Medical Drug Clinical Criteria

Subject:	Crysvita (burosumab-twza)		
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Overview

This document addresses the use of Crysvita (burosumab-twza), the first agent approved by the Food and Drug Administration (FDA) to treat X-linked hypophosphatemia (XLH) in adult and pediatric individuals six months of age and older. Crysvita is also FDA approved for the treatment of FGF-23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric individuals two years of age and older.

X-linked hypophosphatemia (XLH) is a genetic form of rickets caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homolog X-linked (PHEX), resulting in high levels of fibroblast growth factor 23 (FGF-23). Elevated FGF-23 is associated with increased urinary phosphate excretion, leading to phosphate wasting and impaired bone growth. XLH manifests in children as rickets and osteomalacia, which often result in leg bowing and delayed growth. Diagnosis of XLH can be confirmed with genetic testing or elevated FGF-23 levels. Biochemical testing demonstrating low serum phosphate and renal phosphate wasting is another alternative for diagnosis confirmation. Traditional treatment includes phosphate and vitamin D supplementation to correct rickets and increase adult height. There is less consensus regarding treatment of adults. Treatment for adults is typically reserved for symptomatic individuals experiencing bone pain, fragility fractures or osteomalacia. Crysvita is an FGF-23 blocking monoclonal antibody and is the first agent to target the underlying cause of XLH. Crysvita should not be used in combination with oral phosphate or active vitamin D analog supplementation.

Tumor-induced osteomalacia (TIO) is an acquired paraneoplastic syndrome caused by mesenchymal tumors that typically secrete FGF-23. Elevated FGF-23 leads to similar manifestations as seen in XLH including renal phosphate wasting and osteomalacia. Diagnosis of TIO is supported by biochemical testing demonstrating elevated FGF-23 levels and renal phosphate wasting. Localization of the tumor(s) is imperative as complete resection is curative. Studies have shown a 65-80% success rate in tumor identification as the tumors are often small, slow-growing and difficult to localize. When complete tumor resection is not possible, medical management similar to that used for XLH is employed. Crysvita was approved for treatment of individuals with TIO based on two small observational studies in adults.

Crysvita is contraindicated in individuals with severe renal impairment as renal impairment can induce abnormal mineral metabolism that can increase phosphate concentrations higher than expected. Severe renal impairment in pediatric individuals is defined as an estimated glomerular filtration rate (eGFR) of 15-29 mL/min/1.73m^2 or end stage renal disease (eGFR <15 mL/min/1.73m^2). Severe renal impairment in adults is defined as creatinine clearance (CLcr) of 15-29 mL/min or end stage renal disease (CLcr <15 mL/min).

Crysvita Dosing

Indication	Age	Dose	Frequency
X-linked hypophosphatemia	6 months – 17 years	Less than 10 kg: starting dose is 1 mg/kg rounded to the nearest 1 mg 10 kg and greater: starting dose is 0.8 mg/kg rounded to the nearest 10 mg, minimum starting dose is 10 mg up to a maximum dose of 90 mg Dose may be increased up to 2 mg/kg not to exceed 90 mg	Every 2 weeks
X-linked hypophosphatemia	18 years and older	1 mg/kg rounded to the nearest 10 mg up to a maximum dose of 90 mg	Every 4 weeks
Tumor-induced osteomalacia	2 - 17 years	Starting dose is 0.4 mg/kg rounded to the nearest 10 mg Dose may be increased up to 2 mg/kg not to exceed 180 mg	Every 2 weeks

Tumor-induced osteomalacia	18 years and older	Starting dose is 0.5 mg/kg Dose may be increased up to 2 mg/kg not to exceed 180 mg	Every 4 weeks, may be increased to every 2 weeks

Age-Based Normal Serum Phosphate Reference

Age	mg/dL	mmol/L
0-5 days	4.8-8.2	1.55-2.65
1-3 years	3.8-6.5	1.25-2.10
4-11 years	3.7-5.6	1.20-1.80
12-15 years	2.9-5.4	0.95-1.75
>15 years	2.7-4.7	0.90-1.50

Age-Based Normal Tubular Resorption of Phosphate Corrected for Glomerular Filtration Rate (TmP/GFR) Reference

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

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Crysvita (burosumab-twza)

Initial requests for Crysvita (burosumab-twza) for X-linked hypophosphatemia may be approved if the following criteria are met:

I. Individual is using for the treatment of X-linked hypophosphatemia (XLH); **AND**
II. Documentation is provided that diagnosis has been confirmed by (Carpenter 2018; Haffner 2019; Ruppe 2017):
  A. Genetic testing (in the individual or a directly related family member); **OR**
  B. Fibroblast growth factor 23 (FGF-23) greater than 30 pg/mL;
  AND
  C. Reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR);

AND

III. If 18 years of age or older, individual is experiencing clinical signs and symptoms of XLH (including but not limited to bone pain, fractures, limited mobility in adults) (Carpenter 2011, Ruppe 2017); **AND**
IV. Documentation is provided that individual has a serum phosphate level below the reference range for age.

