STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Orphan Drugs (Rare Diseases)
PAM-034

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	07/16/2021
Revision Number:	4	**Last Rev Date:**	01/19/2024
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	01/17/2025
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	07/16/2021

Overview

The purpose of this policy is to support medically appropriate use of select orphan drugs based on FDA-approved labeling. Medications included in this policy are listed here in alphabetical order (drug-specific information is located in Appendix A).

Brand Name	HCPCS	Code Description	Indication	Effective Date
Brineura®	J0567	Injection, cerliponase alfa, 1 mg	**CLN2:** late infantile neuronal ceroid lipofuscinosis type 2	01/21/2022
Cablivi®	C9047	Injection, caplacizumab-yhdp, 1 mg	**aTTP:** acquired thrombotic thrombocytopenic purpura	07/01/2021
Givlaari®	J0223	Injection, givosiran, 0.5 mg	**AHP:** acute hepatic porphyria	07/01/2021

Descriptive Narrative

The 1983 Orphan Drug Act amended the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions. The Orphan Drug Designation Program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders that affect fewer than 200,000 people in the United States, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.[1]

An orphan designation may be assigned by the FDA if criteria are met, as outlined in 21 CFR 316.20 and 316.21.[2] The granting of an orphan drug designation does not alter the standard regulatory requirements and process for obtaining market approval. Safety and effectiveness of a drug must be established through adequate and well-controlled studies.

Criteria

Prior authorization is required. Criteria are specific to the individual medication.

Brineura® (cerliponase alfa)

Brineura® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), as documented by **AT LEAST ONE** of the following:
    a. Demonstration of deficient tripeptidyl peptidase-1 (TPP1) enzyme activity (in leukocytes, fibroblasts, or dried blood spots); **AND/OR**
    b. Molecular analysis that detects one pathogenic variant on each parent allele of the TPP1/CLN2 gene; **AND**
2. Member is 3 years of age or older; **AND**
3. Treatment is being given to slow the loss of ambulation; **AND**
4. Member meets **BOTH** of the following criteria on the CLN2 Clinical Rating Scale *(see Appendix A)*:
    a. A combined score of 3 to 6 on the motor and language domains; **AND**
    b. A score of at least 1 in each of these two domains; **AND**
5. Prescribed by, or in consultation with, a neurologist; **AND**
6. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 300 mg every 2 weeks; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Brineura® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. Member demonstrates a positive response to therapy as evidenced by a score of 1 or higher in the motor domain of the CLN2 Clinical Rating Scale *(see Appendix A)*; **AND**
3. Treatment is being given to slow the loss of ambulation; **AND**
4. Prescribed by, or in consultation with, a neurologist; **AND**
5. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 300 mg every 2 weeks; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Note: To confirm a clinical suspicion of CLN2 disease, the gold standard for laboratory diagnosis is the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) and the identification of pathogenic variants in both alleles of the TPP1/CLN2 gene. When it is not possible to perform both analyses, either demonstration of deficient TPP1 enzyme activity in leukocytes or fibroblasts, or detection of two pathogenic variants *in trans* is diagnostic for CLN2 disease.

Cablivi® (caplacizumab-yhdp)

Cablivi® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of acquired thrombotic thrombocytopenic purpura (aTTP); **AND**
2. Member is 18 years of age or older; **AND**
3. Member meets **ONE** of the following:
    a. Cablivi® will be used in combination with plasma exchange (PEX) and immuno-suppressant therapy (e.g., corticosteroids, rituximab) for the duration of the daily PEX; **OR**
    b. Member is using for 30 days after completion of daily PEX and has not had more than two recurrences of aTTP while on Cablivi® therapy; **AND**
4. Prescribed by, or in consultation with, a hematologist; **AND**
5. The regimen prescribed is within the FDA-approved labeling. If dose or schedule exceeds the FDA-approved regimen, regimen (including dosage) must be supported by clinical practice guidelines (supporting clinical documentation must be provided with any request for which the regimen or dosage prescribed does not align with FDA-approved labeling).

