CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

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

REVIEW DATE: 08/07/2024

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.

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.

*Indications and/or approval conditions noted with **[EviCore]** are managed by EviCore healthcare for those clients who use EviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to EviCore at www.EviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Tumor-Induced Osteomalacia.** ***[EviCore]*** 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.** Patient is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia, as determined by the prescriber; 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)** Per 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.
   - **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 BOTH of the following (a and b):

a) Patient is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia, as determined by the prescriber; AND

Note: Examples of signs and symptoms of X-linked hypophosphatemia in patients ≥ 18 years of age include fractures/pseudofractures, bone and joint pain, muscle weakness, and impaired mobility.

b) Patient meets ONE of the following (1 or 2):

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

(2) Per 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.

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.

REFERENCES

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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