

Drug and Biologic Coverage Policy



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Coverage Policy Number M0002

Burosumab-twza

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Related Coverage Resources

[Genetic Testing for Hereditary and Multifactorial Conditions](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Burosumab-twza (Crysvita®) is considered medically necessary when ONE of the following criteria are met:

- I. Diagnosis of X-Linked Hypophosphatemia and ALL of the following criteria:
 - Documented by ONE of the following:
 - Genetic test confirming pathogenic or likely pathogenic variant in *PHEX* gene
 - Elevated* FGF23 levels consistent with X-linked hypophosphatemia
 - Pretreatment tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) below the normal range for age and gender
 - Individual has had a baseline (prior to any XLH treatment [for example, Crysvita, oral phosphate/vitamin D therapy]) serum phosphorus level that was below the normal range for age
 - Prescribed by or in consultation with an endocrinologist, geneticist, nephrologist, or a physician who specializes in X-linked hypophosphatemia
 - For individuals 18 years of age and older only, ALL of the following:
 - Current signs and symptoms of X-linked hypophosphatemia (for example, musculoskeletal pain, muscle stiffness, muscle weakness, impaired mobility and bone fractures)

- Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for management with oral phosphate and calcitriol

II. Diagnosis of Tumor-Induced Osteomalacia and ALL of the following criteria are met:

- Individual is 2 years of age or older
- Individual has a mesenchymal tumor that cannot be curatively resected or identified/localized
- Per the health care professional, the individual is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia (for example, bone pain, impaired mobility, muscle weakness, and fatigue)
- Individual has had a baseline (prior to any tumor-induced osteomalacia treatment [for example, Crysvida, oral phosphate/vitamin D therapy]) serum phosphorus level that was below the normal range for age
- Pretreatment tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) was below the normal range for age and gender
- Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for management with oral phosphate and calcitriol
- Prescribed by or in consultation with an endocrinologist, nephrologist, or a physician who specializes in tumor-induced osteomalacia

*Above the reference range for the lab

For X-Linked Hypophosphatemia, Burosumab-twza (Crysvida) is considered medically necessary for continued use in individuals 18 years of age and older when the following is met:

- Documentation of positive clinical response from pre-treatment baseline status with burosumab-twza (Crysvida) (for example, increased phosphorus levels, reduction in musculoskeletal pain, improved mobility or decrease in bone fractures).

Initial and reauthorization is up to 12 months.

For Tumor-Induced Osteomalacia, Burosumab-twza (Crysvida) is considered medically necessary for continued use when the following are met:

- Documentation of beneficial response (for example, increased phosphorus levels, decreased symptoms of bone pain and/or muscle weakness, and increased mobility)

Initial authorization is for 6 months. Reauthorization is for 1 year.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Burosumab (Crysvida) is considered experimental, investigational or unproven for ANY other use including the following:

- Chronic Kidney Disease (CKD), Severe Renal Impairment or End Stage Renal Disease
- Epidermal Nevus Syndrome (ENS)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

FDA Approved Indications

FDA Approved Indication

Crysvida, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for¹:

- **X-linked hypophosphatemia** in patients ≥ 6 months of age.

Tumor-induced osteomalacia, for treatment of FGF-related hypophosphatemia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients ≥ 2 years of age.

Background

Disease Overview

X-Linked Hypophosphatemia

X-linked Hypophosphatemia (XLH) is a dominant inherited disease of renal phosphate wasting. (Carpenter, 2011, Scheinman 2019, Bacon, 2018) While it is rare, it is the most common form of hereditary rickets and is estimated to occur in one out of every 20,000 live births. The pathogenesis of XLH is not fully understood; however, an inactivating genetic mutation in phosphate regulating endopeptidase on the X chromosome (PHEX) leads to elevated FGF23. Increased levels of FGF23 increased renal excretion of phosphate and abnormal regulation of vitamin D metabolism. Patients with XLH experience hypophosphatemic rickets (or osteomalacia [i.e., accumulation of unmineralized osteoid/softening of the bones]). (Carpenter, 2011, Scheinman, 2019, Ruppe, 2019) The majority of patients present in the first 2 years of life with bowing deformities of the lower extremities and short stature. In adults, the primary symptom in adults is enthesopathy (i.e., calcification of tendons, ligaments, and joint capsules), which is associated with joint pain and impaired mobility. These patients may also experience spontaneous dental abscesses, stress fractures, and sensorineural hearing loss. The XLH diagnosis can be established in patients with a low serum phosphate concentration, a reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR), an inappropriate calcitriol level for the severity of hypophosphatemia, and/or by identification on molecular genetic testing of a hemizygous PHEX pathogenic variant in a male patient or a heterozygous PHEX pathogenic variant in a female patient. (Carpenter, 2011, Scheinman 2019, Ruppe, 2019) Genetic testing is estimated to identify mutations in the PHEX gene in approximately 70% of patients with hypophosphatemic rickets and 85% to 90% of patients who have familial hypophosphatemic rickets. (Rothenbuhler, 2019)

