disease.

PRACTICE GUIDELINES/PROFESSIONAL SOCIETIES

There are no U.S. practice guidelines or management consensus that were identified addressing the use of Brineura for the treatment of CLN2 disease at the time of this review.

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 [Management Strategies for CLN2 Disease (Williams RE, 2016)].

DEFINITIONS

N/A

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 for CLN2 disease. N Engl J Med. 2018; 378(20):1898-1907.

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

HCPCS	Description
J0567	Injection, cerliponase alfa, 1 mg: 1 billable unit = 1 mg (effective 1/1/19)

ICD-10	Description
E75.4	Neuronal ceroid lipofuscinosis

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Clinical Trials, Definitions, Peer-Reviewed Publications

ClinicalTrials.gov. A Phase 1/2 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.

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Policy History	Approval
Policy Developed Peer Review: AMR Peer Review Network. Practicing Physician. Board certified in Neurology, Sleep Medicine. Date completed: 8/4/2017.	MCPC 08/15/2017
Revision* Peer Review. AMR Peer Review Network. Practicing Physician. Board certified in Neurology, Sleep Medicine. Date completed: 9/11/2019	P&T Q4 2019
Annual Review* No coverage criteria changes with this annual review.	P&T Q3 2020

*Policy Revisions and Annual Reviews: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.