burosumab-twza (Crysvita®)

Medicare Advantage Medical Policy # 078
Original Effective Date: 03/01/2025
Current Effective Date: 03/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider burosumab (Crysvita®)‡ for the treatment of X-linked hypophosphatemia (XLH) or tumor induced osteomalacia (TIO) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for burosumab (Crysvita) will be considered when the following criteria are met:

- Initial therapy:
    - Patient has a diagnosis of XLH AND BOTH of the following:
        - Patient is greater than or equal to 6 months of age; AND
        - Dose requested will not exceed 90 milligrams (mg) every 2 weeks for patients younger than 18 years of age and 90 mg every 4 weeks for patients 18 years of age and older; OR
    - Patient has a diagnosis of TIO AND ALL of the following:
        - Patient is greater than or equal to 2 years of age; AND
        - Patient has a mesenchymal tumor that cannot be curatively resected or identified/localized; AND
        - Patient is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia (e.g. bone pain, impaired mobility, muscle weakness, fatigue); AND
        - Patient has tried and failed (e.g., intolerance or inadequate response) oral phosphate and calcitriol therapy unless there is clinical evidence or patient history that suggests the use of oral phosphate and calcitriol will be ineffective or cause an adverse reaction to the patient; AND
        - Requested dose will not exceed 180 mg every 2 weeks; AND
    - Crysvita will not be given concurrently with oral phosphate and active vitamin D analogs (e.g., calcitriol); AND
    - Patient has a serum phosphorus level that is below the normal range for age (prior to treatment with phosphate and/or vitamin D therapy); AND
    - Patient does NOT have severe renal impairment or end stage renal disease.

- Continuation therapy:
    - Patient has received an initial authorization for Crysvita from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
    - Patient has experienced normalization of serum phosphorus levels while on therapy; AND
    - Patient has experienced a positive clinical response to burosumab (Crysvita) (e.g., enhanced height velocity, improvement in skeletal deformities, reduction of fractures, reduction of generalized bone pain); AND
    - Patient does NOT have severe renal impairment or end stage renal disease; AND
    - The dose requested will not exceed the following:
        - For patients with XLH: 90 mg every 2 weeks for patients younger than 18 years of age and 90 mg every 4 weeks for patients 18 years of age and older; OR
        - For patients with TIO: 180 mg every 2 weeks.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of burosumab (Crysvita) for the treatment of TIO when the patient does not have signs and symptoms of TIO or has not tried and failed oral phosphate and calcitriol therapy to be **not medically necessary.****

Based on review of available data, the Health Plan considers the continued use of burosumab (Crysvita) when the patient has not experienced a normalization in serum phosphorus levels and an improvement in clinical symptoms to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of burosumab (Crysvita) when patient selection criteria are not met (other than those noted above as **not medically necessary****) to be **investigational.***

Background/Overview

Crysvita is a monoclonal antibody indicated for the treatment of the rare conditions, XLH and TIO. Both conditions are associated with renal phosphate wasting mediated by fibroblast growth factor 23 (FGF23), and Crysvita works by binding to and blocking the biological activity of FGF23 which restores renal phosphate reabsorption and increases the serum concentration of active vitamin D. Because severe renal impairment and end stage renal disease are associated with abnormal mineral metabolism, Crysvita is contraindicated in patients with severe renal impairment. It is dosed based

on weight and administered by subcutaneous injection by a healthcare provider either every 2 weeks for pediatric patients or every 2-4 weeks for adults. It should be noted that the initial dose for both indications should be given every 4 weeks for adults, but physicians may consider dividing the total dose administered every 4 weeks and administering every 2 weeks for adults with TIO. Oral phosphate and active vitamin D analogs must be discontinued 1 week prior to initiation of treatment and fasting serum phosphorus concentration should be below the reference range for age prior to initiation of treatment.

The tables below contain commonly accepted normal serum reference ranges for phosphorus based on age and sex.

Males	
Age	**Reference Range (mg/dL)**
0-12 months	Not established
1-4 years	4.3-5.4
5-13 years	3.7-5.4
14-15 years	3.5-5.3
16-17 years	3.1-4.7
≥18 years	2.5-4.5

Females	
Age	**Reference Range (mg/dL)**
0-12 months	Not established
1-7 years	4.3-5.4
8-13 years	4-5.2
14-15 years	3.5-4.9
16-17 years	3.1-4.7
≥18 years	2.5-4.5

XLH is a rare genetic disease that is estimated to occur in one out of every 20,000 live births. Although the pathogenesis is not fully understood, it is known that the disease results in a genetic mutation in the phosphate regulating endopeptidase on the X chromosome (PHEX). PHEX disruption is believed to lead to elevated levels of FGF23 which reduces renal phosphate reabsorption and leads to low or inappropriately normal levels of the active form of vitamin D, 1, 25-dihydroxyvitamin D (calcitriol). Patients with XLH experience hypophosphatemic rickets (or osteomalacia in adults). The majority of patients present in the first 2 years of life with bowing deformities of the lower extremities, but clinical manifestations of the disease vary greatly. Clinical findings and radiographic evidence, along with biochemical findings are used to identify patients with suspected XLH. The two main laboratory findings in XLH are low serum phosphorus levels and reduced TmP/GFR. A genetic test is available to identify PHEX variants, but it is not widely used at this time.

