UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Crysvita Utilization Management Medical Policy
- Crysvita® (burosumab-twza subcutaneous injection – Kyowa Kirin)

REVIEW DATE: 08/27/2025

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 (XLH)** 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

XLH 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 XLH 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 XLH 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. 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 XL was evaluated in several clinical trials in pediatric and adult patients with XLH.[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 XLH.[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

International Working Group clinical practice guidelines for the management of XLH in children (2025)[23] and the management of XLH in adults (2025)[24] recommend that a clinical diagnosis of XLH be confirmed by genetic analysis of the PHEX gene, if feasible. However, guidelines acknowledge that genetic testing may not be available in all cases, and it is possible that not all variants in PHEX can be detected with current methods. Clinical, biochemical, and radiographic evaluation of the patient is also important. It is noted that patients will have persistently low fasting serum phosphorus levels. A low TmP/GFR is indicative of renal phosphate wasting. In regard to treatment of children ≥ 12 months with XLH, Crysvita is recommended over conventional therapy (i.e., active vitamin D and phosphate).[23] Crysvita therapy is also suggested over conventional therapy in younger patients as well. In adults with XLH and fractures or pseudofractures, therapy with Crysvita is recommended over no therapy.[24] Crysvita is also suggested as the preferred treatment compared to conventional therapy in the absence of fractures or pseudofractures. If Crysvita is not available, symptomatic adults should be treated with conventional therapy.

An expert panel also updated their 2019 Clinical Practice Recommendations for the Diagnosis and Management of XLH in 2025.[6] Similar recommendations are made regarding diagnosis of XLH with these

guidelines also noting that if a genetic diagnosis of XLH has been made in an index patient, confirmatory genetic testing may not be necessary in other family members with overt phenotypes. In pediatric patients 1 to 17 years of age, treatment with Crysvita is recommended as soon as the diagnosis is made. Conventional therapy is only recommended if Crysvita is not available. Pediatric patients who are currently receiving conventional therapy should be switched Crysvita if there is an insufficient skeletal response, significant AEs, if they are unable to adhere to conventional therapy, or if they have persistent short stature. In adults, treatment of asymptomatic adults with XLH is not recommended. Treatment should be initiated in adults with significant symptoms and manifestations of XLH, including pseudofractures, musculoskeletal pain, stiffness, or biochemical and/or radiological abnormalities indicative of osteomalacia. Patients who have planned surgery should also be treated. Conventional treatment is recommended in patients with biochemical and/or clinical signs of osteomalacia, musculoskeletal pain or stiffness. Crysvita is recommended in patients with pseudofractures or insufficient musculoskeletal response to therapy with oral phosphate and vitamin D. Crysvita is also recommended in any symptomatic patient with evidence of AEs or intolerance to conventional therapy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Crysvita. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Crysvita, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Crysvita to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Crysvita is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Tumor-Induced Osteomalacia.** Approve Crysvita for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has a mesenchymal tumor that cannot be curatively resected or identified/localized; AND
     - **iii.** According to the prescriber, the patient is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia; AND
       Note: Examples of signs and symptoms of tumor-induced osteomalacia include bone pain, impaired mobility, muscle weakness, and fatigue.
     - **iv.** Patient has had a baseline serum phosphorus level that was below the normal range for age; AND
       Note: "Baseline" is defined as prior to receiving any tumor-induced osteomalacia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.

v. Patient has had a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; AND
Note: "Baseline" is defined as prior to receiving any tumor-induced osteomalacia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.

vi. Patient meets ONE of the following (a or b):

(1) Patient has tried oral phosphate and calcitriol therapy; OR

(2) According to the prescriber, the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND

vii. The medication is prescribed by or in consultation with an endocrinologist or nephrologist; OR

B) Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.
Note: Examples of a response to Crysvita therapy are increased phosphorus levels, decreased symptoms of bone pain and/or muscle weakness, and increased mobility.

Dosing. Approve up to 180 mg given subcutaneously, not more frequently than once every 2 weeks.

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2. X-Linked Hypophosphatemia. Approve Crysvita for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient has had a baseline serum phosphorus level that was below the normal range for age; AND
Note: "Baseline" is defined as prior to receiving any X-linked hypophosphatemia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.

ii. Patient meets ONE of the following (a or b):

a) Patient has had a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; OR
Note: "Baseline" is defined as prior to receiving any X-linked hypophosphatemia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.

b) Patient has had a genetic test confirming the diagnosis of X-linked hypophosphatemia via identification of a PHEX pathogenic variant; AND

iii. If the patient is ≥ 18 years of age, the patient meets ONE of the following (a or b):

a) Patient has fractures and/or pseudofractures; OR

b) Patient meets BOTH of the following (1 and 2):

(1) According to the prescriber, the patient is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia; AND
Note: Examples of signs and symptoms of X-linked hypophosphatemia in patients ≥ 18 years of age include bone and joint pain, stiffness, muscle weakness, impaired mobility, or biochemical and/or clinical signs of osteomalacia.

(2) Patient meets ONE of the following (i or ii):

(i) Patient has tried oral phosphate and calcitriol therapy; OR

(ii) According to the prescriber, the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND

iv. The medication is prescribed by or in consultation with an endocrinologist or nephrologist; OR

B) Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.
Note: Examples of a response to Crysvita therapy are increased phosphorus levels, radiographic improvement in deformities, healing of fractures/pseudofractures, reduction in the incidence of new fractures/pseudofractures.

Dosing. Approve dosing that meets ONE of the following dosing regimens (A or B):

A) If the patient is ≥ 18 years of age, approve up to a maximum dose of 90 mg administered subcutaneously not more frequently than once every 4 weeks; OR

B) If the patient is < 18 years of age, approve up to a maximum dose of 90 mg administered subcutaneously not more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Crysvita is not recommended in the following situations:

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

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/12/2023
Annual Revision	**X-Linked Hypophosphatemia:** The term "mutation" was updated to "pathogenic variant". **Conditions Not Recommended for Approval:** Epidermal Nevus Syndrome was clarified to include Cutaneous Skeletal Hypophosphatemia Syndrome.	08/07/2024
Annual Revision	**X-Linked Hypophosphatemia:** Criteria for a patient ≥ 18 years of age were updated to approve if the patient has fractures and/or pseudofractures OR if according to the prescriber, the patient is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia and has either tried oral phosphate and calcitriol therapy or has a contraindication to oral phosphate therapy, calcitriol therapy, or both, according to the prescriber. Previously, criteria required a patient who had fractures and/or pseudofractures to have either tried oral phosphate and calcitriol therapy or has a contraindication to oral phosphate therapy, calcitriol therapy according to the prescriber. Examples of signs and symptoms of X-linked hypophosphatemia in patients ≥ 18 years of age were updated to remove fractures/pseudofractures (captured in other criteria) and add stiffness and biochemical and/or clinical signs of osteomalacia. Throughout criteria, "Per the prescriber" was changed to "According to the prescriber".	08/27/2025