09-J2000-99

Original Effective Date: 06/15/18

Reviewed: 11/08/23

Revised: 12/15/23

Subject: Burosumab-twza (Crysvita®)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

X-linked hypophosphatemia (XLH) is a rare hereditary form of rickets characterized by renal phosphate wasting due to excess fibroblast growth factor (FGF23) production. Molecular gene testing can detect up to 78% of cases. The prevalence of XLH is 1 in 20,000 individuals and affects approximately 3,000 pediatric patients and 12,000 adults in the United States. It is the most common form of inheritable rickets in the US. XLH causes low concentrations of phosphorus in the blood and leads to impaired bone growth and development in children and adolescents. Most children with XLH experience bowed or bent legs, short stature, bone pain, and severe dental pain. Some adults with XLH experience persistent discomfort or complications, such as joint pain, impaired mobility, tooth abscesses, and hearing loss.

Burosumab-twza (Crysvita), an FGF23 blocking antibody, was approved by the U.S. Food and Drug Administration (FDA) in April 2018 for the treatment of XLH. Burosumab works by restoring renal phosphate reabsorption and increasing the concentration of 1,25 dihydroxy vitamin D. The use of oral phosphate and active vitamin D analogs is contraindicated during burosumab treatment.

The safety and efficacy of burosumab were evaluated in 134 adults with XLH in a placebo controlled, randomized clinical study. Patients were randomized to receive placebo or burosumab-twza 1 mg/kg every 4 weeks. Treatment with burosumab-twza resulted in a higher percentage of patients achieving a mean serum phosphorus level above the lower limit of normal during the midpoints of the dosing intervals (2 weeks post dose) when compared with placebo (94% vs 8%, respectively). Baseline mean serum phosphorus was 2 mg/dL in the burosumab-twza group and 1.9 mg/dL in the placebo group. During the 24 weeks of treatment, the mean serum phosphorus of the burosumab-twza group and placebo group increased when measured at the midpoints of dose intervals (3.2 mg/dL vs 2.1 mg/dL) and at the ends of dose intervals (2.7 mg/dL vs 2 mg/dL). The mean ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate in the treatment group and placebo group was increased from baseline (1.68 mg/dL vs 1.6 mg/dL) at week 22 (midpoint, 2.73 mg/dL vs 1.69 mg/dL) and week 24 (endpoint, 2.21 mg/dL vs 1.73 mg/dL). In addition, the number of active fractures and pseudofractures healed at week 24 in the burosumab-twza group was 50% and 41% compared with 0% and 9% in the placebo group.

In an open-label study in 26 pediatric patients, burosumab-twza improved mean serum phosphorus levels, 10-point Thacher Rickets Severity Score (RSS) scores, and 7-point Radiographic Global

Impression of Change (RGI-C) scores. Mean serum phosphorus levels improved from 2.4 mg/dL at baseline to 3.3 mg/dL and 3.4 mg/dL at weeks 40 and 64. The mean ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate increased from 2.2 mg/dL at baseline to 3.3 mg/dL and 3.4 mg/dL at weeks 40 and 64. Improvements in RSS and RGI-C scores were observed at 40 weeks of treatment. Mean RSS scores decreased from 1.9 to 0.8 and the mean RGI-C Global scores was +1.7; the RGI-C Global score was +1.6 at week 64. The mean serum total alkaline phosphatase activity was 462 units/L at baseline and significantly decreased to 354 units/L at week 64. In addition, burosumab-twza increased the standing mean height Z score from -1.72 at baseline to -1.54 at week 64.

POSITION STATEMENT:

Initiation of burosumab-twza (Crysvita) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

