Policy Number	**RX502.058**
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Burosumab-twza

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Burosumab-twza (Crysvita®) **may be considered medically necessary** in individuals 6 months of age and older for the treatment of X-linked hypophosphatemia (XLH) when **ALL** the following criteria are met:

- Diagnosis of XLH confirmed by 1 of the following:
  - PHEX genetic test; or
  - Elevated serum fibroblast growth factor 23 (FGF23) level; AND
- Fasting serum phosphorus level is below the normal range for the patient's age; AND
- Presence of clinical signs and symptoms of XLH (e.g., rickets, growth retardation, musculoskeletal pain, bone fractures); AND
- The member does not have severe renal impairment or end stage renal disease (defined as a glomerular filtration rate <30 mL/min); AND
- Discontinuation of oral phosphate and active vitamin D analogs one week prior to initiation of therapy.

Burosumab-twza (Crysvita®) **may be considered medically necessary** in individuals 2 years of age and older for the treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors when **ALL** the following criteria are met:

- Diagnosis of tumor-induced osteomalacia, confirmed by elevated serum fibroblast growth factor 23 (FGF23) level; AND
- Fasting serum phosphorus level is below the normal range for the patient's age; AND
- The member does not have severe renal impairment or end stage renal disease (defined as a glomerular filtration rate <30 mL/min); AND
- Discontinuation of oral phosphate and active vitamin D analogs two weeks prior to initiation of therapy; AND
- The tumor cannot be curatively resected or localized.

NOTE 1: If a patient undergoes treatment of the underlying tumor (i.e., surgical excision or radiation therapy), treatment should be interrupted and serum phosphorus reassessed after treatment has been completed.

Burosumab-twza (Crysvita®) **is considered experimental, investigational and/or unproven** when the above criteria are not met, and for the treatment of all other non-Food and Drug Administration (FDA) approved indications.

Policy Guidelines

Burosumab-twza (Crysvita®) is administered by subcutaneous injection and should be administered by a healthcare provider.

Description

X-linked Hypophosphatemia (XLH)
X-linked hypophosphatemia (XLH) is a dominant disorder that affects approximately 1 per 20,000 live births due to mutations in the PHEX (phosphate regulating endopeptidase on the X chromosome) gene. The PHEX gene encodes an enzyme that normally degrades fibroblast growth factor 23 (FGF23). (2) Due to this mutation in the PHEX gene, excessive FGF23 levels are present, which suppresses renal tubular phosphate reabsorption and the renal production of 1,25-dihydroxy vitamin D. (1) Clinical symptoms include hypophosphatemia, slow growth, rickets or osteomalacia. However, it is only at the time of weightbearing that leg deformities (e.g., bowing) and progressive departure from normal growth rate become sufficiently present to attract medical attention. By that time, most children have radiographic evidence of rickets, particularly at the growth plates around the knee, which can cause severe bone pain. The goal of therapy in pediatric patients diagnosed with XLH is to decrease the severity of bone abnormalities (rickets and osteomalacia), reduce the associated bone/joint pain, and improve growth and physical activity. While medical management with phosphate and calcitriol meets some of these objectives, such treatment often leads to significant side effects resulting in poor long-term adherence. (2)

For adult patients who were treated with phosphate and calcitriol during childhood, most have defects in stature due to limitations in growth during childhood. Osteoarthritis is nearly universal in the adult population, with onset decades earlier than observed in a typical adult population. Enthesopathy (calcification of tendons, ligaments, and joint capsules) and/or development of osteophytes are also universally encountered, usually beginning in the late second or third decade of life. Spinal stenosis is a rare and severe late complication (in some cases, related to ossification of the longitudinal spinal ligaments) and can be extremely painful and debilitating. Many adult patients who have discontinued phosphate and calcitriol therapy have subclinical chronic symptoms of weakness, fatigue, bone pain, and gait abnormalities. They may not recognize these symptoms but may seek medical attention when they bring their affected children to a bone specialist for therapy; they tend to report clear improvement after initiation of therapy. The muscle weakness is more often reported by adults with XLH compared with children.

The goal for adults has been to manage generalized bone pain, enhance limited mobility (if either occurs), and cure any nonunion fractures. Histologic evidence of osteomalacia persists regardless of treatment with phosphate and calcitriol and the consequences of the persistent osteomalacia may play a role in the later development of enthesopathy, arthritis, and musculoskeletal pain. However, as conventional therapy with phosphate and calcitriol requires

significant monitoring and may result in complications, a standard approach has often not been employed. If Crysvita therapy is unavailable, offering phosphate and calcitriol therapy to symptomatic adult patients is suggested, provided they are willing to adhere to the clinicians' instructions for dosing and monitoring.

Tumor-induced Osteomalacia

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare acquired paraneoplastic syndrome of abnormal phosphate and vitamin metabolism caused by endocrine tumors that secrete phosphaturic hormone, FGF23. Hypophosphatemia due to renal phosphate wasting, inappropriately normal or low vitamin D, and elevated or inappropriately normal FGF23 are indicators of TIO. Clinical symptoms may include bone pain and tenderness, muscle weakness, difficulty walking, abnormal gait, fractures, loss of height and generalized debilitated status. Radiographs reveal evidence of rickets in children, and bone histomorphometry shows severe osteomalacia. When possible, surgical resection is recommended as complete removal is curative. If resection is not possible, medical management is usually indicated although frequent monitoring is needed to avoid complications such as secondary/tertiary hyperparathyroidism, hypercalciuria, and nephrocalcinosis. Secondary treatment usually involves treatment with phosphate and calcitriol. In some cases, burosumab-twza is used to help increase the levels of phosphate in the blood when there is a failure, contraindication, or intolerance to therapy with calcitriol in combination with an oral phosphate agent. (2-4)

Burosumab-twza (Crysvita®)

