Effective Date **12/1/2023**
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Coverage Policy Number **IP0285**

Burosumab

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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.

Overview

This policy supports medical necessity review for burosumab-twza (Crysvita®).

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

Medical Necessity Criteria

Burosumab-twza (Crysvita) is considered medically necessary when ONE of the following is met (1 or 2):

1. **Tumor-Induced Osteomalacia.** Individual meets **ALL** of the following criteria (A, B, C, D, E, F and G):
   A. 2 years of age or older
   B. Presence of mesenchymal tumor that cannot be curatively resected or identified/localized
   C. According to the prescriber, the individual is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia
   D. Individual has had a baseline serum phosphorus level that was below the normal range for age

E. Pretreatment tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) was below the normal range for age and gender
F. Documented inadequate response, contraindication or intolerance to oral phosphate therapy, calcitriol therapy, or both
G. The medication is prescribed by or in consultation with an endocrinologist, nephrologist, or a physician who specializes in tumor-induced osteomalacia

Dosing for Tumor-Induced Osteomalacia. The maximum dose is 180 mg subcutaneously, every 2 weeks.

2. **X-Linked Hypophosphatemia.** Individual meets **ALL** of the following criteria (A, B, C, and D):
   A. Has had a baseline serum phosphorus level that was below the normal range for age
   B. Documented diagnosis confirmed by **ONE** of the following (i, ii, or iii)
      i. Genetic test confirming pathogenic or likely pathogenic variant in *PHEX* gene
      ii. Elevated FGF23 levels consistent with X-linked hypophosphatemia
      iii. Pretreatment tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) below the normal range for age and gender
   C. If the individual is 18 years of age or older, the individual meets **BOTH** of the following additional criteria (i and ii):
      i. According to the prescriber, the individual is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia
      ii. Documented inadequate response, contraindication or intolerance to oral phosphate therapy, calcitriol therapy, or both
   D. Medication is prescribed by or in consultation with an endocrinologist, geneticist, nephrologist, or a physician who specializes in X-linked hypophosphatemia

   Dosing for X-Linked Hypophosphatemia. ONE of the following dosing regimens (A or B):
   A. If 18 years of age or older, the maximum dose is 90 mg subcutaneously, every 4 weeks.
   B. If less than 18 years of age, the maximum dose is 90 mg subcutaneously, every 2 weeks.

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.

Reauthorization Criteria

Burosumab-twza (Crysvita) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response

Authorization Duration

Initial approval duration:
- **Tumor-Induced Osteomalacia**: up to 6 months
- **X-Linked Hypophosphatemia**: up to 12 months

Reauthorization approval duration:
- **Tumor-Induced Osteomalacia**: up to 12 months
- **X-Linked Hypophosphatemia**: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Chronic Kidney Disease, Severe Renal Impairment or End Stage Renal Disease.**
   Crysvita is contraindicated in individuals with severe renal impairment or end stage renal disease.[1] These individuals often have abnormal mineral metabolism which may be associated with FGF23. However, Crysvita has not been studied for the treatment of individuals with chronic kidney disease who have elevations of FGF23 impacting phosphate regulation.[1,9]

2. **Epidermal Nevus Syndrome.**
   More data are necessary to establish the efficacy and safety of Crysvita in individuals with epidermal nevus syndrome. Individuals with epidermal nevus syndrome were eligible to enroll in one of the Phase II tumor-induced osteomalacia studies of Crysvita.[15] However, no individuals with epidermal nevus syndrome enrolled.

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

Background

OVERVIEW

Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for[1]:

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

Disease Overview

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia is an extremely rare condition caused by tumors that produce the phosphaturic hormone FGF23, which causes renal phosphate wasting, and 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 bone pain, which can lead to impaired mobility.[8] 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 (e.g., calcitriol).