1. X-linked hypophosphatemia (XLH)
    a. Member's diagnosis of XLH is supported by at least **ONE**:
        i. PHEX (phosphate regulating endopeptidase homolog X-linked) gene mutation – laboratory documentation must be provided
        ii. PHEX gene mutation in a directly related family member with appropriate X-linked inheritance – laboratory and medical record documentation must be provided
        iii. Serum fibroblast growth factor 23 (FGF23) level greater than 30 pg/mL by Kainos assay – laboratory documentation must be provided
    b. Member's fasting serum phosphorus level is below age-based normal level (table 1) – laboratory documentation must be provided
    c. Member has radiographic evidence of rickets or other bone disease attributed to XLH – imaging or radiographic documentation must be provided
    d. Use will not be in combination with oral phosphate or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol)
    e. Member is 6 months of age or older
    f. Dose does not exceed any of the following:
        i. Age 6 months to 17 years: 90 mg every two weeks
        ii. Age 18 years and older: 90 mg every four weeks
2. Tumor-induced osteomalacia (TIO) syndrome associated with phosphaturic mesenchymal tumors
    a. Member's serum fibroblast growth factor 23 (FGF23) level is greater than 100 pg/mL by Kainos assay – laboratory documentation must be provided
    b. Member's fasting serum phosphorus level is below age-based normal level (table 1) – laboratory documentation must be provided
    c. Member's disease is not amenable to cure by surgical excision of the underlying tumor/lesion

d. Use will not be in combination with oral phosphate or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol)

e. Member is 2 years of age or older

f. Dose does not exceed 180 mg every two weeks

Approval duration: 6 months

Continuation of burosumab-twza (Crysvita) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue for treatment of x-linked hypophosphatemia (XLH) or tumor-induced osteomalacia (TIO) syndrome, **OR** the member has previously met all indication-specific criteria
2. Member has demonstrated a clinically meaningful response to treatment with burosumab – documentation from the medical record must be provided
3. Use will not be in combination with oral phosphate or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol)
4. Dose does not exceed any of the following:
    a. XLH:
        i. Age 6 months to 17 years: 90 mg every two weeks
        ii. Age 18 years and older: 90 mg every four weeks
    b. TIO: 180 mg every two weeks

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

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.
- 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.

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.

Pediatric TIO:

- The recommended starting dose for pediatrics is 0.4 mg/kg body weight administered every 2 weeks, rounded to the nearest 10mg, up to a maximum dose of 2 mg/kg not to exceed 180 mg, administered every 2 weeks.

Adult TIO:

- The recommended starting dose for adults is 0.5 mg/kg body weight administered every 4 weeks, rounded to the nearest 10 mg, up to a maximum dose of 2 mg/kg not to exceed 180 mg, administered every 2 weeks.

Dose Adjustments

- Reassess fasting serum phosphorus level 2 weeks after dose adjustment (4 weeks for pediatric patients)
- Refer to product labeling for recommended dose decreases

Drug Availability

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

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Use with oral phosphate and active vitamin D analogs
- Serum phosphorus is within or above normal range for age
- Severe renal impairment or end stage renal disease

Precautions/Warnings

- Hypersensitivity
- Hyperphosphatemia and risk of nephrocalcinosis
- Injection site reactions

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0584	Injection, burosumab-twza 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E83.31	Familial hypophosphatemia
M83.8	Other adult osteomalacia [tumor-induced osteomalacia (TIO)]

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Asfotase alfa (Strensiq), 09-J2000-58

OTHER:

Table 1. Age-Based Normal Serum Phosphate Reference Intervals

Age	mg/dL	mmol/L
0-5 days	4.8-8.2	1.55-2.65
1-3 yrs	3.8-6.5	1.25-2.10
4-11 yrs	3.7-5.6	1.20-1.80
12-15 yrs	2.9-5.4	0.95-1.75
>15 yrs	2.7-4.7	0.90-1.50

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2023 [cited 10/24/23]. Available from: http://www.clinicalpharmacology.com/.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 10/24/23]. Available from: http://clinicaltrials.gov/.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 10/24/23].
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2023 [cited 10/24/23]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Rupe MD. X-Linked Hypophosphatemia. In: GeneReviews; 2018. Available at: https://www-ncbi-nlm-nih-gov.lp.hscl.ufl.edu/books/NBK83985/.

6. Ultragenyx. Crysvita (burosumab-twza) solution. 2020 [cited 11/25/20]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: http://www.ultragenyx.com/file.cfm/29/docs/Crysvita_Full_Prescribing_Information.pdf/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/08/23.

GUIDELINE UPDATE INFORMATION:

06/15/18	New Medical Coverage Guideline.
01/01/19	Revision: HCPCS code updates. Added J0584 and removed J3590.
01/15/20	Review and revision; updated position statement, dosing, references.
01/15/21	Review and revision; updated position statement, dosing, references.
05/15/21	Revision to position statement and coding.
12/15/21	Review and revision; updated references.
12/15/22	Review and revision; updated references.
12/15/23	Review and revision; updated references.