Continuation requests for Crysvita (burosumab-twza) for X-linked hypophosphatemia may be approved if the following criteria are met:

I. Documentation is provided that individual achieved and sustained a clinically significant improvement in serum phosphate level; **AND**
II. Individual has achieved and sustained clinically significant improvement of clinical signs and symptoms of XLH.

Initial requests for Crysvita (burosumab-twza) for tumor-induced osteomalacia may be approved if the following criteria are met:

I. Individual has a diagnosis of tumor-induced osteomalacia; **AND**
II. The tumor(s) cannot be curatively resected or localized; **AND**
III. The diagnosis is supported by (NCT02722798, NCT02304367):
  A. Fibroblast growth factor 23 (FGF-23) greater than or equal to 100 pg/mL, and documentation is provided; **AND**
  B. Reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR); **AND**
IV. Documentation is provided that individual has a serum phosphate level below the reference range for age.

Continuation requests for Crysvita (burosumab-twza) for tumor-induced osteomalacia may be approved if the following criterion is met:

I. Documentation is provided that individual achieved and sustained a clinically significant improvement in serum phosphate level; **AND**
II. Individual achieved and sustained clinically significant improvement of clinical signs and symptoms of osteomalacia.

Crysvita (burosumab-twza) may not be approved for any of the following:

I. Individual will be utilizing Crysvita in combination with a phosphate supplement or vitamin D analog (for example, calcitriol); **OR**
II. Individual has severe renal impairment or end stage renal disease; **OR**
III. May not be approved when the above criteria are not met and for all other indications.

Initial Approval Duration: 6 months
Continuation Approval Duration: 1 year

Quantity Limits

Crysvita (burosumab-twza) Quantity Limits

Drug	Limit
Crysvita (burosumab-twza) 10 mg/mL	2 vials per 28 days
Crysvita (burosumab-twza) 20 mg/mL	8 vials per 28 days
Crysvita (burosumab-twza) 30 mg/mL*	6 vials per 28 days
Override Criteria	
*For individuals using Crysvita (burosumab-twza) to treat tumor-induced osteomalacia, may approve up to 360 mg (12 30 mg/mL vials) per 28 days.	

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0584	Injection, burosumab-twza 1 mg [Crysvita]

ICD-10 Diagnosis

E83.30	Disorder of phosphorus metabolism, unspecified
E83.31	Familial hypophosphatemia
E83.39	Other disorders of phosphorus metabolism
M83.8	Other adult osteomalacia
M83.9	Adult osteomalacia, unspecified

Document History

Reviewed: 09/09/2024
Document History:

- 09/09/2024 – Annual Review: No Change. Coding Reviewed: No changes. 09/11/2023 – Annual Review: No Change. Coding Reviewed: No changes.
- 9/12/2022 – Annual Review: Wording and formatting changes. Coding Reviewed: Added ICD-10-CM M83.8, M83.9, Removed M83.0-M83.9.
- 8/20/2021 – Annual Review: Update XLH diagnosis criteria; add initial approval duration of 6 months. Add quantity limits. Wording and formatting changes. Update references. Coding reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 9/14/2020 – Annual Review: Added new indication for tumor-induced osteomalacia to Crysvita clinical criteria. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM M83.0-M83.9.
- 09/9/2019 – Wording and formatting changes. Coding reviewed: No changes. Coding update: Added ICD-10 E83.39.
- 11/21/2018 – Deleted HCPCS C9399, J3590. Added J0584 effective 1/1/2019.

- 11/8/2018 – Updated diagnosis codes to be consistent with criteria.
- 11/2/2018 – Added HCPCS codes: C9399 and J3590.
- 08/17/2018 – New clinical criteria for Crysvita.

References

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5. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. 2019;15(7):435-455.
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7. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.