PHARMACY POLICY STATEMENT
North Carolina Marketplace

DRUG NAME	Crysvita (burosumab-twza)
BILLING CODE	J0584
BENEFIT TYPE	Medical
SITE OF SERVICE ALLOWED	Home, Office
STATUS	Prior Authorization Required

Crysvita is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for: 1) The treatment of X-linked hypophosphatemia (XLH), and 2) The treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors (PMT) that cannot be curatively resected or localized.
XLH is a rare, inherited form of rickets with renal phosphate wasting caused by excessive FGF23 activity that results from mutations of the PHEX gene. Phosphorus is essential for bone mineralization. Crysvita binds to and inhibits the activity of FGF23, restoring renal phosphate reabsorption and increasing the serum concentration of 1,25 dihydroxy vitamin D to repair the skeleton.
TIO, also known as oncogenic osteomalacia, is a rare, acquired hypophosphatemic osteomalacia. TIO is characterized by phosphate wasting caused by a tumor that secretes FGF23. Cure is possible if the tumor can be removed, but often it cannot be localized.

Crysvita (burosumab-twza) will be considered for coverage when the following criteria are met:

X-Linked Hypophosphatemia (XLH)

For **initial** authorization:

1. Member is 6 months old or older; AND
2. Medication must be prescribed by or in consultation with an endocrinologist, nephrologist, or rheumatologist; AND
3. Member has a diagnosis of XLH confirmed by at least one of the following:
   a) PHEX (Phosphate regulating gene with homology to endopeptidases located on the X chromosome) mutation per genetic testing
   b) Family history positive for XLH (first-degree relative)
   c) Elevated plasma levels of intact fibroblast growth factor 23 (FGF23); AND
4. Lab results show fasting serum phosphorus level BELOW the reference range for age; AND
5. Member has chart notes documenting one of the following:
   a) Pediatric: Radiographic evidence of active bone disease including rickets and/or lower extremity bowing
   b) Adult: Persistent bone and/or joint pain due to XLH and/or osteomalacia that limits daily activities; pseudofractures or osteomalacia-related fractures; AND
6. Member is refractory to or develops complications from conventional treatment with phosphate and active vitamin D (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol); AND
7. Member does NOT have any of the following:
   a) Concurrent use of oral phosphate and active vitamin D analogs

b) Severe renal impairment or ESRD.

8. **Dosage allowed/Quantity limit:**
   Adult XLH (18 years of age and older): 1 mg/kg to the nearest 10 mg up to a maximum dose of 90 mg subQ every four weeks.
   Pediatric XLH (6 months to less than 18 years): For members who weigh < 10 kg, starting dose is 1 mg/kg to the nearest 1 mg, subQ every two weeks. For members who weigh 10 kg or greater, starting dose is 0.8 mg/kg to the nearest 10 mg, subQ every two weeks. The minimum starting dose is 10 mg up to a maximum of 90 mg. Dose may be increased up to 2 mg/kg (max 90 mg), every two weeks.
   QL: 6 vials per 28 days

If all the above requirements are met, the medication will be approved for 6 months.

For **reauthorization**:

1. Lab results show an improved serum phosphorus level compared to baseline; AND
2. Chart notes have been provided that show the member has improvement of signs and symptoms of disease (e.g., severity of rickets, linear growth, reduced pain/stiffness, fracture healing, physical function [6MWT]); AND
3. Member is not taking oral phosphate or active vitamin D analogs; AND
4. Member does not have severe renal impairment or ESRD.

If all the above requirements are met, the medication will be approved for an additional 12 months.

Tumor-Induced Osteomalacia (TIO)

For **initial** authorization:

1. Member is 2 years old or older; AND
2. Medication must be prescribed by or in consultation with an oncologist, endocrinologist, nephrologist, or rheumatologist; AND
3. Member has chart notes showing a diagnosis of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO); AND
4. The tumor is not amenable to surgical excision or cannot be localized; AND
5. Chart notes show elevated fibroblast growth factor 23 (FGF23); AND
6. Lab results show fasting serum phosphorus level below the normal range for age; AND
7. Pretreatment renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR ratio) is below the normal range for age; AND
8. Member does not have ANY of the following:
   a) Concurrent use of oral phosphate and active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol);
   b) Severe renal impairment or ESRD.
9. **Dosage allowed/Quantity limit:**
   Adult TIO (18 years and older): Starting dosage: 0.5 mg/kg, rounded to nearest 10 mg, up to a max of 180mg subQ every 4 weeks; Maximum dosage: 2 mg/kg not to exceed 180 mg every 2 weeks.
   Pediatric TIO (2 to less than 18 years): Starting dosage: 0.4 mg/kg, rounded to nearest 10 mg, up to 180mg subQ every 2 weeks; Maximum dosage: 2 mg/kg not to exceed 180 mg every 2 weeks.
   QL: 12 vials per 28 days

If all the above requirements are met, the medication will be approved for 6 months.

For **reauthorization**:

1. Lab results show an improved serum phosphorus level compared to baseline; AND
2. Chart notes demonstrate improvement of signs and symptoms of disease compared to baseline (e.g. bone pain, muscle weakness, fractures); AND
3. Member is not taking oral phosphate or active vitamin D analogs; AND
4. Member does not have severe renal impairment or ESRD.