X-Linked Hypophosphatemia

X-linked hypophosphatemia is a condition that is believed to result from an inactivating genetic mutation in phosphate regulating endopeptidase on the X chromosome (PHEX).[2-5] This mutation leads to increased levels of FGF23, which increases phosphate excretion and abnormal vitamin D metabolism, ultimately leading to hypophosphatemic rickets.[2-4,6] Signs and symptoms of X-linked hypophosphatemia differ in pediatric patients who are still growing vs. adults whose epiphyseal plates have fused. In adults, symptoms include calcification of tendons, ligaments, and joint capsules; joint pain; impaired mobility; spontaneous dental abscesses; stress fractures; and sensorineural hearing loss. The X-linked hypophosphatemia 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. Genetic testing can provide a negative or positive confirmation in 70 to 90% of patients with suspected X-linked hypophosphatemia who lack a family history.[5] If a genetic test is unavailable, an elevated FGF23 level can also support the diagnosis. However, FGF23 levels may be influenced by other factors, particularly phosphate and vitamin D therapy. FGF23 levels may be elevated in several other forms of hypophosphatemic rickets as well. Finally, the normal range of FGF23 varies according to the assay used.

Clinical Efficacy

Tumor-Induced Osteomalacia

Two studies evaluated the efficacy of Crysvita in patients with tumor-induced osteomalacia.[1,14,15] Eligible patients were adults 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. 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.

X-Linked Hypophosphatemia

The efficacy of Crysvita for the treatment of X-linked hypophosphatemia was evaluated in several clinical trials in pediatric and adult patients with X-linked hypophosphatemia.[1] Eligible patients had baseline serum phosphorus levels less than the lower limit of normal for age.[1,9-11] 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. Sustained efficacy has been demonstrated out to Week 96.[12,16] One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia.[13] 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. In patients 5 to 12 years of age, sustained efficacy has been observed for up to 160 weeks, while there are extension data up to 168 weeks in adults.[17-19]

GUIDELINES

An expert panel has published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia (2019).[5] It is recommended that a clinical diagnosis of X-linked hypophosphatemia be confirmed by genetic analysis of the PHEX gene if feasible. In regard to treatment, oral phosphate and active vitamin D (e.g., calcitriol) are recommended 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.

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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.

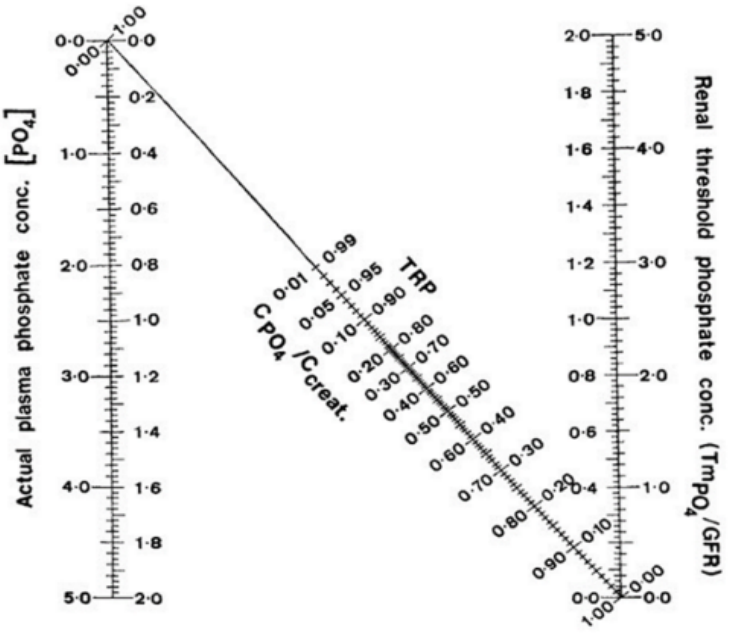
To use the nomogram, first calculate the tubular resorption of phosphate (TRP) as follows:

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

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

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

2. 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):

- (urinary phosphate x serum creatinine)/(serum phosphate x 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

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