Effective Date.....**12/15/2024**
Coverage Policy Number.....**IP0285**

Burosumab

Table of Contents

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 (including Cutaneous Skeletal Hypophosphatemia Syndrome)**. More data are necessary to establish the efficacy and safety of Crysvita in patients with epidermal nevus syndrome. Patients with epidermal nevus syndrome were eligible to enroll in one of the Phase II tumor-induced osteomalacia studies of Crysvita.[9] However, no patients with epidermal nevus syndrome enrolled. There are a few case reports of Crysvita in patients with cutaneous skeletal hypophosphatemia syndrome (a variant of epidermal nevus syndrome).[21,22] However, more data are needed to support the use of Crysvita for this indication.

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.[2] 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. They may also experience decreased bone mineral density and frequent fractures. 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).[3-6] This mutation leads to increased levels of FGF23, which increases phosphate excretion and abnormal vitamin D metabolism, ultimately leading to hypophosphatemic rickets.[3-5,7] 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.[6] 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.[1,8,9] 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 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.[1,10-12] 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.[13,14] One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia.[15] 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.[16-19]

GUIDELINES

Tumor-Induced Osteomalacia

An expert panel published global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia in 2023.[20] In patients who present with chronic muscle pain or weakness, fragility fractures, or bone pain, a serum phosphate measurement is recommended, along with a physical examination to establish features of myopathy and to identify masses that could potentially be causative tumors. Several other laboratory tests are recommended as well, including urine/serum phosphate, TmP/GFR, alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, $1,25(OH)_2D$, and FGF23 (may be elevated or inappropriately normal). It is recommended that patients be referred to a specialist for diagnosis confirmation if tumor-induced

osteomalacia is suspected. Tumor resection is recommended, but if the tumor is unresectable or unidentifiable, treatment with phosphate and active vitamin D or Crysvita is recommended.

X-Linked Hypophosphatemia
An expert panel has published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia (2019).[6] 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.

Coding 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

References

1. Crysvita® injection [prescribing information]. Bedminster, NJ/Novato, CA: Kyowa/Ultragenyx; June 2020.
2. Data on file. Tumor-induced osteomalacia (TIO): mechanism of disease. Ultragenyx; July 2020.
3. Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to x-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388.
4. Scheinman SJ, Drezner MK. Hereditary hypophosphatemic rickets and tumor-induced osteomalacia. UpToDate, Inc. Available at: www.uptodate.com. Updated May 11, 2023. Accessed on July 24, 2024.
5. Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. *Ther Adv Chronic Dis*. 2018; 9:51-60.
6. Haffner D, Francesco E, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphatemia. *Nat Rev Nephrol*. 2019;15(7):435-455.
7. Laurent MR, Harvengt P, Mortier GR, et al. X-linked hypophosphatemia. GeneReviews®. Available at: https://www.ncbi.nlm.nih.gov/books/NBK83985/. Updated December 14, 2023. Accessed on July 24, 2024.
8. Jan de Beur SM, Miller PD, Weber TJ, et al. Burosumab for the treatment of tumor-induced osteomalacia. *J Bone Miner Res*. 2021;36(4):627-635.
9. Imanishi Y, Ito N, Rhee Y, et al. Interim analysis of a phase 2 open-label trial assessing burosumab efficacy and safety in patients with tumor-induced osteomalacia. *J Bone Miner Res*. 2021;36(2):262-270.

10. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. *N Engl J Med*. 2018;378(21):1987-1998.
11. Whyte MP, Carpenter TO, Gottesman GS, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicenter, open-label, phase 2 trial. *Lancet Diabetes Endocrinol*. 2019;7(3):189-199.
12. Insogna KL, Briot K, Imel EA, et al. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res*. 2018;33(8):1383-1393.
13. Portale AA, Carpenter TO, Brandi ML, et al. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int.* 2019;105(3):271-284.
14. Briot K, Portale AA, Brandi ML, et al. Burosumab treatment in adults with X-linked hypophosphatemia: 96-week patient-reported outcomes and ambulatory function from a randomized phase 3 trial and open-label extension. *RMD Open*. 2021;7(3): e001714.
15. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomized, active-controlled, open-label, phase 3 trial. *Lancet*. 2019; 393:2416-2427.
16. Linglart A, Imel EA, Whyte MP, et al. Sustained efficacy, and safety of burosumab, a monoclonal antibody to FGF23, in children with X-linked hypophosphatemia. *J Clin Endocrinol Metab*. 2022;107(3):813-824.
17. Weber TJ, Imel EA, Carpenter TO, et al. Long-term burosumab administration is safe and effective in adults with X-linked hypophosphatemia. *J Clin Endorinol Metab*. 2022;108(1):155-165.
18. Kamenicky P, Briot K, Brandi ML, et al. Benefit of burosumab in adults with X-linked hypophosphataemia (XLH) is maintained with long-term treatment. *RMD Open*. 2023;9(1): e002676.
19. Ward LM, Hogler W, Glorieux FH, et al. Burosumab vs. conventional therapy in children with X-linked hypophosphatemia: results of the open-label, phase 3 extension period. *JBMR Plus*. 2024;8(1): ziad001.
20. Jan de Beur SM, Minisola S, Xia WB, et al. Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia. *J Intern Med*. 2021;293(3):309-328.
21. Sugarman J, Maruri A, Hamilton DJ, et al. The efficacy and safety of burosumab in two patients with cutaneous skeletal hypophosphatemia syndrome. *Bone*. 2023; 166:116598.
22. Merz LM, Buerger F, Ziegelasch N, et al. A case report: first long-term treatment with burosumab in a patient with cutaneous-skeletal hypophosphatemia syndrome. *Front Endocrinol (Lausanne)*. 2022; 13:866831.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Updated** review date, disclaimer, refreshed background and references, addition of change history. **Conditions Not Recommended for Approval:** Epidermal Nevus Syndrome was clarified to include Cutaneous Skeletal Hypophosphatemia Syndrome.	12/15/2024

The policy effective date is in force until updated or retired.