Cablivi® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. Member has completed the initial treatment course with Cablivi for treatment of acquired thrombotic thrombocytopenic purpura (aTTP) [daily treatment during plasma exchange (PEX)/immunosuppressive therapy, followed by 30 days of daily treatment after the last day of PEX with no more than two recurrences/exacerbations of aTTP while on therapy with Cablivi®; **AND**
3. Member displays positive response to therapy but has confirmed signs of persistent underlying disease; **AND**
4. Member has not received more than 58 days of Cablivi® therapy after the last dose of daily PEX; **AND**
5. Prescribed by, or in consultation with, a hematologist; **AND**
6. The regimen prescribed is within the FDA-approved labeling. If dose or schedule exceeds the FDA-approved regimen, regimen (including dosage) must be supported by clinical practice guidelines (supporting clinical documentation must be provided with any request for which the regimen or dosage prescribed does not align with FDA-approved labeling).

Givlaari® (givosiran)

Givlaari® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of an acute hepatic porphyria (AHP) (e.g., acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, or ALA dehydratase-deficient porphyria); **AND**
2. Member is 18 years of age or older; **AND**
3. Documentation that member meets **AT LEAST ONE** of the following:
    a. Has experienced a minimum of two porphyria attacks within the past 6 months which required hospitalization, an urgent healthcare visit, or IV hemin administration at home; **AND/OR**
    b. Is currently on prophylactic hemin treatment due to history of severe or frequent porphyria attacks; **AND**
4. Member will not receive concomitant *prophylactic* hemin treatment while on Givlaari® (note: use of hemin for treatment of *acute* porphyria attacks is appropriate); **AND**
5. Prescribed by, or in consultation with, a gastroenterologist, hematologist, hepatologist, or neurologist; **AND**
6. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 2.5 mg/kg once monthly, based on actual body weight; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Givlaari® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. Evidence of positive clinical response to therapy, as documented by:
    a. A reduction in the rate and/or number of porphyria attacks; **AND**
    b. Improvement of signs/symptoms of acute hepatic porphyrias (AHPs); **AND**
    c. Reduction in hemin administration requirements (treatment doses), if applicable; **AND**
3. Prescribed by, or in consultation with, a gastroenterologist, hematologist, hepatologist, or neurologist; **AND**
4. Member has not had a liver transplant or liver transplant is not anticipated; **AND**
5. Member will not receive concomitant *prophylactic* hemin treatment while on Givlaari® (note: use of hemin for treatment of *acute* porphyria attacks is appropriate); **AND**
6. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 2.5 mg/kg once monthly, based on actual body weight; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Approval Duration and Quantity Limits

Brand Name	Quantity Limits	Approval Duration
Brineura®	300 mg every 2 weeks	Initial request and continuation: up to 12 months per request
Cablivi®	Daily limit: 22 mg on day 1, then 11 mg/day on subsequent days. Limited to no more than 58 days after last daily plasma exchange (PEX).	Initial request: may approve for one course of treatment (beginning at onset of PEX therapy and continuing for 30 days after last daily PEX). Continuation: up to 28 additional days (only approved if Member is responding to therapy but has confirmed signs of persistent underlying disease).
Givlaari®	Limited to 2.5 mg/kg once monthly, based on actual body weight.	Initial request: up to 6 months Continuation: up to 12 months per request.

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

Brand Name	HCPCS	Description
n/a	85397	Coagulation and fibrinolysis, functional activity, not otherwise specified (e.g., ADAMTS-13), each analyte
Brineura®	J0567	Injection, cerliponase alfa, 1 mg
Cablivi®	C9047	Injection, caplacizumab-yhdp, 1 mg
Givlaari®	J0223	Injection, givosiran, 0.5 mg

Brand Name	ICD-10	Description
Brineura®	E75.4	Neuronal ceroid lipofuscinosis
Cablivi®	M31.1	Thrombotic microangiopathy (there is no specific code for aTTP)
Givlaari®	E80.20	Unspecified porphyria
	E80.21	Acute intermittent (hepatic) porphyria
	E80.29	Other porphyria

Brand Name	NDC	Labeler	Dosage	Pkg Size	Pkg Qty	Units/ Pkg
Brineura®	68135-0811-02	BioMarin Pharmaceutical (68135)	1 mg	1	EA	300
Cablivi®	58468-0225-01	Genzyme Corporation (58468)	1 mg	1	EA	11
Givlaari®	71336-1001-01	Alnylam Pharmaceuticals (71336)	0.5 mg	1	EA	378