If all the above requirements are met, the medication will be approved for an additional 12 months.

CareSource considers Crysvita (burosumab-twza) not medically necessary for the treatment of conditions that are not listed in this document. For any other indication, please refer to the Off-Label policy.

DATE	ACTION/DESCRIPTION
05/16/2018	New policy for Crysvita created.
09/26/2019	Kainos assay requirement for XLH diagnosis was removed. RSS score requirement was replaced with clinical finding requirement. Criteria about HIV presence, presence of hypocalcemia or hypercalcemia were removed.
09/21/2020	Added criteria for new indication of TIO. Revised XLH criteria: added rheumatology as an acceptable specialist, edited diagnostic confirmation to match clinical guideline by Haffner et al (added FGF23), simplified/summarized the section on radiologic and clinical findings, added trial of conventional therapy per guideline, changed exclusions to match TIO section, simplified and made slight correction to dosing, changed initial auth duration to be 6 months, modified the re-auth criteria to more closely match TIO.
03/08/2022	Transferred to new template. Updated references. Cleaned up the dosing sections and added QL. Added 'home' to SOC. TIO: Added oncology as specialist. Added reduced TmP/GFR ratio to initial criteria.

References:

1. Crysvita [package insert]. Novato, CA: Ultragenyx Pharmaceutical Inc.; June 2020.
2. ClinicalTrials.gov. Identifier: NCT 02537431. Open Label Study of KRN23 on Osteomalacia in Adults With X-linked Hypophosphatemia (XLH). Available at: https://clinicaltrials.gov/ct2/show/NCT02537431?term=02537431&rank=1.
3. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab Therapy in Children with X-Linked Hypophosphatemia. N Engl J Med 2018; 378:1987-1998. DOI: 10.1056/NEJMoa1714641.
4. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014;3(1):R13-R30. doi:10.1530/EC-13-0103
5. Carpenter TO. New perspectives on the biology and treatment of X-linked hypophosphatemic rickets. [Review] [109 refs]. Pediatr Clin North Am. 1997;44(2):443-466.
6. Foster BL, Ramnitz MS, Gafni RI, et al. Rare Bone Diseases and Their Dental, Oral, and Craniofacial Manifestations. J Dent Res. 2014;93(7):7S-19S. doi:10.1177/0022034514529150
7. Linglart A, Dvorak-Ewell M, Marshall A, Martin JS, Skrinar A. Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia (XLH). Int Conf Child Bone Heal. 2015:P198. doi:10.1530/boneabs.4.P198
8. Skrinar A, Marshall A, Martin JS, Dvorak-Ewell M. X-Linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Endocr Soc Meet. 2015:SAT-244. doi:doi:10.1210/endo-meetings.2015.BCHVD.11.SAT-244
9. Veilleux LN, Cheung M, Amor M Ben, Rauch F. Abnormalities in muscle density and muscle function in hypophosphatemic rickets. J Clin Endocrinol Metab. 2012;97(8). doi:10.1210/jc.2012-1336

10. Beck-Nielsen SS, Mughal Z, Haffner D, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019;14(1):58. doi:10.1186/s13023-019-1014-8.
11. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014;3(1). doi:10.1530/EC-13-0103.
12. Oncogenic osteomalacia. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/9652/tumor-induced-osteomalacia. Published October 19, 2017. Accessed September 22, 2020.
13. Zuo QY, Wang H, Li W, et al. Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients. *BMC Musculoskelet Disord*. 2017;18(1):403. Published 2017 Sep 21. doi:10.1186/s12891-017-1756-1
14. Ruppe MD. X-Linked Hypophosphatemia. 2012 Feb 9 [Updated 2017 Apr 13]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK83985/
15. Whyte MP, Carpenter TO, Gottesman GS, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *Lancet Diabetes Endocrinol*. 2019;7(3):189-199. doi:10.1016/S2213-8587(18)30338-3
16. 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. doi:10.1007/s00223-019-00568-3
17. 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. doi:10.1002/jbmr.3475
18. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial [published correction appears in *Lancet*. 2019 Jul 13;394(10193):120]. *Lancet*. 2019;393(10189):2416-2427. doi:10.1016/S0140-6736(19)30654-3
19. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nature Reviews Nephrology*. 2019;15(7):435-455. doi:10.1038/s41581-019-s0152-5
20. 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. doi:10.1210/clinem/dgab729
21. Dahir K, Zanchetta MB, Stanciu I, et al. Diagnosis and Management of Tumor-induced Osteomalacia: Perspectives From Clinical Experience. *J Endocr Soc*. 2021;5(9):bvab099. Published 2021 Jun 2. doi:10.1210/jendso/bvab099
22. 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. doi:10.1002/jbmr.4233
23. 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. doi:10.1002/jbmr.4184
24. Laurent MR, De Schepper J, Trouet D, et al. Consensus Recommendations for the Diagnosis and Management of X-Linked Hypophosphatemia in Belgium [published correction appears in Front Endocrinol (Lausanne). 2021 May 25;12:686401]. Front Endocrinol (Lausanne). 2021;12:641543. Published 2021 Mar 19. doi:10.3389/fendo.2021.641543

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