CLINICAL MEDICATION POLICY	
Policy Name:	Brineura™ (cerliponase alfa)
Policy Number:	MP-064-MD-DE
Approved By:	Medical Management; Clinical Pharmacy
Provider Notice Date:	01/15/2018
Issue Date:	02/15/2018
Effective Date:	02/15/2018
Annual Approval Date:	12/15/2018
Revision Date:	N/A
Products:	Delaware Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 7

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options provides coverage under the medical-surgical benefits of the Company's Medicaid products for the medically necessary administration via intracerebroventricular infusion of Brineura (cerliponase alfa) in patients diagnosed with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2).

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 – Neuronal ceroid lipofuscinosis type 2 disease, also known as tripeptidyl peptidase (TPP1) deficiency.

Tripeptidyl (TPP1) - Tripeptidyl peptidase-1 (TPP1) is a CNS enzyme which catabolizes polypeptides in the CNS. CLN2 disease results from deficient activity of the TPP1 enzyme caused by mutations in the TPP1/CLN2 gene.

CLN2 - Neuronal ceroid lipofuscinosis type 2 disease, also known as tripeptidyl peptidase (TPP1) deficiency.

Brineura (Cerliponase alfa) - A recombinant human replacement (rhTPP1) enzyme for the treatment of CLN2. The proenzyme Cerliponase alfa, also known as rhTPP-1, is taken up in CNS cells and translocated to lysosomes where it is activated and can function to cleave proteins normally, preventing accumulation of lysosomal storage materials.

PROCEDURES

1. Brineura (cerliponase alfa) is considered medically necessary for the treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) when the member meets all of the following criteria:
    A. Must be prescribed by, or in consultation with, a neurologist or physician that specializes in the treatment of NCL diseases; **AND**
    B. The administration of Brineura is administered by, or under the direction of, a physician knowledgeable in intraventricular administration; **AND**
    C. The member is a symptomatic pediatric patient (at least 3 years of age or older) with a confirmed diagnosis of CLN2 disease by submission of laboratory testing demonstrating deficient TPP1 enzyme activity **AND** molecular analysis that has detected two pathogenic variants/mutations in the TPP1/CLN2 gene; **AND**
    D. There is documentation of a baseline evaluation, including an assessment of motor (ambulatory) function (see Appendix I for CLN2 Disease Clinical Rating Scale used in clinical trials); **AND**
    E. The prescribed dose and frequency of Brineura is consistent with FDA-approved labeling:
        1) The recommended dose of Brineura is 300 mg administered once every other week.
    F. The medical record must contain the following documentation for **reauthorization**:
        1) Documentation that the member is tolerating and receiving a clinical benefit from Brineura treatment based on the prescriber's clinical judgment (e.g., slowed loss of ambulation, motor skills maintained, etc.); **AND**
        2) Member is being monitored for infection and cardiovascular adverse reactions (e.g., vital signs [blood pressure, heart rate] prior to, during, and post-infusion; ECG monitoring)

Appendix I:
The CLN2 Clinical Rating Scale, adapted from the Hamburg Scale, was used to assess disease progression in two major functional areas (motor and language) in Brineura clinical trials. Each functional area is scored on a scale of 3 (grossly normal) to 0 (profoundly impaired). The highest possible score when assessing both motor and language function is 6.

Table 1*: The CLN2 Clinical Rating Scale

Domain	Rating criteria	Score
Motor function	**Normal**: grossly normal gait	3
	Clumsy, falls: abnormal gait; independent gait, as defined by ability to walk without support for 10 steps; may have obvious instability and intermittent falls	2
	No unaided walking: requires assistance to walk, or can crawl only	1
	Immobile: can no longer walk or crawl, mostly bedridden	0
Language function	**Normal**: apparently normal language; intelligible and grossly age appropriate	3
	Abnormal: language has become recognizably abnormal; some intelligible words; may form short sentences to convey concepts, requests, or needs	2
	Minimal: hardly understandable, few intelligible words	1
	Unintelligible: no intelligible words or vocalizations	0

* Table adopted from BioMarin Pharmaceutical Inc.

2. Contraindications
The administration of Brineura is contraindicated as follows:
    - Acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection);
    - In patients with ventriculoperitoneal shunts

3. When Brineura services are not covered
The administration of Brineura is not covered for conditions other than those listed above because the scientific evidence has not been established.

Coverage may be provided for any non-FDA labeled indication or a medically accepted indication that is supported by nationally recognized pharmacy compendia or peer-reviewed medical literature for treatment of the diagnosis (es) for which it is prescribed and will be reviewed on a case-by-case basis to determine medical necessity.

When non-formulary prior authorization criteria are not met, the request will be forwarded to a Medical Director for review. The physician reviewer must override criteria when, in their professional judgement, the requested medication is medically necessary.

4. Post-payment Audit Statement
The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

5. Place of Service
   The place of service for the administration of Brineura is outpatient.

GOVERNING BODIES APPROVAL

In 2013, the United States Food and Drug Administration (FDA) granted Orphan Drug designation for cerliponase alfa for the treatment of CLN2. On April 27, 2017, the FDA approved Brineura, an enzyme replacement therapy, indicated to slow the loss of ambulation symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase (TPPI) deficiency.