Mechanism of Action

Crysvita binds to and inhibits the biological activity of FGF23 restoring renal phosphate reabsorption and increasing the serum concentration of 1,25 dihydroxy vitamin D. (1) Crysvita binds and inhibits the biological activity of FGF23 restoring renal phosphate reabsorption and increasing the serum concentration of 1,25-dihydroxy vitamin D. Selection of patients for Crysvita therapy depends on the patient's age, symptoms, and treatment history. (2)

Crysvita is contraindicated in patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism. It is also contraindicated if serum phosphorus is within or above the normal range for the patient’s age and should not be used with oral phosphate or active vitamin D analogs. Oral phosphate and active vitamin D analogs should be discontinued one week prior to initiation of treatment. (1)

Laboratory Monitoring

X-linked Hypophosphatemia (XLH)

- Pediatric patients with XLH (6 months to less than 18 years of age): After initiation of treatment, fasting serum phosphorus should be measured every 4 weeks for the first 3 months of treatment, and thereafter as appropriate. If serum phosphorus is above the lower limit of the reference range for age and below 5 mg/dL, continue treatment with the same dose. Follow dose adjustment schedule on the United States (U.S.) Food and Drug Administration (FDA) label to maintain serum phosphorus within the reference range for age. (1)

- Adult patients with XLH (18 years of age and older): After initiation of treatment, assess fasting serum phosphorus monthly, measured 2 weeks post-dose, for the first 3 months of treatment, and thereafter as appropriate based on the U.S. FDA label. (1)

Tumor-Induced Osteomalacia (TIO)

- Pediatric patients with TIO (2 years to less than 18 years of age): After initiation of treatment, assess fasting serum phosphorus monthly, measured 2 weeks post-dose, for the first 3 months of treatment, and thereafter as appropriate based on the U.S. FDA label.
- Adult patients with TIO (18 years of age and older): After initiation of treatment, assess fasting serum phosphorus monthly, measured 2 weeks post-dose, for the first 3 months of treatment, and thereafter as appropriate based on the U.S. FDA label. (1)

Regulatory Status

- On April 17, 2018, the U.S. FDA approved burosumab-twza (Crysvita; Ultragenyx Pharmaceutical, Novato, CA) through the Biologics License Application (BLA) process for the treatment of XLH in adult and pediatric patients one year of age and older.
- On September 30, 2019, the U.S. FDA revised the label to include the use of Crysvita for the treatment of XLH in patients 6 months of age and older.
- On June 18, 2020, Crysvita was approved through the BLA process for the treatment of FGF23-related hypophosphatemia in tumor induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older. (5)

<u>Contraindications</u>

Per the FDA label, Crysvita is contraindicated:

- *In concomitant use with oral phosphate and/or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol) due to the risk of hyperphosphatemia.* Concomitant use of Crysvita with oral phosphate and/or active vitamin D analogs will increase phosphate concentrations greater than expected with Crysvita alone. This increase may result in hyperphosphatemia which can induce nephrocalcinosis. Therefore, concomitant use of Crysvita with oral phosphate and/or active vitamin D analogs is contraindicated. The FDA recommends discontinuation of oral phosphate and/or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol) 1 week prior to initiation of treatment.
- *When serum phosphorus is within or above the normal range for age.* Increases in serum phosphorus to above the upper limit of normal may be associated with an increased 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. Patients with TIO who undergo treatment of the underlying tumor should have dosing interrupted and adjusted to prevent hyperphosphatemia.
- *In patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.*

The effect of renal impairment on the pharmacokinetics of burosumab-twza is unknown. However, renal impairment can induce abnormal mineral metabolism which will increase phosphate concentrations greater than expected with Crysvita alone. This increase may result in hyperphosphatemia which can induce nephrocalcinosis. Crysvita is contraindicated in patients with severe renal impairment, defined as:

- Pediatric patients with estimated glomerular filtration rate (eGFR) 15 mL/min/1.73m^2 to 29 mL/min/1.73m^2 or end stage renal disease (eGFR < 15 mL/min/1.73m^2).
- Adult patients with creatinine clearance (CLcr) 15 mL/min to 29 mL/min or end stage renal disease (CLcr < 15 mL/min).

Pediatric Use

- *Pediatric Patients 1 Year and Older With XLH*
  The safety and effectiveness of Crysvita have been established in pediatric patients 6 months and older. The safety and effectiveness in pediatric patients 1 year and older with XLH are based on one phase 3, open-label, active control study (61 patients 1-12 years of age [Study 1]) and two open-label studies (52 patients 5 to 12 years of age [Study 2], and 13 patients 1 to 4 years of age [Study 3]) evaluating serum phosphorus and radiographic findings. Safety and effectiveness in patients 6 months to 1 year and adolescents are supported by evidence from the studies in pediatric patients 1 year to less than 13 years of age with additional modeling and simulation of adult and pediatric pharmacokinetic (PK) and pharmacodynamic (PD) data to inform dosing.
- *Pediatric Patients with XLH Below the Age of 6 Months*
  The safety and effectiveness for Crysvita in pediatric patients with XLH below the age of 6 months have not been established.
- *Pediatric Patients 2 Years and Older with TIO*
  The safety and effectiveness of Crysvita in pediatric patients 2 years and older with TIO are supported by evidence from the studies in adult patients with TIO with additional modeling and simulation of PK data from adult and pediatric XLH patients and adult TIO patients to inform dosing.
- *Pediatric Patients with TIO Below the Age of 2 Years*
  The safety and effectiveness for Crysvita in pediatric patients with TIO below the age of 2 years have not been established.

Dose Interruption

If a patient undergoes treatment of the underlying tumor (i.e., surgical excision or radiation therapy), Crysvita treatment should be interrupted and serum phosphorus reassessed after treatment has been completed. Crysvita dose should be restarted at the patient's initiation dose if serum phosphorus remains below the lower limit of normal. Follow dose adjustment on the FDA label to maintain serum phosphorus within the reference range for age.

