BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Burosumab-twza (Crysvita®)

File Name:	burosumab_crysvita
Origination:	8/2018
Last CAP Review:	6/2020
Next CAP Review:	6/2021
Last Review:	6/2020

Description of Procedure or Service

Crysvita® (burosumab-twza) is a human monoclonal antibody indicated for the treatment of adult and pediatric patients 6 months of age and older with X-linked hypophosphatemia (XLH).

X-linked hypophosphatemia is a rare, inherited form of rickets that bears resemblance to vitamin D deficiency; however, treatment with vitamin D supplementation is ineffective, as it is a disorder of renal phosphate wasting. XLH is associated with genetic abnormality on the PHEX (Phosphate-regulating Endopeptidase on the X chromosome) gene, in which pathogenic variants lead to elevated serum fibroblast growth factor 23 (FGF23) levels in turn causing suppression of renal tubular phosphate reabsorption and renal production of 1,25 dihydroxy vitamin D. Poor bone mineralization and fractures are ultimately the result of this process.

Clinical presentation of XLH is most commonly seen in early childhood with bowing deformities of the legs, short stature, and bone and dental pain. In contrast, signs and symptoms of XLH are not identified in some patients until adulthood, and may instead present initially as joint pain and impaired mobility. Spontaneous dental abscesses and hearing loss are also sometimes present in patients with this disease. Characteristic laboratory abnormalities include a low serum phosphorus level and decreased renal tubular resorption of phosphate corrected for glomerular filtration rate. Standard treatment has historically involved various dosing regimens using oral phosphate and calcitriol with therapy usually initiated at diagnosis in pediatric patients and continued until completion of long bone growth. While treatment goals in pediatric patients are improved growth function, reduced severity of bone abnormalities, and decreased bone and joint pain, treatment benefit in adult patients is more difficult to assess given absence of active rickets and established height. However, as hypophosphatemia may also contribute to symptoms of bone and joint pain, fractures, and other weakness, treatment benefit may be seen in such adult patient population.

Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, was approved by the U.S. Food and Drug Administration (FDA) in April 2018 for the treatment of XLH. It works by binding to and inhibiting the activity of FGF23, which results in restoration of renal phosphate reabsorption and increased serum concentration of 1,25 dihydroxy vitamin D.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Crysvita (burosumab-twza) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When it is covered

Initial Therapy

Crysvita is considered medically necessary in pediatric patients (6 months of age and older) and adults for the treatment of X-linked hypophosphatemia (XLH) when **all** of the following criteria are met:

1. Diagnosis of XLH has been confirmed by any of the following:
    a. Documented PHEX pathogenic variant; **or**
    b. Known PHEX pathogenic variant in a directly related family member, and the patient shows evidence of radiographic and/or biochemical abnormalities consistent with diagnosis; **or**
    c. Elevated serum fibroblast growth factor 23 (FGF23) levels that support the diagnosis; **and**
2. Documentation of laboratory testing to support the diagnosis of XLH, including serum phosphorus level below the normal limit for age and reduced renal tubular resorption of phosphate corrected for glomerular filtration rate; **and**
3. In **adult** patients, presence of clinical symptoms of XLH (e.g. skeletal pain, bone fractures); **and**
4. Patient does not have severe renal impairment or end stage renal disease; **and**
5. Patient will not be taking Crysvita in combination with an oral phosphate or active vitamin D analog; **and**
6. Crysvita has been prescribed by or in consultation with a specialist in bone metabolic disorders.

Initial authorization: 12 months

Continuation Therapy

Continuation of treatment with Crysvita beyond 12 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of XLH when patients meet both of the following criteria:

1. Initial therapy was determined to meet the above criteria; **and**
2. Patient has documentation of positive clinical response (e.g. improvement in severity of rickets, serum phosphorus level increase, reduction of fractures and bone pain)

When it is not covered

Crysvita is considered **investigational** and therefore not covered when the above criteria are not met.

Policy Guidelines

Crysvita (burosumab-twza) is given as a subcutaneous injection and should be administered by a healthcare provider.