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia is an extremely rare condition caused by tumors that produce the phosphaturic hormone FGF23. (Florenzano, 2020) Elevated FGF23 causes renal phosphate wasting, which ultimately leads to hypophosphatemia, rickets, and osteomalacia. Tumor-induced osteomalacia is generally caused by small, slow-growing, benign phosphaturic mesenchymal tumors; complete resection of the tumor results in cure. However, in some cases, locating the tumor is not possible or the tumor may be inoperable. Patients usually present in adulthood with symptoms of fatigue, muscle weakness, and pain. (Ultragenyx data on file, 2020) They may also experience decreased bone mineral density and frequent fractures. Current treatment of patients with inoperable or unidentifiable tumors has been phosphate supplementation and active vitamin D.

Age-Based Normal Serum Phosphate Reference Intervals (Lockitch, 1988)

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

Information regarding TmP/GFR calculation

1. Use the urine and plasma creatinine, and also urine and plasma phosphate to calculate TRP using the formula provided below.

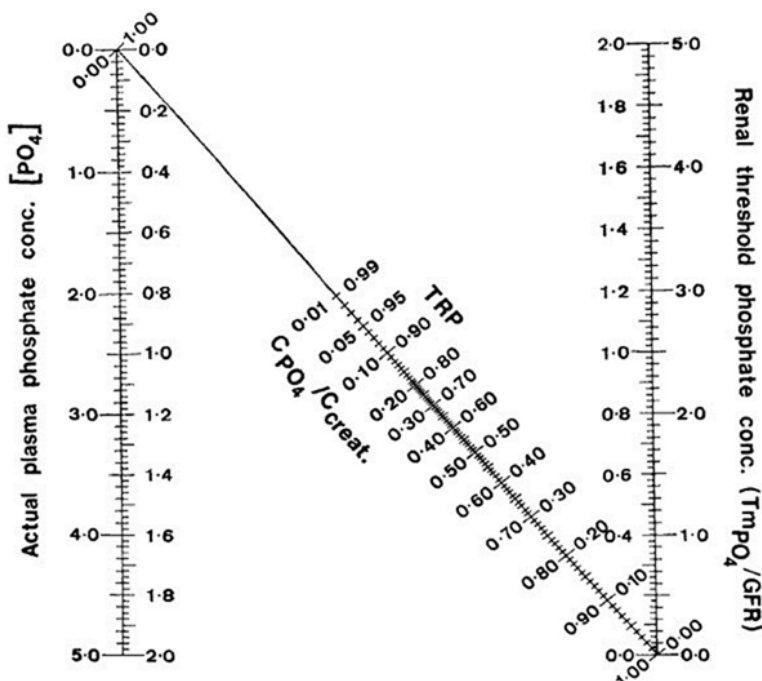
To use the nomogram, first calculate the tubular resorption of phosphate (TRP) as follows:

- $TRP = 1 - [(urine_{phosphate} / plasma_{phosphate}) / (urine_{creatinine} / plasma_{creatinine})]$

When the TRP is less than 0.86, the TmP/GFR can be calculated directly using the following equation:

- $TmP/GFR = TRP \times Plasma_{phosphate}$

- Chart the plasma phosphate level and calculated TRP on the nomogram below and draw a line through the data points to determine the TmP/GFR.



Nomogram for calculation of the tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) utilizing the plasma phosphate concentration and the calculated tubular resorption of phosphate (Walton & Bijvoet, 1975):

- $(\text{urinary phosphate} \times \text{serum creatinine}) / (\text{serum phosphate} \times \text{urinary creatinine})$
- Use the chart of age-based normal values to determine whether TmP/GFR is below normal range.