Rationale

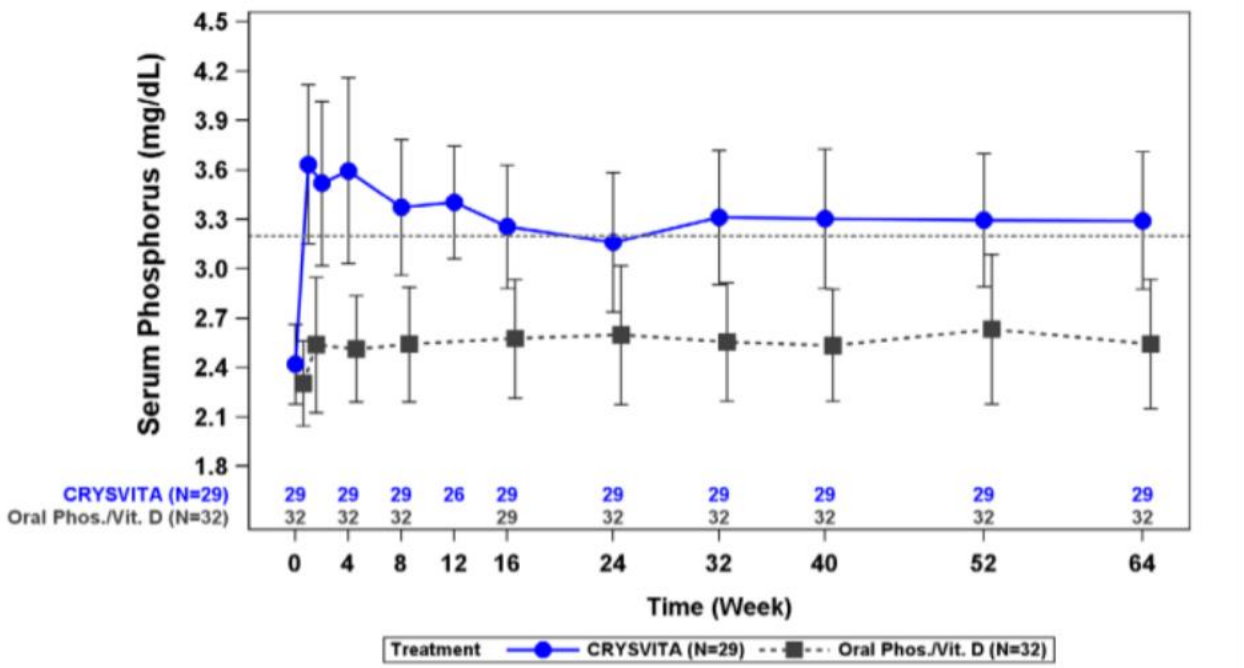
This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for burosumab-twza (Crysvita®) and a review of relevant professional guidelines and position statements.

Pediatric X-linked Hypophosphatemia (XLH)
Crysvita has been evaluated in three studies enrolling a total of 126 pediatric patients with XLH. (1)

Study 1 (NCT02915705) is a 64-week randomized, open-label study in 61 pediatric XLH patients, 1 to 12 years old that compared treatment with Crysvita to active control (oral phosphate and active vitamin D). At time of first dose the mean age of patients was 6.3 years and 44% were male. All patients had radiographic evidence of rickets at baseline, with a Rickets Severity Score (RSS) of ≥ 2.0 and had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 4 (3.1) years. Oral phosphate and active vitamin D analogs ere discontinued prior to study enrollment for a 7-day washout period and then reinitiated for patients in the active control group. Patients were randomized to receive either Crysvita at a starting dose of 0.8 mg/kg every two weeks or oral phosphate (recommended dose 20-60 mg/kg/day) and active vitamin D (recommended doses calcitriol 20-30 ng/kg/day or alfacalcidol 40-60 ng/kg/day). Patients randomized to active control received a mean oral phosphate dose of approximately 41 mg/kg/day (range 18 to 110 mg/kg/day) at Week 40 and approximately 46 mg/kg/day (range 18 mg/kg/day to 166 mg/kg/day) at Week 64. They also received either a mean oral calcitriol dose of 26 ng/kg/day at Week 40 and 27 ng/kg/day at Week 64 or a therapeutically equivalent amount of alfacalcidol. Eight patients in the Crysvita arm titrated up to 1.2 mg/kg based on serum phosphorus measurements. All patients completed at least 64 weeks on study.

Serum Phosphorus
In Study 1, Crysvita increased mean (SD) serum phosphorus levels from 2.4 (0.24) mg/dL at baseline to 3.3 (0.43) mg/dL at Week 40 and to 3.3 (0.42) mg/dL at Week 64. In the active control group, mean (SD) serum phosphorus concentrations increased from 2.3 (0.26) mg/dL at baseline to 2.5 (0.34) mg/dL at Week 40 and to 2.5 (0.39) mg/dL at Week 64. The renal phosphate reabsorptive capacity as assessed by tubular maximum phosphate/glomerular filtration rate (TmP/GFR) increased in the Crysvita treated patients from a mean (SD) of 2.2 (0.37) mg/dL at baseline to 3.4 (0.67) mg/dL and 3.3 (0.65) mg/dL at Week 40 and Week 64, respectively. In the active control group, mean (SD) TmP/GFR decreased from 2.0 (0.33) mg/dL at Baseline to 1.8 (0.35) mg/dL at Week 40, and remained below baseline at Week 64 at 1.9 (0.49) mg/dL.

Figure 1: Serum Phosphorus Concentration and Change from Baseline (mg/dL) (Mean ± SD) by Treatment Group in Children 1-12 Years in Study 1



The dotted line represents the lower limit of normal (3.2 mg/dL) for patients in Study 1.

