Clinical Policy: Burosumab-twza (Crysvita)

Reference Number: CP.PHAR.11
Effective Date: 09.01.18
Last Review Date: 08.22
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Burosumab-twza (Crysvita®) is a fibroblast growth factor 23 (FGF23) blocking antibody.

FDA Approved Indication(s)

Crysvita is indicated for the treatment of:

- X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.
- 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Crysvita is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. X-Linked Hypophosphatemia (must meet all)**:**

1. Diagnosis of XLH confirmed by one of the following (a or b):
   a. DNA testing confirms the presence of mutations in the *PHEX* gene;
   b. Elevated serum FGF23 levels;
2. Prescribed by or in consultation with an endocrinologist or metabolic disease specialist;
3. Age ≥ 6 months;
4. Current (within the last 30 days) serum phosphorus levels are one of the following (a or b):
   a. Below the reference range for age and gender (*use laboratory-specific reference ranges if available; otherwise, see Appendix D for ranges*), and member has not received oral phosphate or vitamin D replacement therapy and serum phosphorus;
   b. In normal range, but member remains symptomatic (e.g., rickets, growth impairment, musculoskeletal pain, bone fractures) despite currently receiving oral phosphate and/or vitamin D replacement therapy;
5. Presence of clinical signs and symptoms of the disease (e.g., rickets, growth impairment, musculoskeletal pain, bone fractures);
6. Crysvita is not prescribed concurrently with oral phosphate or vitamin D replacement therapy;

7. Dose does not exceed one of the following (a or b):
   a. Age 6 months to < 18 years: 2 mg/kg up to 90 mg every two weeks;
   b. Age ≥ 18 years: 1 mg/kg up to 90 mg every four weeks.

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Tumor-Induced Osteomalacia (must meet all)**:**
1. Diagnosis of TIO with confirmed elevated serum FGF23 levels;
2. Prescribed by or in consultation with an endocrinologist or metabolic disease specialist;
3. Age ≥ 2 years;
4. Failure of a ≥ 3 consecutive month trial of oral phosphate and vitamin D replacement therapy, unless contraindicated or clinically significant adverse effects are experienced;
5. Current (within the last 30 days) serum phosphorus levels are one of the following (a or b):
   a. Below the reference range for age and gender (*use laboratory-specific reference ranges if available; otherwise, see Appendix D for ranges*), and member has not received oral phosphate or vitamin D replacement therapy;
   b. In normal range, but member remains symptomatic (e.g., osteomalacia, muscle weakness, fatigue, bone pain, fractures) despite currently receiving oral phosphate and/or vitamin D replacement therapy;
6. Documentation confirms that the causative tumor(s) is/are not amenable to surgical excision or resection;
7. Crysvita is not prescribed concurrently with oral phosphate or vitamin D replacement therapy;
8. Documentation of member's current weight, for dose calculation purposes;
9. Dose does not exceed 2 mg/kg (maximum of 180 mg) every two weeks.

Approval duration:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. X-Linked Hypophosphatemia (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by both of the following (a and b):
   a. An increase in serum phosphorus levels from baseline and/or maintenance within the normal range for age and gender, not to exceed the upper limit of that normal range (*use laboratory-specific reference ranges if available; otherwise, see Appendix D for ranges*);
   b. A positive clinical response including any of the following: enhanced height velocity, improvement in skeletal deformities, reduction of fractures, reduction of generalized bone pain;
3. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Age 6 months to < 18 years: 2 mg/kg up to 90 mg every two weeks;
   b. Age ≥ 18 years: 1 mg/kg up to 90 mg every four weeks.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to member's renewal date, whichever is longer

B. Tumor-Induced Osteomalacia (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by both of the following (a and b):
   a. An increase in serum phosphorus levels from baseline and/or maintenance within the normal range for age and gender, not to exceed the upper limit of that normal range (*use laboratory-specific reference ranges if available; otherwise, see Appendix D for ranges*);
   b. Documentation confirms improvement in symptoms (e.g., osteomalacia, muscle weakness, fatigue, bone pain, fractures);

3. Documentation of member's current weight, for dose calculation purposes;
4. If request is for a dose increase, new dose does not exceed 2 mg/kg (maximum of 180 mg) every two weeks.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to member's renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
FGF23: fibroblast growth factor 23
TIO: tumor-induced osteomalacia
XLH: X-linked hypophosphatemia