Brineura is administered into the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). Brineura is intended to be administered via the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman® Ventricular Catheter (Part Number: 82-1650). The intraventricular access device must be implanted prior to the first infusion. It is recommended that the first dose be administered at least 5 to 7 days after device implantation.

Brineura is intended to be administered with the B Braun Perfusor® Space Infusion Pump System.
The essential performance requirements for this syringe pump used to deliver Brineura are as follow:

- Delivery rate of 2.5 mL/hr with delivery accuracy of +/- 1 mL/hr
- Compatible with 20 mL syringes provided in the Administration Kit for use with Brineura
- Occlusion alarm setting to ≤ 281 mm Hg

Administer Brineura and the Intraventricular Electrolytes using the provided Administration Kit for use with Brineura components. Administer Brineura first followed by infusion of the Intraventricular Electrolytes each at an infusion rate of 2.5 mL/hr. The complete Brineura infusion time, including the required infusion of Intraventricular Electrolytes, is approximately 4.5 hours.

Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion.
The most common side effects include fever, electrocardiogram abnormalities, decrease or increase of cerebrospinal fluid protein, vomiting, seizures, hypersensitivity, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension.

CODING REQUIREMENTS

Procedure Codes

HCPCS Codes	Description
J3490	Unclassified drugs
J3590	Unclassified biologics

Covered Diagnosis Codes

ICD-10 Code	Description
E75.4	Neuronal ceroid lipofuscinosis

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), collectively referred to as Batten disease. CLN2 is a rare inherited disorder that primarily affects the nervous system. In the late infantile form of the disease, signs and symptoms typically begin between ages 2 and 4. The initial symptoms usually include language delay, recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects essential motor skills, such as sitting and walking. Individuals with this disease often require the use of a wheelchair by late childhood and typically do not survive past their teens. Batten disease is relatively rare, occurring in an estimated two to four of every 100,000 live births in the United States. Brineura is the first FDA-approved drug to treat CLN2. Continuing studies will test its use for children under two years of age and its long-term effects of over 10 years.

Brineura is a recombinant form of human tripeptidyl peptidase 1 (TPP1), the enzyme deficiency in patients with CLN2 disease. It is an enzyme replacement therapy designed to restore TPP1 enzyme activity and break down the storage materials that cause CLN2 disease. In order to reach the cells of the brain and central nervous system, the treatment is delivered directly into the cerebrospinal fluid using BioMarin's patented technology.

An open-label, dose-escalation study for Brineura, 24 patients with CLN2 disease between 3 and 8 years of age, was completed. 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 clinical study has shown that at 48 weeks, 87 percent of the children (20 of the 23) who completed the trial did not decline in motor and language score. In the study, the mean rate of decline in patients treated with Brineura at 300 mg. every other week was 0.40 points per 48 weeks. When compared to the expected rate of decline based on the natural history, the study results are statistically significant ($p < 0.0001$).

The observed treatment effect was considered clinically meaningful in light of the natural history of untreated CLN2 disease. In the ongoing study as of June 3, 2016, the rate of decline in patients treated with Brineura compared to the natural history control group (N=42 patients) continues to show durability of the treatment effect.

In the clinical study, intraventricular access device-related infections were observed in two patients. In each case, antibiotics were administered, the intraventricular access device was replaced, and the patient continued on Brineura treatment.

POLICY SOURCE(S)

Brineura [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; April 2017.

Brineura [AMCP Dossier]. Novato, CA: BioMarin Pharmaceutical Inc.; May 2017.

Brineura. In: Micromedex 2.0 online. Ann Arbor, MI. Truven Health Analytics, LLC. Accessed June 2017.
BioMarin Pharmaceutical. A multicenter, multinational, extension study to evaluate the long-term efficacy and safety of BMN 190 in patients with CLN2 disease. NLM Identifier: NCT02485899. Last updated on October 28, 2016. Accessed on June 22, 2017 and available at: https://clinicaltrials.gov/ct2/show/NCT02485899?term=cerliponase+alfa&rank=2.

BioMarin Pharmaceutical. 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. NLM Identifier: NCT01907087. Last updated on April 25, 2016. Accessed on June 22, 2017 and available at: https://clinicaltrials.gov/ct2/show/NCT01907087?term=cerliponase+alfa&rank=1.

Brineura™ [Product Information], San Rafael, CA. BioMarin, April 2017. Accessed on June 22, 2017 and available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761052lbl.pdf.

Cerliponase alfa. In: DrugPoints System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated April 27, 2017. Accessed on June 22, 2017 and available at: http://www.micromedexsolutions.com.

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. Accessed June 2017.

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 Gen Met*. 2016; 119:160-167. https://www.ncbi.nlm.nih.gov/pubmed/?term=Fietz+M+et+al.+Diagnosis+of+neuronal+ceroid+lipofucscinosis+Type+2+(CLN2+disease)%3A+Expert++recommendations+....+Molecular+Genetics+and+Metabolism+2016

National Institute of Neurological Disorders and Stroke. Batten disease fact sheet. 2011. Accessed on June 22, 2017 and available at: http://www.ninds.nih.gov/disorders/batten/detail_batten.htm.

Natural History. CLN2 Connection. BioMarin International. Updated December 2016. Accessed June 2017. Available at: http://www.cln2connection.com/overview/natural-history/.

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

Policy History:

Date	Activity
06/22/2017	Initial policy developed
12/12/2017	QI/UM Committee
02/15/2018	Provider effective date