Age-Based Normal TmP/GFR Reference Intervals (Payne, 1993)

Age	Sex	Range (mg/dL)	Range (mmol/L)
Birth	Both	3.6 - 8.6	1.43 - 3.43
3 mos	Both	3.7 - 8.25	1.48 - 3.30
6 mos	Both	2.9 - 6.5	1.15 - 2.60
2-15 yrs	Both	2.9 - 6.5	1.15 - 2.44
25-35 yrs	Male	2.5 - 3.4	1.00 - 1.35
25-35 yrs	Female	2.4 - 3.6	0.96 - 1.44
45-55 yrs	Male	2.2 - 3.4	0.90 - 1.35
45-55 yrs	Female	2.2 - 3.6	0.88 - 1.42
65-75 yrs	Both	2.0 - 3.4	0.80 - 1.35

Clinical Efficacy

X-Linked Hypophosphatemia

The efficacy of Crysvisa for the treatment of X-linked hypophosphatemia was evaluated in several clinical in pediatric and adult patients with X-linked hypophosphatemia. (Crysvisa Prescribing Information, 2020) Eligible patients had baseline serum phosphorus levels less than the lower limit of normal for age. (Carpenter, 2018, Whyte,

2019, Insogna, 2018) Across the studies, Crysvita was found to increase mean serum phosphorus levels significantly from baseline. Radiographic improvements and healing of fractures/pseudofractures were also observed. In a single-arm extension of the adult study, normalization of serum phosphorous was maintained during an additional 24 weeks of Crysvita therapy. (Portale, 2019) Improvements in healing of fractures/pseudofractures were also observed. One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia. (Imel, 2019) Following 64 weeks of therapy, patients receiving Crysvita had demonstrated a significantly greater improvement in the Radiographic Global Impression of Change global score compared with the conventional therapy group.

Tumor-Induced Osteomalacia

Two studies evaluated the efficacy of Crysvita in patients with tumor-induced osteomalacia. (Crysvita Prescribing information, Ultragenyx data on file, 2020) Eligible patients were adults with a confirmed diagnosis of FGF-23-related hypophosphatemia produced by an underlying tumor that was not amenable to surgical excision or could not be located. In addition to low baseline serum phosphorus, patients were also required to have a low tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) and a high FGF23 level. The vast majority of patients had previously received phosphate and active vitamin D therapy. Crysvita was found to increase the mean serum phosphorus level from baseline through Week 24 (Month 6) when levels stabilized. These increases were sustained near or above the lower limit of normal through Week 144.

Professional Societies/Organizations

X-Linked Hypophosphatemia

In 2019, an expert panel published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia. (Imel, 2019) This document recommends treatment with oral phosphate and active vitamin D (e.g., calcitriol) for symptomatic adults with X-linked hypophosphatemia. Crysvita therapy should be considered for the treatment of adults with X-linked hypophosphatemia with the following features: persistent bone/joint pain due to X-linked hypophosphatemia and/or osteomalacia that limits daily activities; pseudofractures or osteomalacia-related fractures; and insufficient response or refractory to oral phosphate and active vitamin D. If patients experience complications related to oral phosphate and active vitamin D, Crysvita is recommended as well.

Off Label Uses

AHFS Drug Information 2019 Edition supports no off-label uses of Crysvita.

Experimental, Investigational, Unproven Uses

Chronic Kidney Disease (CKD), Severe Renal Impairment or End Stage Renal Disease

Crysvita is contraindicated in patients with severe renal impairment or end stage renal disease (ESRD). (Crysvita Prescribing Information, 2011) These patients often have abnormal mineral metabolism which may be associated with FGF23. However, Crysvita has not been studied for the treatment of patients with CKD who have elevations of FGF23 impacting phosphate regulation. (Crysvita Prescribing Information, 2011, US National Institutes of Health, 2000)

Epidermal Nevus Syndrome (ENS)

A Phase II single-arm, open-label, dose-finding study (unpublished) included 16 adult patients with tumor induced osteomalacia (TIO) [n = 15] or ENS (n = 1) with hypophosphatemia and an elevated FGF23. (Jan de Beur, 2017) Crysvita Q4W improved mean serum phosphorus levels and increased markers of bone turnover (as measured by biopsy) at Weeks 16 and 24. More data are necessary to establish the efficacy and safety of Crysvita in patients with ENS.

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed

above are met:

HCPCS Codes	Description
J0584	Injection, burosumab-twza, 1 mg

*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.

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