

Orphan Drug Policy: Prior Authorization Update

Purpose of the Update:

This update identifies 3 candidates for addition to the orphan drug policy due to lack of utilization in FFS since FDA approval (**Table 1**). See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Table 1. Candidates for Addition to the Orphan Drug Policy

Generic Name (Brand)	Diagnosis	Year of Approval	FFS Utilization Since Approval	Relevant ICD-10 codes	FFS patients with claims for relevant ICD-10 codes*
Burosumab-twza (Crysvita®)	X-linked hypophosphatemia (XLH) in children and adults	2018	0	E83.31 Familial hypophosphatemia	5
Cerliponase alfa (Brineura®)	To slow the loss of ambulation in symptomatic pediatric and adolescent patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (also known as tripeptidyl peptidase 1 deficiency or Batten Disease).	2017	0	E75.4 Neuronal ceroid lipofuscinosis	0
Luspatercept (Reblozyl®)	<ul style="list-style-type: none"> Anemia in adults with beta thalassemia who require regular red blood cell transfusion Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis 	2019	0	D56.1 Beta thalassemia D56.5 Hemoglobin E-beta thalassemia D46.1 Refractory anemia with ring sideroblasts	D56.1: 18 D56.5: 3 D46.1: 5

* Estimated based on number of patients with FFS medical claims with the indicated diagnosis over a 1 year period (7/01/2018 to 6/30/2019). Diagnoses are based on ICD-10 codes associated with medical claims data, may not exactly match the FDA-approved indication, and may not reflect members *currently* enrolled in FFS.

Recommendation:

- Implement PA to support medically appropriate use of burosumab-twza, cerliponase alfa, luspatercept based on FDA labeling.

Appendix 1. Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CRYSVITA safely and effectively. See full prescribing information for CRYSVITA.

CRYSVITA® (burosumab-twza) injection, for subcutaneous use
Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1)	9/2019
Dosage and Administration, 25-Hydroxy Vitamin D Supplementation (2.5)	9/2019

INDICATIONS AND USAGE

CRYSVITA is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older. (1)

DOSAGE AND ADMINISTRATION

For subcutaneous use only (2)

- **Pediatric XLH (6 months and older):**
 - For patients who weigh less than 10 kg, starting dose regimen is 1 mg/kg of body weight rounded to the nearest 1 mg, administered every two weeks (2.2)
 - For patients who weigh more than 10 kg, starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. (2.2)Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus. (2.2)
- **Adult XLH:** Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every four weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL in a single-dose vial (3)

CONTRAINDICATIONS

- With oral phosphate and/or active vitamin D analogs. (4)

- When serum phosphorus is within or above the normal range for age. (4)
- In patients with severe renal impairment or end stage renal disease. (4)

WARNINGS AND PRECAUTIONS

- **Hypersensitivity:** Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment. (5.1)
- **Hyperphosphatemia and Risk of Nephrocalcinosis:** For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels. (5.2, 6.1)
- **Injection Site Reactions:** Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment. (5.3, 6.1)

ADVERSE REACTIONS

Most common adverse reactions (≥25% in the CRYSVITA group and > Active Control) in pediatric XLH patients are: pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, dental caries. (6.1)

Most common adverse reactions (>5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, blood phosphorus increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin, Inc. at 1-888-756-8657 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRINEURA safely and effectively. See full prescribing information for BRINEURA.

BRINEURA (cerliponase alfa) injection, for intraventricular use
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	12/2018, 12/2019
Contraindications (4)	12/2018
Warnings and Precautions (5.1, 5.2)	12/2018

INDICATIONS AND USAGE

Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase 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. (1)

DOSAGE AND ADMINISTRATION

- Aseptic technique must be strictly observed during preparation and administration. (2.1)
- Brineura should be administered by, or under the direction of, a physician experienced in intraventricular administration. (2.1)
- Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage, failure or potential infection.
- Obtain a sample of CSF for cell count and culture prior to each infusion and if clinically indicated. (2.1)
- Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter. (2.1)
- Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion. (2.2)
- The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of Intraventricular Electrolytes over approximately 4.5 hours. (2.2)
- For complete information on preparation, specific intraventricular access device for use, and administration, see the full prescribing information. (2.1, 2.3, 2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Injection: Brineura 150 mg/5 mL (30 mg/mL) solution, two single-dose vials per carton co-packaged with Intraventricular Electrolytes Injection 5 mL in a single-dose vial. (3)

CONTRAINDICATIONS

- Any sign or symptom of acute or unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or suspected or confirmed CNS infection (e.g., cloudy CSF or positive CSF gram stain, or meningitis). (4)
- Any acute intraventricular access device-related complication (e.g., leakage, extravasation of fluid, or device failure). (4)
- Patients with ventriculoperitoneal shunts. (4)