Radiographic Evaluation of Rickets

Radiographs were examined to assess XLH-related rickets using the 10-point Thacher RSS and the 7-point Radiographic Global Impression of Change (RGI-C). The RSS score is assigned based on images of the wrist and knee from a single timepoint, with higher scores indicating greater rickets severity. The RGI-C score is assigned based on side-by-side comparisons of wrist and knee radiographs from two timepoints, with higher scores indicating greater improvement in radiographic evidence of rickets. A RGI-C score of +2.0 was defined as radiographic evidence of substantial healing.

In Study 1, baseline mean (SD) total RSS was 3.2 (0.98) in the Crysvita group and 3.2 (1.14) in the active control group. After 40 weeks of treatment with Crysvita, mean total RSS decreased from 3.2 to 1.1 (0.72) and from 3.2 to 2.5 (1.09) in the active control group. Least square (LS) mean (SE) RGI-C Global score was +1.9 (0.11) in the Crysvita group and +0.8 (0.11) in the active control group at Week 40 (see Table 1). At Week 40, 21 of the 29 patients in the Crysvita group and 2 of the 32 patients in the active control arm achieved a RGI-C global score ≥ +2.0. These findings were maintained at Week 64 as shown in Table 1.

Table 1. Rickets Response in Children 1-12 Years Receiving Crysvita Every 2 Weeks in Study 1

Endpoint Timepoint	**Crysvita Every 2 Weeks (N=29)**	**Active Control (N=32)**
RSS Total Score		
Baseline Mean (SD)	3.2 (0.98)	3.2 (1.14)
LS Mean change from baseline in total score[a] (reduction indicates improvement) with 95% CI		
Week 40	-2.0 (-2.33, -1.75)	-0.7 (-0.98, -0.43)

Week 64	-2.2 (-2.46, -2.00)	-1.0 (-1.31, -0.72)
RGI-C Global Score[b]		
LS Mean score[a] (positive indicates healing) with 95% CI		
Week 40	+1.9 (+1.70, +2.14)	+0.8 (+0.56, +0.99)
Week 64	+2.06 (+1.91, +2.20)	+1.03 (+0.77, +1.30)

CI: Confidence interval; LS: least squares; N: Number; RGI-C: Radiographic Global Impression of Change; RSS: Rickets Severity Score; SD: standard deviation.

[a] The estimates of LS mean and 95% CI for Week 40 are from an ANCOVA model accounting for treatment group, baseline RSS and baseline age stratification factor; the estimates for Week 64 are from a generalized estimating equation (GEE) model accounting for treatment group, visit, treatment by visit interaction, baseline RSS and baseline age stratification factor.

[b] RGI-C at Week 40 is the primary endpoint of Study 1.

Lower Extremity Skeletal Abnormality

In Study 1, lower extremity skeletal abnormalities were assessed by RGI-C in standing long leg radiographs. At Week 64, the Crysvita group maintained greater improvement compared with the active control group (LS mean [SE]: +1.25 [0.17] versus +0.29 [0.12]; difference of +0.97 [95% CI: +0.57, +1.37, GEE model]).

Serum Alkaline Phosphatase Activity

For Study 1, mean (SD) serum total alkaline phosphatase activity decreased from 511 (125) at baseline to 337 (86) U/L in the Crysvita group (mean change: -33%) and from 523 (154) at baseline to 495 (182) U/L in the active control group (mean change: -5%) at Week 64.

Growth

In Study 1, Crysvita treatment for 64 weeks increased standing mean (SD) height Z score from -2.32 (1.17) at baseline to -2.11 (1.11) at Week 64 (LS mean change [SE] of +0.17 [0.07]). In the active control group, mean (SD) height Z score increased from -2.05 (0.87) at baseline to -2.03 (0.83) at Week 64 (LS mean [SE] change of +0.02 [0.04]). The difference between the treatment groups at Week 64 was +0.14 (95% CI: 0.00, +0.29).

Study 2 (NCT02163577) is a randomized, open-label study in 52 prepubescent XLH patients, 5 to 12 years old, which compared treatment with Crysvita administered every 2 weeks versus every 4 weeks. Following an initial 16-week dose titration phase, patients completed 48-weeks of treatment with Crysvita every 2 weeks. All 52 patients completed at least 64 weeks on study; no patient discontinued. Burosumab-twza dose was adjusted to target a fasting serum phosphorus concentration of 3.5 to 5.0 mg/dL based on the fasting phosphorus level the day of dosing. Twenty-six of 52 patients received Crysvita every two weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 mg/kg (range: 0.3, 1.5) at Week 16, 0.98 mg/kg (range: 0.4, 2.0) at Week 40 and 1.04 mg/kg (range: 0.4, 2.0) at Week 60. The remaining 26 patients received Crysvita every four weeks. At study entry, the mean age of patients was 8.5 years and 46% were male. Ninety-six percent had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 7 (2.4) years. Oral phosphate and active vitamin D analogs

were discontinued prior to study enrollment. Ninety-four percent of patients had radiographic evidence of rickets at baseline.

Study 3 (NCT02750618) is a 64-week open-label study in 13 pediatric XLH patients, 1 to 4 years old. Patients received Crysvita at a dose of 0.8 mg/kg every two weeks with 3 patients titrating up to 1.2 mg/kg based on serum phosphorus measurements. All patients completed at least 40 weeks on study; no patients discontinued. At study entry, the mean age of patients was 2.9 years and 69% were male. All patients had radiographic evidence of rickets at baseline and 12 patients had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 16.7 (14.4) months. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment.

Serum Phosphorus
In Study 2, Crysvita increased mean (SD) serum phosphorus levels from 2.4 (0.40) at baseline to 3.3 (0.40) and 3.4 (0.45) mg/dL at Week 40 and Week 64 in the patients who received Crysvita every 2 weeks. The ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) increased in these patients from mean (SD) of 2.2 (0.49) at baseline to 3.3 (0.60) and 3.4 (0.53) mg/dL at Week 40 and Week 64.