Prior to the availability of Crysvita, the standard therapy for XLH was phosphorus and calcitriol supplementation to counteract the hypophosphatemia. However, this therapy is associated with abdominal pain and diarrhea that may be dose-limiting and the therapy is cumbersome due to requiring multiple administrations throughout the day. Early treatment with phosphate replacement therapy has been found to optimize final height, but leg deformities may persist and adult height is usually compromised. Most pediatric patients with XLH are treated from the time of diagnosis until growth is complete, and many discontinue treatment as adults. Phosphate replacement therapy is

recommended for symptomatic adults including those with spontaneous insufficiency fractures, pending orthopedic procedures, biochemical evidence of osteomalacia, or disabling skeletal pain. In addition to phosphate therapy, surgical interventions are also commonly used to manage the disease sequelae not improved by medical management.

TIO is an extremely rare condition caused by tumors that produce the phosphaturic hormone, FGF23. Elevated FGF23 causes renal phosphate wasting, which ultimately leads to hypophosphatemia, rickets, and osteomalacia. TIO 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. 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 (calcitriol).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Crysvita is indicated for the treatment of XLH in adult and pediatric patients 6 months of age and older and for the treatment of FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients 2 years of age and older.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

XLH

Crysvita was approved for XLH based on 3 pivotal studies in pediatric and adult patients with XLH.

Study 1 was a randomized, open-label study in 52 prepubescent XLH patients aged 5-12 years old. It compared treatment with Crysvita administered every 2 weeks versus every 4 weeks. Following an initial 16-week dose titration phase, patients completed 48 weeks of treatment with Cyrsvita. The dose was adjusted to target a fasting serum phosphorus concentration of 3.5-5 mg/dL based on the fasting phosphorus level the day of dosing. 26 of the 52 patients received Crysvita every two weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 at week 16, 0.98 mg/kg at week 40, and 1.04 mg/kg at week 60. The remaining 26 patients received Crysvita every 4 weeks. Crysvita was found to increase mean serum phosphorus levels from 2.4 mg/dL at baseline to 3.3 and 3.4 at week 40 and week 64 in the patients who received Crysvita every 2 weeks. The Thacher Rickets

Severity Score (RSS) decreased from a baseline of 1.9 to 0.8 after 40 weeks of treatment in those receiving Crysvita every 2 weeks. These findings were maintained at week 64.

Study 2 was a 64-week, open-label study in 13 pediatric XLH patients 1 to 4 years old. Patients received Crysvita at a dose of 0.8 mg/kg every 2 weeks with titration up to 1.2 mg/kg based on serum phosphorus measurements. Crysvita was found to increase mean serum phosphorus levels from 2.5 mg/dL at baseline to 3.5 at week 40. In addition, the mean total RSS decreased from 2.9 at baseline to 1.2 at week 40.

Study 3 was a 24-week, randomized, double-blind, placebo-controlled study in 134 adult XLH patients. Cyrsvita was administered at a dose of 1 mg/kg every 4 weeks. At baseline, the mean serum phosphorus was 1.9 in the placebo group and 2.0 in the Crysvita group. From baseline to week 24, significantly more patients receiving Crysvita (94.1%) achieved a mean serum phosphorus level >2.5 mg/dL across the midpoints of dosing intervals vs. placebo (7.6% of patients) [P<0.0001]. At week 24, significantly more active baseline fractures/pseudofractures were healed with Crysvita (43%) compared with placebo (8%).

TIO
Two studies evaluated the efficacy of Crysvita in patients with TIO in a total of 27 patients.

Study 6 was a single-arm open-label study that enrolled 14 adult patients with a confirmed diagnosis of FGFR23-related hypophosphatemia produced by an underlying tumor that was not amenable to surgical excision or could not be located. Patients received Crysvita every 4 weeks at a weight based starting dose of 0.3 mg/kg that was titrated to achieve a fasting serum phosphorus level of 2.5-4 mg/dL. The mean dose was 0.83 mg/kg at week 20, 0.87 mg/kg at week 48, 0.77 mg/kg at week 96, and 0.71 mg/kg at week 144. Crysvita was found to increase the mean serum phosphorus levels from 1.6 (0.47) mg/dL at baseline to 2.64 (0.76) mg/dL averaged across the midpoint of the dose intervals through week 24 with 50% of patients achieving a mean serum phosphorus level above the lower limit of normal averaged across the midpoint of dose intervals through week 24.

Study 7 was a single-arm open-label study in 13 patients with a confirmed diagnosis of TIO. Patients received Crysvita every 4 weeks at a weight based starting dose of 0.3 mg/kg that was titrated to achieve a fasting serum phosphorus level of 2.5 to 4 mg/dL. The mean (SD) dose was 0.91 (0.59) mg/kg at week 48, and 0.96 (0.7) mg/kg at week 88. Crysvita increased mean (SD) serum phosphorus levels from 1.62 (0.49) mg/dL at baseline to 2.63 (0.87) mg/dL averaged across the midpoint of dose intervals through week 24 with 69% of patients achieving a mean serum phosphorus level above the lower limit of normal averaged across the midpoint on dose interval through week 24. Mean serum phosphorus concentrations were sustained above the lower limit of normal through week 88.

References

1. Crysvita [package insert]. Ultragenyx Pharmaceutical Inc. Novato, CA. June 2020
2. Phosphate (phosphorus) reference range. Medscape. Updated March 2015.
3. Crysvita Drug Evaluation. Express Scripts. Updated April 2018.
4. Crysvita Prior Authorization Policy. Express Scripts. Updated July 2020.

Policy History

Original Effective Date: 03/01/2025
Current Effective Date: 03/01/2025
12/17/2024 UM Committee review. New policy.
Next Scheduled Review Date: 12/2025

Coding

The five character codes included in the Health plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0584
ICD-10 Diagnosis	E83.30-E83.39, M83.0-M83.9

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.