WARNINGS AND PRECAUTIONS

- **Meningitis and Other Intraventricular Access Device-Related Infections:** Monitor the device insertion site for signs of infection. (4, 5.1)
- **Intraventricular Access Device-Related Complications:** Consult a neurosurgeon for any complications with the implanted device. In case of device-related complication, discontinue the infusion and refer to the device labeling for further instructions. (4, 5.2)
- **Cardiovascular Adverse Reactions:** Monitor vital signs before, during, and post-infusion. Monitor Electrocardiogram (ECG) in patients with a history of bradycardia, conduction disorder, or with structural heart disease, during the infusion. In patients without cardiac abnormalities, perform regular 12-lead ECG evaluations every 6 months. (2.5, 5.3)
- **Hypersensitivity Reactions:** Observe patients during and after the infusion. If a severe hypersensitivity reaction occurs, immediately stop the infusion and initiate appropriate treatment. (5.4)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 8\%$) are: pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin at 1-866-906-6100 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REBLOZYL safely and effectively. See full prescribing information for REBLOZYL.

REBLOZYL® (luspaterecept-aamt) for injection, for subcutaneous use
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Indications and Usage, Myelodysplastic Syndromes (1.2)	04/2020
Dosage and Administration, Beta Thalassemia (2.1)	04/2020
Dosage and Administration, Myelodysplastic Syndromes (2.2)	04/2020
Warnings and Precautions, Hypertension (5.2)	04/2020

INDICATIONS AND USAGE

REBLOZYL is an erythroid maturation agent indicated for the treatment of:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions (1.1).
- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (1.2).
- Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia (1.3).

DOSAGE AND ADMINISTRATION

- The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection (2.1, 2.2).
- Review hemoglobin (Hgb) results prior to each administration (2.1, 2.2).
- See full prescribing information for preparation and administration instructions (2.3).

DOSAGE FORMS AND STRENGTHS

- For injection: 25 mg lyophilized powder in a single-dose vial for reconstitution (3)
- For injection: 75 mg lyophilized powder in a single-dose vial for reconstitution (3)

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Thrombosis/Thromboembolism: Increased risk in patients with beta thalassemia. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly (5.1).
- Hypertension: Monitor blood pressure (BP) during treatment. Initiate anti-hypertensive treatment if necessary (5.2).
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.3, 8.1, 8.3).

ADVERSE REACTIONS

The most common (>10%) adverse reactions were fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, and hypersensitivity (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revised: 04/2020

Appendix 2. Proposed Prior Authorization Criteria

Orphan Drugs

Goal(s):

To support medically appropriate use of orphan drugs (as designated by the FDA) which are indicated for rare conditions
 To limit off-label use of orphan drugs

Length of Authorization:

Up to 6 months

Requires PA:

See Table 1 (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH)	≥ 6 months	<p><u>Pediatric <18 years:</u> Initial (administered subcutaneously every 2 weeks):</p> <ul style="list-style-type: none"> • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg <p>Max dose of 2 mg/kg (not to exceed 90 mg)</p> <p><u>Adult:</u> 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg)</p>	<p><u>Baseline and Ongoing Monitoring</u></p> <ul style="list-style-type: none"> • Use of active vitamin D analogues or oral phosphate within prior week; concurrent use is contraindicated • Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m² for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed.
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic	3-17 years	300 mg every other week via intraventricular route	<p><u>Baseline Monitoring</u></p> <ul style="list-style-type: none"> • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation

	Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)			<ul style="list-style-type: none"> Baseline motor symptoms (e.g., ataxia, motor function, etc) ECG in patients with a history of bradycardia, conduction disorders or structural heart disease <u>Ongoing Monitoring</u> <ul style="list-style-type: none"> Disease stabilization or lack of decline in motor symptoms compared to natural history
Luspatercept (REBLOZYL)	<p>Anemia (Hg <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions</p> <p>Anemia (Hg <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis</p>	≥ 18 years	<p>Initial: 1 mg/kg subcutaneously</p> <p>Max dose of 1.25 mg/kg every 3 weeks for beta thalassemia</p> <p>Max dose of 1.75 mg/kg every 3 weeks for myelodysplastic syndromes</p>	<u>Baseline Monitoring/Documentation</u> <ul style="list-style-type: none"> Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 weeks in patients with myelodysplastic syndromes Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes Hemoglobin level Blood pressure <u>Ongoing Monitoring</u> <ul style="list-style-type: none"> Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 weeks) Hemoglobin level Blood pressure

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in Table 1 ?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
4. Is the request for continuation of therapy in a patient previously approved by FFS?	Yes: Go to Renewal Criteria	No: Go to #5
5. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness.
7. Have other therapies been tried and failed?	Yes: Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	No: Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	Yes: Go to #2	No: Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	Yes: Go to #3 Document provider attestation	No: Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	Yes: Go to #4	No: Go to #5

Renewal Criteria

4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	Yes: Approve for up to 6 months Document benefit	No: Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	Yes: Approve for up to 6 months Document benefit and provider attestation	No: Pass to RPh. Deny; medical appropriateness

*P&T/DUR Review: 6/2020 (SS); 2/2020
Implementation: 7/1/20*