In Study 3, Crysvita 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.

Radiographic Evaluation of Rickets
In Study 2, baseline mean (SD) RSS total score was 1.9 (1.17) in patients receiving Crysvita every two weeks. After 40 weeks of treatment with Crysvita, mean total RSS decreased from 1.9 to 0.8 (see Table 2). After 40 weeks of treatment with Crysvita, the mean RGI-C Global score was +1.7 in patients receiving Crysvita every two weeks. Eighteen out of 26 patients achieved an RGI-C score of ≥ +2.0. These findings were maintained at Week 64 as shown in Table 2.

In Study 3, baseline mean (SD) total RSS was 2.9 (1.37) in 13 patients. After 40 weeks of treatment with Crysvita, mean total RSS decreased from 2.9 to 1.2 and the mean (SE) RGI-C Global score was +2.3 (0.08) (see Table 2). All 13 patients achieved a RGI-C global score ≥ +2.0.

Table 2. Rickets Response in Children 1-12 Years Receiving Crysvita Every 2 Weeks in Study 2 and Study 3

Endpoint Timepoint	**Crysvita Every 2 Weeks**	
	Study 2[a] (N=26)	**Study 3[b] (N=13)**
RSS Total Score		
Baseline Mean (SD)	1.9 (1.17)	2.9 (1.37)
LS Mean change from baseline in total score (reduction indicates improvement) with 95% CI		
Week 40	-1.1 (-1.28, -0.85)	-1.7 (-2.03, -1.44)
Week 64	-1.0 (-1.2, -0.79)	
RGI-C Global Score		

LS Mean score (positive indicates healing) with 95% CI		
Week 40	+1.7 (+1.48, +1.84)	+2.3 (+2.16, +2.51)
Week 64	+1 (+1.34, +1.78)	

CI: Confidence interval; LS: least square; N: Number; RGI-C: Radiographic Global Impression of Change; RSS: Rickets Severity Score; SD: standard deviation.

[a] The estimates of LS mean and 95% CI are from a generalized estimating equation (GEE) model accounting for regimen, visit, regimen by visit interaction, baseline RSS for study 2.

[b] The estimates of LS mean and 95% CI for Week 40 are from an ANCOVA model accounting for age and baseline RSS for study 3.

Lower Extremity Skeletal Abnormality

In Study 3, the mean (SE) change in lower limb deformity as assessed by RGI-C, using standing long leg radiographs, was +1.3 (0.14) at Week 40.

Serum Alkaline Phosphatase Activity

For Study 2, mean (SD) serum total alkaline phosphatase activity was 462 (110) U/L at baseline and decreased to 354 (73) U/L at Week 64 (-23%) in the patients who received Crysvita every 2 weeks. For Study 3, mean (SD) serum total alkaline phosphatase activity was 549 (194) U/L at baseline and decreased to 335 (88) U/L at Week 40 (mean change: -36%).

For Study 3, mean (SD) serum total alkaline phosphatase activity was 549 (194) U/L at baseline and decreased to 335 (88) U/L at Week 40 (mean change: -36%).

Growth

In Study 2, Crysvita treatment for 64 weeks increased standing mean (SD) height Z score from -1.72 (1.03) at baseline to -1.54 (1.13) in the patients who received Crysvita every two weeks (LS mean change of +0.19 (95% CI: 0.09 to 0.29).

Adult X-linked Hypophosphatemia (XLH)

Study 4 (NCT02526160) is a randomized, double-blind, placebo-controlled study in 134 adult XLH patients. The study comprises a 24-week placebo-controlled treatment phase followed by a 24-week open-label treatment period in which all patients received Crysvita. Crysvita was administered at a dose of 1 mg/kg every 4 weeks. At study entry, the mean age of patients was 40 years (range 19 to 66 years) and 35% were male. All patients had skeletal pain associated with XLH/osteomalacia at baseline. The baseline mean (SD) serum phosphorus concentration was below the lower limit of normal at 1.98 (0.31) mg/dL. Oral phosphate and active vitamin D analogs were not allowed during the study. Out of the 134 patients enrolled in the study, one patient in the Crysvita group discontinued treatment during the 24-week placebo-controlled treatment period, and 7 patients discontinued Crysvita during the open-label treatment period.

Study 5 (NCT02537431) is a 48-week, open-label, single-arm study in 14 adult XLH patients to assess the effects of Crysvita on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received 1 mg/kg

Crysvita every four weeks. At study entry, the mean age of patients was 40 years (range 25 to 52 years) and 43% were male. Oral phosphate and active vitamin D analogs were not allowed during the study.

Serum Phosphorus

In Study 4 at baseline, mean (SD) serum phosphorus was 1.9 (0.32) and 2.0 (0.30) mg/dL in the placebo and Crysvita groups respectively. During the initial 24-week double-blind, placebo-controlled period, mean (SD) serum phosphorus across the midpoints of dose intervals (2 weeks post dose) was 2.1 (0.30) and 3.2 (0.53) mg/dL in the placebo and Crysvita groups, and mean (SD) serum phosphorus across the ends of dose intervals was 2.0 (0.30) and 2.7 (0.45) mg/dL in the placebo and Crysvita groups.

A total of 94% of patients treated with Crysvita achieved a serum phosphorus level above the lower limit of normal (LLN) compared to 8% in the placebo group through Week 24 (see Table 3).