The recommended initial dosing regimen for pediatric patients age 6 months to less than 18 years is 1 mg/kg of body weight rounded to the nearest 1 mg for patients weighing less than 10 kg, and 0.8 mg/kg of body weight rounded to the nearest 10 mg for patients weighing 10 kg or greater, administered every two (2) weeks. The minimum starting does is 10 mg up to a maximum dose of 90 mg. The dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two (2) weeks to achieve normal serum phosphorus.

The recommended dosing regimen for adult patients is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every four (4) weeks.

Prior to initiation of therapy with Crysvita, oral phosphate and active vitamin D analogs should be discontinued for at least one week and fasting serum phosphorus concentration should be below the reference range for age.

Use of Crysvita is contraindicated in combination with oral phosphate and active vitamin D analogs. In addition, its use is contraindicated in patients with severe renal impairment or end stage renal disease, as these conditions are associated with abnormal mineral metabolism. Crysvita should not be initiated in patients with normal or high serum phosphorus levels based on age. Possible adverse reactions from Crysvita administration include hypersensitivity and injection site reactions, as well as hyperphosphatemia and risk of nephrocalcinosis.

Clinical Trial Evidence

The FDA approval of Crysvita was based on evidence from four clinical trials assessing safety and efficacy in both pediatric (Study 1 and Study 2) and adult (Study 3 and Study 4) patient populations.

Study 1 (NCT 02163577) was a randomized, open-label, parallel-group, phase 2 trial evaluating use of burosumab in 52 children, age 5 to 12 years old, with XLH. Patients were randomized in a 1:1 ratio to receive subcutaneous burosumab either every 2 weeks or every 4 weeks during a 16-week dose-titration period, with dose adjustment to achieve serum phosphorus level at the low end of the normal range, followed by 48 weeks of treatment, for a total of 64 weeks. The primary endpoint was change from baseline to 40 weeks and to 64 weeks in the Thacher rickets severity total score (range 0 to 10, with higher scores indicating more severe disease), and rachitic changes from baseline to 40 weeks and 64 weeks using the Radiographic Global Impression of Change (range 3 to -3 on a 7-point scale). Additional endpoints included change from baseline in pharmacodynamic markers (e.g. renal tubular phosphate resorption, serum phosphorus level, serum 1,25-dihydroxyvitamin D level, and serum alkaline phosphatase level), linear growth, physical ability, and patient-reported pain and functional disability. The mean Thacher rickets severity total score decreased from 1.9 at baseline to 0.8 at week 40 with every-2-week dosing and from 1.7 at baseline to 1.1 at week 40 with every-4-week dosing ($p<0.001$ for both comparisons), with improvements maintained at week 64. The Radiographic Global Impression of Change score indicated reduction in rickets severity in both dosing regimens at week 40 with substantial healing of rickets (change from baseline represented by a score of ≥ 2.0) achieved in 54% of patients, and maintained at week 64. The mean serum phosphorus level increased from baseline in both groups, with overall mean increase of 0.75 mg/dl (34%) at week 40 and 0.84 mg/dl (38%) at week 64, and more than half of patients in both groups achieving levels within normal range by week 6. Stable serum phosphorus levels were maintained through week 64 in the every-2-week dosing group. Renal tubular phosphate reabsorption increased from baseline in both groups, with an overall mean increase of 0.98 mg/dl at week 40.

Study 2 (NCT 02750618) was a 64-week open-label, phase 2 study evaluating use of burosumab in 13 pediatric patients, age 1 to 4 years old, with XLH. In this study, patients received burosumab 0.8 mg/kg every 2 weeks with titration up to 1.2 mg/kg based on serum phosphorus levels. Upon enrollment, mean age of patients was 2.9 years and 69% were male. At baseline, all

patients had radiographic evidence of rickets and had previously received oral phosphate and active vitamin D analogs for a mean (SD) duration of 16.9 (13.9) months with such treatments discontinued prior to study enrollment. Patients demonstrated increased mean (SD) serum phosphorus levels from 2.5 (0.28) mg/dl at baseline to 3.5 (0.49) mg/dl at week 40. After 40 weeks of treatment, mean Thacher rickets severity total score decreased from 2.9 to 1.2 and the mean (SE) Radiographic Global Impression of Change (RGI-C) score was +2.3 (0.08). All 13 patients achieved a RGI-C score ≥ +2.0. The mean (SE) lower limb deformity as assessed by RGI-C, using standing long leg radiographs, was +1.3 (0.14).