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): concomitant use with oral phosphates and active vitamin D analogs, initiation of Crysvita therapy when serum phosphorus is within or above the normal range for age, severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.
- Boxed warning(s): none reported

Appendix D: General Information

- Laboratory-specific reference ranges for serum phosphorus levels should be used when available; otherwise, the age- and gender-based reference ranges found below may be used:

Females	Males
1-7 years: 4.3-5.4 mg/dL	1-4 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL	5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-4.9 mg/dL	14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL	16-17 years: 3.1-4.7 mg/dL
≥ 18 years: 2.5-4.5 mg/dL	≥ 18 years: 2.5-4.5 mg/dL

- For pediatric patients continuing on Crysvita therapy, if serum phosphorus is > 5 mg/dL, it is recommended to withhold the dose until the serum phosphorus level falls below the reference range per age.
- For adult patients continuing on Crysvita therapy, if serum phosphorus is above the upper limit of the normal range, it is recommended to withhold the dose until the serum phosphorus level falls below the reference range.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
XLH	**Pediatric XLH** • Weight < 10 kg: 1 mg/kg rounded to the nearest 1 mg, SC every two weeks • Weight ≥ 10 kg: 0.8 mg/kg rounded to the nearest 10 mg, SC every two weeks Increase dose up to approximately 2 mg/kg, SC every two weeks to achieve normal serum phosphorus. **Adult XLH** 1 mg/kg body weight rounded to the nearest 10 mg SC every four weeks. Crysvita should only be administered by a healthcare professional.	Pediatric XLH: 2 mg/kg up to 90 mg every two weeks Adult XLH: 1 mg/kg up to 90 mg every four weeks
TIO	**Pediatric TIO (2 years and older)** • Starting dose is 0.4 mg/kg of body weight rounded to the nearest 10 mg SC every two weeks • Dose may be increased up to 2 mg/kg **Adult TIO** • Starting dose is 0.5 mg/kg SC every four weeks • Dose may be increased up to 2 mg/kg	180 mg, administered every two weeks

VI. Product Availability

Single-dose vials for injection: 10 mg/mL, 20 mg/mL, 30 mg/mL

VII. References

1. Crysvita Prescribing Information. Novato, CA: Ultragenyx Pharmaceutical Inc; June 2020. Available at: www.crysvita.com. Accessed May 12, 2022.
2. Carpenter TO, et al. A clinician's guide to X-linked hypophosphatemia. JBMR 2011; 26(7):1381-8. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jbmr.340.
3. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nature Reviews Nephrology 2019 May; 15: 435-455.
4. Athonvarangkul D and Insogna KL. New therapies for hypophosphatemia-related to FGF23 excess. *Calcif Tissue Int*. 2020. https://doi.org/10.1007/s00223-020-00705-3.
5. Florenzano P, Hartley I, Jimenez M, et al. Tumor-induced osteomalacia. *Calcif Tissue Int*. 2020. https://doi.org/10.1007/s00223-020-00691-6.
6. Dahir K, Zanchetta MB, Stanciu I, et al. Diagnosis and management of tumor-induced osteomalacia: perspectives from clinical experience. *J Endocrine Society.* September 2021;5(9):bvab099. https://doi.org/10.1210/jendso/bvab099.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	05.08.18	08.18
No significant changes: added HIM-Medical Benefit line of business per SDC.	10.23.18	
3Q 2019 annual review: removed the requirement for a prior trial of calcitriol plus oral phosphates based on updated clinical trial data demonstrating superiority of Crysvita over calcitriol plus oral phosphates; references reviewed and updated.	05.14.19	08.19
RT4: updated FDA approved pediatric age extension to ≥ 6 months from ≥ 1 year.	10.09.19	
Revised HIM-medical benefit to HIM line of business.	02.13.20	
3Q 2020 annual review: clarified weight-based dosing limits in initial and continued approval criteria; references reviewed and updated.	04.27.20	08.20
RT2: Criteria added for new FDA indication: TIO; references reviewed and updated.	08.11.20	11.20
3Q 2021 annual review: no significant changes; revised HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	05.10.21	08.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2022 annual review: no significant changes; for TIO added requirement for documentation of member's current weight, for dose calculation purposes; references reviewed and updated.	05.12.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.29.22	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.