VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Crysvita Prior Authorization Policy
- Crysvita® (burosumab-twza injection, subcutaneous use – Ultragenyx)

REVIEW DATE: 05/27/2020; selected revision 07/22/2020

OVERVIEW

Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for[1]:
- **X-linked hypophosphatemia** in patients ≥ 6 months of age.
- **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.

Disease Overview

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).[2-4] This mutation leads to increased levels of FGF23, which increases phosphate excretion and abnormal vitamin D metabolism, ultimately leading to hypophosphatemic rickets.[2-5] Pediatric patients (usually < 2 years of age) usually present with bowing deformities of the lower extremities and short stature. 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 is estimated to identify mutations in the PHEX gene in approximately 70% of patients with hypophosphatemic rickets and 85% to 90% of patients who have familial hypophosphatemic rickets.[6]

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia is an extremely rare condition caused by tumors that produce the phosphaturic hormone FGF23.[7] Elevated FGF23 causes renal phosphate wasting, which ultimately leads to hypophosphatemia, rickets, and osteomalacia. 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 pain.[8] They may also experience decreased bone mineral density and frequent fractures. Current treatment of patients with inoperable or unidentifiable tumors has been phosphate supplementation and active vitamin D.

Clinical Efficacy

X-Linked Hypophosphatemia

The efficacy of Crysvita for the treatment of X-linked hypophosphatemia was evaluated in several clinical 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.[1,9-11] 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. In a single-arm extension of the adult study,

normalization of serum phosphorous was maintained during an additional 24 weeks of Crysvita therapy.[12] Improvements in healing of fractures/pseudofractures were also observed. One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia.[13] 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.

Tumor-Induced Osteomalacia

Two studies evaluated the efficacy of Crysvita in patients with tumor-induced osteomalacia.[1,14] Eligible patients were adults with a confirmed diagnosis of FGF-23-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 tubular reabsorption of phosphate corrected for glomerular filtration rate (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. These increases were sustained near or above the lower limit of normal through Week 144.

Guidelines

X-Linked Hypophosphatemia

In 2019, an expert panel published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia.[13] This document recommends treatment with oral phosphate and active vitamin D (e.g., calcitriol) 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 prescription benefit coverage of Crysvita. 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, approval requires Crysvita to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. **X-Linked Hypophosphatemia.** Approve Crysvita for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv):

i. Patient has had a baseline (prior to any X-linked hypophosphatemia treatment) serum phosphorus level that was below the normal range for age; AND
Note: Examples of X-linked hypophosphatemia treatment include Crysvita, oral phosphate/vitamin D therapy.

ii. Patient meets ONE of the following (a or b):
- **a)** Patient has had a baseline (prior to any X-linked hypophosphatemia treatment) tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; OR
  Note: Examples of X-linked hypophosphatemia treatment include Crysvita, oral phosphate/vitamin D therapy.
- **b)** Patient has had a genetic test confirming the diagnosis of X-linked hypophosphatemia via identification of a PHEX mutation; AND

iii. If the patient is ≥ 18 years of age, the patient meets BOTH of the following (a and b):
- **a)** Per 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 fractures/pseudofractures, bone and joint pain, muscle weakness, and impaired mobility.
- **b)** Patient meets ONE of the following (1 or 2):
  - **a)** Patient has tried oral phosphate and calcitriol therapy; OR
  - **b)** 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.

2. Tumor-Induced Osteomalacia. Approve Crysvita for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (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. Per 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 (prior to any tumor-induced osteomalacia treatment) serum phosphorus level that was below the normal range for age; AND
Note: Examples of tumor-induced osteomalacia treatment include Crysvita, oral phosphate/vitamin D therapy.

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

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

a) Patient has tried oral phosphate and calcitriol therapy; OR
b) 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.

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 studied for the treatment of patients with chronic kidney disease who have elevations of FGF23 impacting phosphate regulation.[1,9]

2. **Epidermal Nevus Syndrome**. More data are necessary to establish the efficacy and safety of Crysvita in patients with epidermal nevus syndrome. A Phase II single-arm, open-label, dose-finding study (unpublished) included 16 adults with tumor induced osteomalacia (n = 15) or epidermal nevus syndrome (n = 1) with hypophosphatemia and an elevated FGF23.[10] Crysvita administered every 4 weeks improved mean serum phosphorus levels and increased markers of bone turnover (as measured by biopsy) at Weeks 16 and 24.

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

1. Crysvita® injection [prescribing information]. Novato, CA: Ultragenyx Pharmaceuticals Inc.; June 2020.
2. Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to x-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388.
3. Scheinman SJ, Drezner MK. Hereditary hypophosphatemia rickets and tumor-induced osteomalacia. UpToDate, Inc. Available at: www.uptodate.com. Updated February 7, 2020. Accessed on April 8, 2020.
4. Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. *Ther Adv Chronic Dis*. 2018;9:51-60.
5. Ruppe MD. X-linked hypophosphatemia. GeneReviews®. Available at: https://www.ncbi.nlm.nih.gov/books/NBK83985/. Updated April 13, 2017. Accessed on April 8, 2020.
6. Rothenbuhler A, Schnabel D, Hogler W, et al. Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH). *Metabolism*. 2020;103S:153892.
7. Florenzano P, Hartley IR, Jimenez M, et al. Tumor-induced osteomalacia. *Calcif Tissue Int*. 2020 June 5. Online ahead of print.
8. Data on file. Tumor-induced osteomalacia (TIO): mechanism of disease. Ultragenyx Pharmaceutical, Inc.; July 2020.
9. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. *N Engl J Med*. 2018;378(21):1987-1998.
10. Whyte MP, Carpenter TO, Gottesman GS, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicenter, open-label, phase 2 trial. *Lancet Diabetes Endocrinol*. 2019;7(3):189-199.
11. 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.

12. 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.
13. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomized, active-controlled, open-label, phase 3 trial. *Lancet*. 2019;393:2416-2427.
14. Data on file. Burosumab-twza for tumor-induced osteomalacia (TIO) clinical summary program. Ultragenyx Pharmaceutical, Inc.; July 2020.