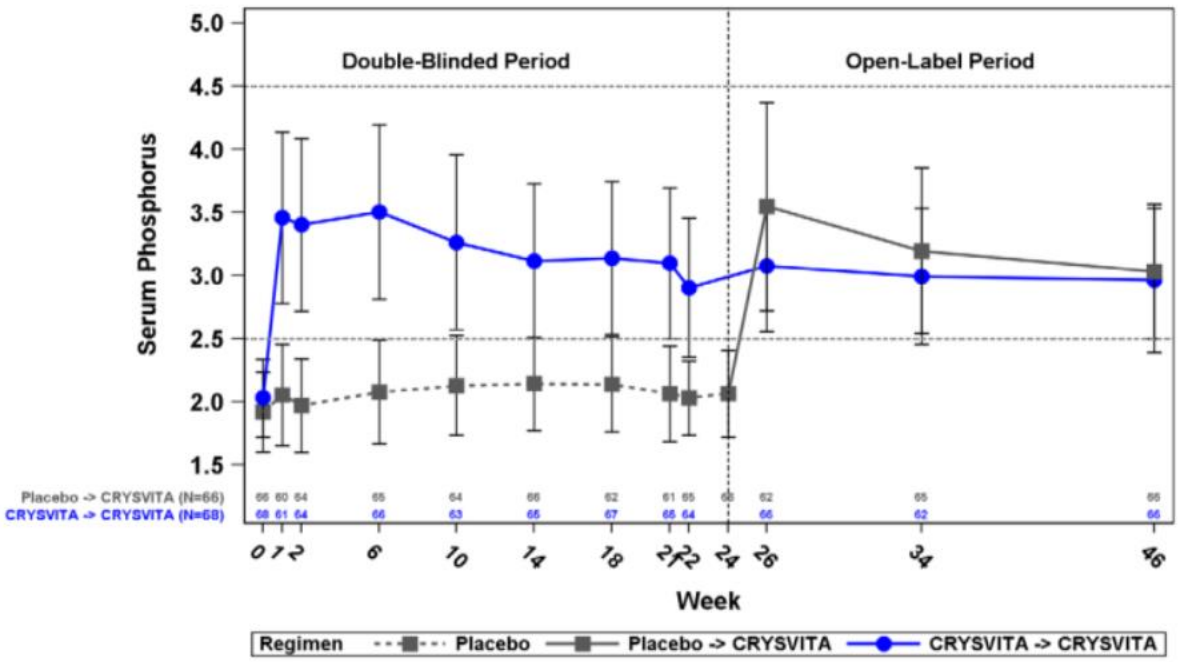
Table 3. Proportion of Adult Patients Achieving Mean Serum Phosphorus Levels Above the LLN at the Midpoint of the Dose Interval During the 24-Week Placebo-Controlled Period of Study 4

	Placebo (N = 66)	**Crysvita (N = 68)**
Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	5 (8%)	64 (94%)
95% CI	(3.3, 16.5)	(85.8, 97.7)
p-value[a]		< 0.0001

CI: confidence interval; LLN: lower limit of normal; N: number.
The 95% CIs are calculated using the Wilson score method.
[a] P-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving the primary endpoint and treatment group, adjusting for randomization stratifications.

During the open-label treatment period, serum phosphorus was maintained during continued Crysvita therapy, with no evidence of loss of effect through Week 48.

Figure 2: Mean (± SD) Serum Phosphorus Peak Concentrations (mg/dL) in Study 4[a, b]



[a] Placebo subjects cross over to receive open-label Crysvita treatment at Week 24.
[b] The dotted lines represent the upper limit of normal (4.5 mg/dL) and lower limit of normal (2.5 mg/dL) for patients in Study 4.

At baseline, the mean (SD) ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) was 1.60 (0.37) and 1.68 (0.40) mg/dL in the placebo and Crysvita groups respectively. At Week 22 (midpoint of a dose interval), mean (SD) TmP/GFR was 1.69 (0.37) and 2.73 (0.75) mg/dL in the placebo and Crysvita groups. At Week 24 (end of a dose interval), mean (SD) TmP/GFR was 1.73 (0.42) and 2.21 (0.48) mg/dL in the placebo and Crysvita groups. During the open-label treatment period, TmP/GFR remained stable during continued Crysvita therapy through Week 48.

Radiographic Evaluation of Osteomalacia

In Study 4, a skeletal survey was conducted at baseline to identify osteomalacia-related fractures and pseudofractures. Osteomalacia-related fractures are defined as atraumatic lucencies extending across both bone cortices and pseudofractures are defined as atraumatic lucencies extending across one cortex. There were 52% of patients who had either active (unhealed) fractures (12%) or active pseudofractures (47%) at baseline. The active fractures and pseudofractures were predominantly located in the femurs, tibia/fibula, and metatarsals of the feet. Assessment of these active fracture/pseudofracture sites at Week 24 demonstrated a higher rate of complete healing in the Crysvita group compared to placebo as shown in Table 4. During the double-blind, placebo-controlled treatment period through Week 24, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving Crysvita, compared to 8 new abnormalities in 66 patients receiving placebo (see Table 4).

Table 4. Comparison of Fracture Healing with Crysvita versus Placebo in Study 4 Double Blind Period

	Active Fractures		Active Pseudofractures		Total Fractures	
	Placebo n (%)	Crysvita n (%)	Placebo n (%)	Crysvita n (%)	Placebo n (%)	Crysvita n (%)
Number of fractures at baseline	13	14	78	51	91	65
Healed at Week 24	0 (0%)	7 (50%)	7 (9%)	21 (41%)	7 (8%)	28 (43%)

n: number

During the open-label treatment period, the patients who continued receiving Crysvita showed continued healing of fractures at Week 48 [active fractures (n = 8, 57%), active pseudofractures (n = 33, 65%)]. In the 'placebo to Crysvita' group, fracture healing at Week 48 was observed for active fractures (n = 6, 46%), and active pseudofractures (n = 26, 33%).

Patient Reported Outcomes

Study 4 evaluated patient-reported XLH-related symptoms (pain, joint stiffness, and physical function).