Appendix A: Product-specific indications, dosing, categories, and packaging

Brineura® (cerliponase alfa)[3]	
Pharmacologic Category:	Hydrolytic lysosomal n-terminal tripeptidyl peptidase
FDA-Approved Indication(s):	Indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.
How Supplied:	Supplied as a part of a kit containing 2 vials of Brineura® injection (150 mg/5 mL each) and 1 vial (5 mL) of an intraventricular electrolytes injection.
Dosage and Administration:	• 300 mg every other week administered via intraventricular infusion. • Administered into the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). • Brineura® is administered first, followed by infusion of the intraventricular electrolytes. • Intended to be administered with the B Braun Perfusor® Space Infusion Pump System (prescribing information contains requirements if an alternate system is used).
Benefit Category:	Medical

Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) is also known as tripeptidyl peptidase 1 (TPP1) deficiency. CLN2 is a rare, rapidly progressing, irreversible neurodegenerative disease that is characterized by the deficiency of TPP1 resulted from mutations in the TPP1/CLN2 gene. Deficiency in TPP1 activity in the central nervous system (CNS) results in the accumulation of lysosomal storage materials normally metabolized by this enzyme in the CNS, resulting in neurodegeneration, loss of neurological function and ultimately death.[4]

Brineura® is taken up by target cells in the CNS and is translocated to the lysosomes through the Cation Independent Mannose-6-Phosphate Receptor (CI-MPR, also known as M6P/IGF2 receptor). Cerliponase alfa is activated in the lysosome and the activated proteolytic form of rhTPP1 cleaves tripeptides from the N-terminus of proteins.

CLN2 Clinical Rating Scale[5]

This scale was adapted from the common subscales of the Hamburg and Weill Cornell CLN2 clinical rating scales to be used as an assessment tool for multicenter efficacy studies supporting the development of cerliponase alfa. Motor and language functions are fundamental disease domains, decline rapidly and predictably as a function of age, and are relatively insensitive to standard of care.

The rating scale consists of a Motor Domain and a Language Domain. The rating is structured so that a score of 3 indicates a normal condition, 2 is a slight or just noticeable abnormality, 1 is a severe abnormality, and 0 denotes a complete loss of functioning.

Scale Domain		Description
Motor	3	Grossly normal gait. No prominent ataxia, no pathologic falls.
	2	Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability and may have intermittent falls.
	1	Requires external assistance to walk or can crawl only.
	0	Can no longer walk or crawl.
Language	3	Apparently normal language. Intelligible and grossly age appropriate. No decline noted yet.
	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 by the child).
	1	Hardly understandable. Few intelligible words.
	0	No intelligible words or vocalizations.

Cablivi® (caplacizumab-yhdp)[6]	
Pharmacologic Category:	von Willebrand factor (vWF)-directed antibody fragment
FDA-Approved Indication(s):	Treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange (PEX) and immunosuppressive therapy
How Supplied:	• Lyophilized powder in a single-dose vial (11 mg per vial) • Packaging includes a 1 mL sterile water for injection diluent
Dosage and Administration:	• Day 1: 11 mg IV bolus at least 15 minutes prior to plasma exchange (PEX) and 11 mg SC injection after completion of PEX • Subsequent (during daily PEX): 11 mg SC injection once daily following PEX • Treatment after PEX period: 11 mg SC injection once daily continuing for 30 days following the last daily PEX. If after initial treatment course, signs of persistent underlying disease remain present, treatment may be extended for a maximum of 28 days.
Benefit Category:	Medical

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially fatal blood disorder. TTP may be caused by inherited severe deficiency of plasma ADAMTS13 activity resulting from mutations in *ADAMTS13*, referred to as hereditary or congenital TTP (or cTTP); more commonly, TTP is acquired and due to autoantibodies that inhibit plasma ADAMTS13 activity, referred to as immune-mediated or acquired TTP (aTTP or iTTP). More than 95 percent of all TTP cases are iTTP, whereas cTTP accounts for less than 5 percent of cases.[7]

Cablivi® is a von Willebrand Factor (vWF)-directed antibody fragment. It targets the A1-domain of vWF and inhibits the interaction between vWF and platelets, thereby reducing both vWF-mediated platelet adhesion and platelet consumption.