Study 3 (NCT 02526160) was a randomized, double-blind, placebo-controlled, phase 3 study evaluating treatment with burosumab in 134 adults with XLH. Patients underwent a 24-week placebo-controlled treatment phase, followed treatment with burosumab at a dose of 1 mg/kg every four weeks for the duration of the study. At study enrollment, mean patient age was 40 years (range 19 to 66 years). All patients had skeletal pain associated with XLH/osteomalacia at baseline and baseline mean (SD) serum phosphorus level was below the lower limit of normal at 1.98 (0.31) mg/dl. Oral phosphate and active vitamin D analogs were not allowed to be taken during the study. Through week 24, a total of 94% of patients receiving burosumab treatment achieved a serum phosphorus level above the lower limit of normal versus 8% in the placebo group. Active fracture/pseudofracture sites were assessed at week 24 and a higher rate of complete healing was shown in the burosumab group compared to placebo. Additionally, during treatment through week 24, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving burosumab, compared to 8 new abnormalities in 66 patients receiving placebo.

Study 4 (NCT 02537431) was an open-label, single-arm, 48-week study assessing effects of burosumab on improvement of osteomalacia in 14 adult patients with XLH, as based on histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received burosumab at a dose of 1 mg/kg every four weeks. Upon study enrollment, mean patient age was 40 years (range 25 to 52 years). Oral phosphate and active vitamin D analogs were not permitted during the study. At 48 weeks, healing of osteomalacia was observed in ten patients as shown by decreases in Osteoid volume/Bone volume (OV/BV) from a mean (SD) score of 26% (12.4) at baseline to 11% (6.5), a change of -57%. Osteoid thickness (O.Th) declined in 11 patients from a mean (SD) of 17 (4.1) micrometers to 12 (3.1) micrometers, a change of -33%. Mineralization lag time (MLt) declined in 6 patients from a mean (SD) of 594 (675) days to 156 (77) days, a change of -74%.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J0584*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Ultragenyx Pharmaceutical Inc. Crysvita (burosumab-twza). Highlights of prescribing information. April 2018. Available at: https://www.ultragenyx.com/file.cfm/29/docs/Crysvita_Full_Prescribing_Information.pdf. Accessed August 2018.

U.S. Food and Drug Administration. FDA approved first therapy for rare inherited form of rickets, x-linked hypophosphatemia. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm604810.htm. Accessed August 2018.

Ruppe, MD. X-linked hypophosphatemia. Available at: https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed August 2018.

Carpenter TO, Imel EA, Holm, IA, et al. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011 Jul; 26(7): 1381-1388. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3157040/. Accessed August 2018.

Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. N Engl J Med. 2018 May 24;378(21): 1987-1998.

Medical Director review 8/2018

Specialty Matched Consultant Advisory Panel 6/2019

Ultragenyx Pharmaceutical Inc. Crysvita (burosumab-twza) injection, for subcutaneous use. Highlights of prescribing information. September 2019. Available at: https://www.ultragenyx.com/file.cfm/29/docs/Crysvita_Full_Prescribing_Information.pdf. Last accessed May 2020.

Specialty Matched Consultant Advisory Panel 6/2020

Policy Implementation/Update Information

9/7/18	New policy developed. Crysvita is considered medically necessary for pediatric patients (1 year of age and older) and adults for the treatment of X-linked hypophosphatemia (XLH). Added HCPCS codes C9399, J3490, and J3590 to "Billing/Coding" section. References added. Medical Director review 8/2018. Policy noticed 9/7/2018 for effective date of 12/7/2018 with PPA effective as of 1/1/19. (krc)
12/31/18	Added HCPCS code J0584 to Billing/Coding section and deleted codes C9399, J3490, and J3590 effective 1/1/19. (krc)
7/16/19	Specialty Matched Consultant Advisory Panel review 6/19/2019. No change to policy intent. (krc)
7/14/20	Updated "Description" and "When Covered" sections with indication expanded to XLH in pediatric patients 6 months of age and older. Reference added. Specialty Matched Consultant Advisory Panel review 6/17/2020. (krc)