At 24 weeks, the Crysvita arm showed a mean improvement from baseline (-7.9) compared to the placebo arm (+0.3) in the stiffness severity score (range 0 to 100; lower scores are reflective of symptom improvement).

At 24 weeks, no significant difference between Crysvita and placebo was demonstrated in patient-reported pain intensity or physical function score.

Bone Histomorphometry

In Study 5, after 48 weeks of treatment, healing of osteomalacia was observed in ten patients as demonstrated 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 eleven 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 mean change of -74%.

Tumor-induced Osteomalacia

Crysvita has been evaluated in two studies enrolling a total of 27 patients with tumor-induced osteomalacia (TIO).

Study 6 (NCT02304367) is a single-arm open-label study that enrolled 14 adult patients with a confirmed diagnosis of FGF23-related hypophosphatemia produced by an underlying tumor that was not amenable to surgical excision or could not be located. Of the 14 TIO patients enrolled in Study 6, eight were male, and patients ranged from 33 years to 68 years of age (Median 59.5 years). Oral phosphate and active vitamin D analogs were discontinued two

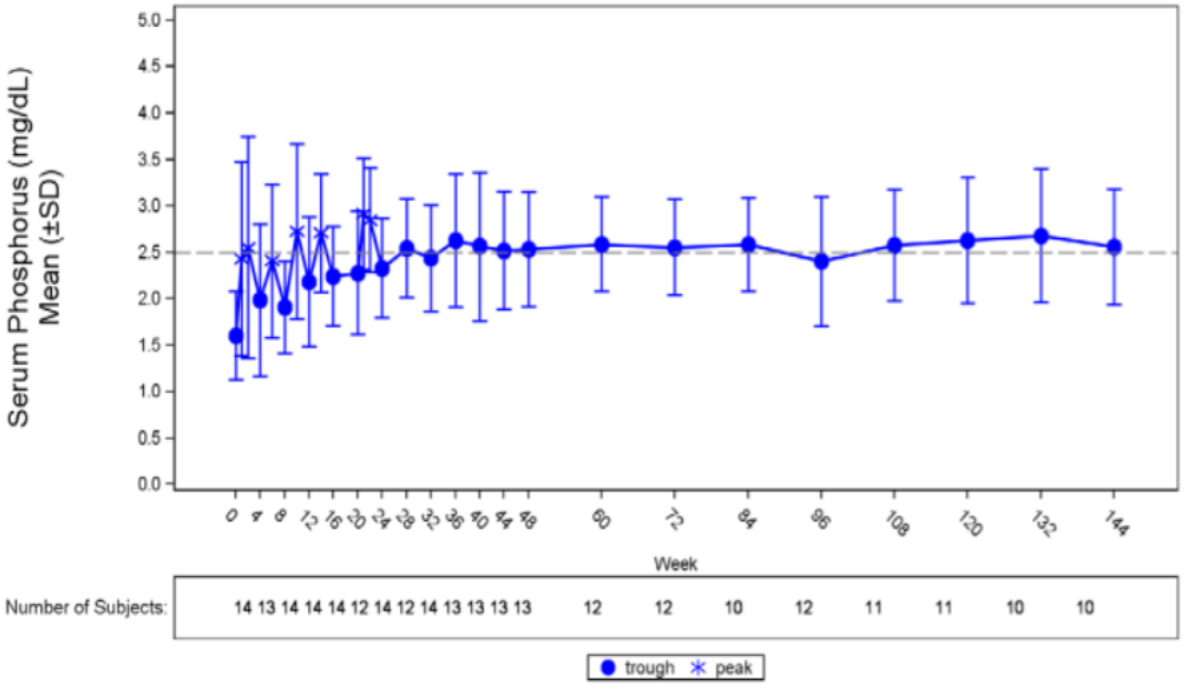
weeks prior to study enrollment. Patients received Crysvita every 4 weeks at a weight based starting dose of 0.3 mg/kg that was titrated to achieve a fasting serum phosphorus level of 2.5 to 4.0 mg/dL. The mean dose was 0.83 mg/kg at Week 20, 0.87 mg/kg at Week 48, 0.77 mg/kg at Week 96 and 0.71 mg/kg at Week 144.

Study 7 (NCT02722798) is a single-arm open-label study. In Study 7, 13 adult patients with a confirmed diagnosis of TIO received Crysvita. Of the 13 TIO patients who received treatment in Study 7, six were male, and patients ranged from 41 years to 73 years of age (Median 58.0 years). Oral phosphate and active vitamin D analogs were discontinued two weeks prior to study enrollment. Patients received Crysvita every 4 weeks at a weight based starting dose of 0.3 mg/kg that was titrated to achieve a fasting serum phosphorus level of 2.5 to 4.0 mg/dL. The mean (SD) dose was 0.91 (0.59) mg/kg at Week 48, and 0.96 (0.70) mg/kg at Week 88.

Serum Phosphorus

In Study 6, Crysvita increased mean (SD) serum phosphorus levels from 1.60 (0.47) mg/dL at baseline to 2.64 (0.76) mg/dL averaged across the midpoint of dose intervals through Week 24 with 50% of patients (7/14) achieving a mean serum phosphorus level above the LLN averaged across the midpoint of dose intervals through Week 24. Increase in the mean serum phosphorus concentrations was sustained near or above the LLN through Week 144 (Figure 3). The ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) increased in these patients from a mean (SD) of 1.12 (0.54) mg/dL at baseline to 2.12 (0.64) mg/dL at Week 48 and remained stable through Week 144.

Figure 3: Serum Phosphorus Concentration and Change from Baseline in Study 6 (mg/dL)



The dotted line represents the lower limit of normal (2.5 mg/dL) for patients in study 6.

In Study 7, Crysvita increased mean (SD) serum phosphorus levels from 1.62 (0.49) mg/dL at baseline to 2.63 (0.87) mg/dL averaged across the midpoint of dose intervals through Week 24 with 69% of patients (9/13) achieving a mean serum phosphorus level above the LLN averaged across the midpoint on dose interval through Week 24. Mean serum phosphorus concentrations were sustained above LLN through Week 88. The renal phosphate reabsorptive capacity, as assessed by TmP/GFR, increased from a mean (SD) of 1.15 (0.43) mg/dL at baseline to 2.30 mg/dL (0.48) mg/dL at Week 48.

Bone Histomorphometry

In Study 6, osteomalacia was present at baseline in nine out of 11 patients with paired bone biopsies, and healing was assessed after 48 weeks of treatment. In these 9 patients with osteomalacia at baseline, OV/BV decreased from a mean (SD) score of 21.2% (19.9) at baseline to 13.9% (16.7), a change of -34%. O.Th declined from a mean (SD) of 18.9 (11.9) micrometers to 12.1 (10.1) micrometers, a change of -36%. MLt declined in 3 patients from a mean (SD) of 667 (414) days to 331 (396) days, a change of -50%.

In Study 7, osteomalacia was present at baseline in all 3 patients with paired bone biopsies, and healing was assessed after 48 weeks of treatment. In these 3 patients, OV/BV decreased from a mean (SD) score of 14.0% (15.2) at baseline to 9.2% (5.5), a change of -34%. O.Th declined from a mean (SD) of 16.0 (13.7) micrometers to 13.5 (7.1) micrometers, a change of -16%.

Radiographic Evaluation of Osteomalacia

In Study 6, ^{99m}technetium-labelled whole body bone scans were performed at baseline and subsequent timepoints during the study on all 14 patients. Bone scans allow for assessment of sites of increased tracer uptake in a wide range of bone conditions, including osteomalacia. In patients with TIO, increased tracer uptake on bone scan is presumed to be nontraumatic fractures and pseudofractures. At baseline, all patients had areas of tracer uptake with a total of 249 bone abnormalities across 14 patients. The number of areas of tracer uptake decreased from Week 48 through Week 144, suggesting healing of the bone abnormalities.

Professional Guidelines and Position Statements

International Working Group

In 2025, the International Working Group created the practice guidelines for the management of XLH (6) which states the diagnosis of XLH is based on integrating clinical evaluation, laboratory findings confirming renal phosphate wasting (following exclusion of conditions mimicking XLH), and skeletal imaging. Fibroblast growth factor 23 measurement and DNA (deoxyribonucleic acid) analysis are of value in the diagnosis, if available. Pathogenic or likely pathogenic variants in the PHEX gene are confirmatory. The guideline recommends “confirming the clinical diagnosis of XLH by genetic analysis in children and adults, if available (grade B, moderate recommendation).”

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0584

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. Prescribing Label: Crysvita (burosumab-twza) injection, for subcutaneous use. Aug 2025. Available at: <https://www.accessdata.fda.gov> (accessed January 14, 2026).

Other:

2. Scheinman S, Carpenter T. Hereditary hypophosphatemic rickets and tumor-induced osteomalacia. In: UpToDate, Kremen J. (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 14, 2026).
3. Florenzano P, Gafni R, Collins M. Tumor-induced osteomalacia. Bone Rep. Sep 2017; (7):90-97. PMID 29021995
4. FDA – FDA News release: FDA approves first therapy for rare disease that causes low phosphate blood levels, bone softening. Food and Drug Administration (Jun 2020). Available at: <https://www.prnewswire.com> (accessed January 14, 2026).
5. Crysvita FDA approval history. (June 2020). Available at: <https://www.drugs.com> (accessed January 14, 2025).
6. Khan A, Ali D, Appelman-Dijkstra N, et al. X-linked hypophosphatemia management in adults: An international working group clinical practice guideline. J Clin Endocrinol Metab. Jul 15, 2025; 110(8):2353-2370. PMID 40243526

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
04/01/2026	Document updated. Coverage unchanged. Added reference 6; others updated.
10/01/2025	Document updated with literature review. The following changes were made in Coverage: 1) Revised criteria for both X-linked hypophosphatemia (XLH) and for tumor-induced osteomalacia (TIO) to align with the FDA label; 2) Removed both initial and continued therapy distinctions; and 3) Updated existing experimental, investigational and/or unproven statement to include "for the treatment of all other non-Food and Drug Administration (FDA) approved indications". No new references; others updated and 1 removed.
04/01/2024	Document updated with literature review. Coverage unchanged. No new references added; others updated.
05/01/2023	Reviewed. No changes.
12/01/2022	Document updated with literature review. Coverage unchanged. No new references added; some updated.
07/01/2021	Reviewed. No changes.
09/01/2020	Document updated with literature review. The following changes were made in Coverage: 1) Initial therapy for X-linked hypophosphatemia: A) Changed age requirement from " 1 year of age and older" to "6 months of age or older", B) Added "Documented failure, contraindication, or intolerance to therapy or not a candidate for management with oral phosphate and calcitriol"; 2) Added conditional criteria for initial therapy for Burosumabtwza for up to 12 months duration in patients 2 years of age and older for the treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors; 3) Added NOTE 1: If a patient undergoes treatment of the underlying tumor (i.e., surgical excision or radiation therapy) treatment should be interrupted and serum phosphorus reassessed after treatment has been completed; 4) Removed "In patients 1 year of age and older for the treatment of XLH" from the continuation of therapy criteria. Added references 2-6. Title changed from Burosumab-twza (Crysvita).
01/01/2019	New medical document. Burosumab-twza (Crysvita) for the treatment of Xlinked hypophosphatemia (XLH) may be considered medically necessary when conditional criteria is met. Burosumab-twza (Crysvita) is considered experimental, investigational and/or unproven when the criteria for initial or continued therapy are not met.