Givlaari® (givosiran)[8]	
Pharmacologic Category:	Aminolevulinate synthase 1-directed small interfering ribonucleic acid (siRNA)
FDA-Approved Indication(s):	Treatment of adults with acute hepatic porphyria (AHP)
How Supplied:	1 mL single-dose vial, containing 189 mg/mL of givosiran
Dosage and Administration:	2.5 mg/kg SC injection once monthly (administration by a healthcare professional only, with medical support to appropriately manage anaphylactic reactions)
Benefit Category:	Medical

Acute hepatic porphyrias (AHPs) are a family of rare inherited disorders characterized by enzyme dysfunctions in the hepatic pathway of heme biosynthesis. In AHPs, accumulation of the neurotoxic porphyrin precursors delta-aminolevulinic acid and porphobilinogen, caused by enhanced activity of hepatic aminolevulinate synthase 1 (ALAS1), is associated with acute, potentially life-threatening neurovisceral attacks.[9] The four types of AHPs are 5-aminolevulinic acid (ALA) dehydratase deficiency porphyria, acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. Their diagnoses are often missed or delayed because the clinical symptoms mimic other more common disorders.[10]

Givlaari® is a small interfering RNA (siRNA) therapeutic that reduces hepatic activity of ALAS1 and decreases accumulation of neurotoxic porphyrin precursors in patients with AHPs, ultimately reducing the number of acute attacks and improving symptoms and quality of life between attacks.

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

[1] Office of Orphan Products Development. Food and Drug Administration. Available online at: www.fda.gov/about-fda/office-clinical-policy-and-programs/office-orphan-products-development. Updated November 18, 2019. Accessed June 2, 2021.

[2] Orphan Drugs, 21 C.F.R. §316.

[3] Brineura prescribing information (03/2020). BioMarin Pharmaceutical Inc.: Novato, CA. Available online at www.brineura.com/hcp. Accessed December 17, 2023.

[4] Fietz M, AlSayed M, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab. 2016 Sep;119(1-2):160-7. Epub 2016 Jul 25. PMID: 27553878.

[5] Wyrwich KW, Schulz A, Nickel M, et al. An Adapted Clinical Measurement Tool for the Key Symptoms of CLN2 Disease. *Journal of Inborn Errors of Metabolism and Screening*. January 2018.

[6] Cablivi prescribing information (04/2023). Genzyme Corporation: Cambridge, MA. Available online at www.cablivi.com/hcp. Accessed December 17, 2023.

[7] Zheng XL, Vesely SK, et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10). Epub 2020 Sep 11. Erratum in: J Thromb Haemost. 2021 May;19(5): 1381. PMID: 32914582.

[8] Givlaari prescribing information (02/2023). Alnylam Pharmaceuticals, Inc.: Cambridge, MA. Available online at www.givlaarihcp.com. Accessed December 17, 2023.

[9] Ricci A, Ventura P. Givosiran for the treatment of acute hepatic porphyria. Expert Rev Clin Pharmacol. 2022 Apr;15(4):383-393. Epub 2022 May 11. PMID: 35531651.

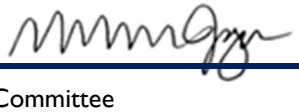
[10] Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatol Commun. 2018 Dec 20;3(2):193-206. PMID: 30766957.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
01/19/2024	CAC	Annual review. Added dosing information into criteria for Brineura and Givlaari.	4
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
01/20/2023	CAC	• Brineura: Diagnosis criteria 1, changed to "AND/OR" to allow either a or b, instead of requiring both. • Cablivi: added CPT 85397 to Coding and Product Information. • Givlaari: added gastroenterologist, hepatologist, or neurologist to specialty types (in addition to existing specialist: hematologist).	3
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
01/21/2022	CAC	Brineura added to policy.	2
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
07/16/2021	CAC	Criteria implementation with Cablivi and Givlaari.	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee