Medical Policy Bulletin

Title:
Burosumab-twza (Crysvita®)
Policy #:
MA08.099b

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition

MEDICALLY NECESSARY

INITIAL THERAPY
Burosumab-twza (Crysvita®) is considered medically necessary and, therefore, covered for:

1. Individuals at least 6 months of age and older with X-linked hypophosphatemia (XLH)
2. Individuals at least 2 years of age and older with tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors (PMT) that cannot be curatively resected or localized when all of the following criteria listed below are met:

- Diagnosis of XLH or TIO associated with PMT supported by one of the following:
  - For XLH: Documented PHEX pathogenic (i.e., disease-causing) mutation in either the individual or in a directly related family member with appropriate x-linked inheritance
  - For TIO: Documented evidence of TIO associated with PMT
  - Serum fibroblast growth factor 23 FGF23 (FGF23) level > 30 pg/mL
- Documentation of classic clinical features of disease (e.g., rickets, growth abnormalities [short stature or lower extremity bowing], bone pain, bone fractures)
- Fasting serum phosphorus is below the normal range for age
- Does not have renal impairment or end stage renal disease defined as a glomerular filtration rate < 30 mL/min
- Individual has or is willing to discontinue use of oral phosphate and active vitamin D analogs within one week prior to treatment initiation

CONTINUATION THERAPY
Burosumab-twza (Crysvita®) is considered medically necessary and, therefore, covered during continuation therapy for individuals at least 6 months of age and older with XLH and individuals at least 2 years of age and older with TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized when all of the following criteria listed below are met:

- Normalized serum phosphate during therapy, and the absence of hyperphosphatemia
- Documented clinical improvement in the following:
    - Adult individuals --- (e.g., improvement in bone pain, enhanced mobility, radiographic evidence of improvement in osteomalacia/ fracture healing)
    - Pediatric individuals --- (e.g., enhanced height velocity, improvement in lower extremity bowing and associated abnormalities, improved walking ability, radiographic evidence of improvements of rickets/ osteomalacia/ epiphyseal healing)

EXPERIMENTAL/INVESTIGATIONAL

All other uses of burosumab-twza (Crysvita®) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, burosumab-twza (Crysvita ®) is covered under the medical benefits of the Company’s Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

There is no Medicare coverage determination addressing this drug; therefore, the Company policy is applicable.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when burosumab-twza (Crysvita®) is covered under a member's medical benefit (Part B benefit). It does not address instances when burosumab-twza (Crysvita®) is covered under a member’s pharmacy benefit (Part D benefit).

AGE- AND GENDER-BASED NORMAL SERUM PHOSPHATE REFERENCE INTERVALS

Serum phosphorus is measured in milligrams of phosphorus per deciliter of blood (mg/dL). The Pathology and Laboratory Medicine Department of Children's Hospital of Philadelphia (CHOP) established the following normative serum phosphate reference intervals based on gender and age:

Male	Female
0D-11 Mos: 4.8-8.2 mg/dL	0D-11 Mos: 4.8-8.2 mg/dL
1-3 Yrs: 3.8-6.5 mg/dL	1-3 Yrs: 3.8-6.5 mg/dL
4-6 Yrs: 4.1-5.4 mg/dL	4-6 Yrs: 4.1-5.4 mg/dL
7-11 Yrs: 3.7-5.6 mg/dL	7-11 Yrs: 3.7-5.6 mg/dL

12-13 Yrs: 3.3-5.4 mg/dL	12-13 Yrs: 3.3-5.4 mg/dL
14-15 Yrs: 2.9-5.4 mg/dL	14-15 Yrs: 2.9-5.4 mg/dL
16-20 Yrs: 2.7-4.7 mg/dL	16-20 Yrs: 2.7-4.7 mg/dL
≥ 21 Yrs: 2.5-4.5 mg/dL	≥ 21Yrs: 2.5-4.5 mg/dL

*CHOP: Reference Range Document

DOSING REGIMEN

Burosumab-twza (Crysvita®) for subcutaneous injection is administered by subcutaneous injection in children and adults with the following dosing regimen.

In pediatric individuals with XLH:

- For patients weighing less than 10kg, starting dose regimen is 1mg/kg of body weight rounded to the nearest 1 mg, admistered every two weeks
- For patients weighing 10kg or more, starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every 1 weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every 2 weeks to achieve normal serum phosphorus.

In adult individuals with XLH: Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every 4 weeks.

In pediatric individuals with TIO: Starting dose regimen is 0.4 mg/kg of body weight rounded to the nearest 10 mg administered every 2 weeks. Dose may be increased up to 2 mg/kg (maximum 180 mg), administered every two weeks to achieve normal serum phosphorus.

In adult individuals with TIO: Starting dose regimen is 0.5 mg/kg of body weight rounded to the nearest 10 mg administered every four weeks. The dose may be increased up to 2 mg/kg (maximum 180 mg), administered every two weeks to achieve normal serum phosphorus.

If an individual undergoes treatment of the underlying tumor (i.e., surgical excision or radiation therapy), burosumab-twza (Crysvita®) treatment should be interrupted and serum phosphorus reassessed after treatment has been completed. The dose should be restarted at the individual's initiation dose if the serum phosphorus level remains below the lower limit of normal.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Burosumab-twza (Crysvita®) was approved by the FDA on April 17, 2018 for treatment of individuals at least one year of age and older (and expanded to individuals 6 months of age and older) with X-linked Hypophosphatemia when the criteria listed above are met.
Supplemental approvals for Burosumab-twza (Crysvita®) have since been issued by the FDA.

Description

Burosumab-twza (Crysvita®) is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric individuals 6 months of age and older, and for the treatment of fibroblast growth factor 23 (FGF23)-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors (PMTs) that cannot be curatively resected or localized in individuals at least 2 years of age.

XLH is associated with a mutation in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) gene sequence. The PHEX protein regulates a second hormone called fibroblast growth factor 23 (FGF23). The disease is characterized by excess activity of FGF23, which is responsible for reducing serum levels of phosphorus and vitamin D by regulating phosphate excretion and vitamin D production by the kidney. Phosphate wasting in XLH is caused by excessive levels and activity of FGF23. KRN23 is a recombinant human IgG1 monoclonal antibody designed to bind to FGF23 and thereby inhibit the excessive biological activity of FGF23. By blocking excess FGF23 in individuals with XLH, KRN23 is intended to increase phosphate reabsorption from the kidney and increase the production of vitamin D, increasing the overall serum concentration, which enhances

intestinal absorption of phosphate and calcium.

X-linked dominant disorders are caused by mutations in genes on the X chromosome, one of the two sex chromosomes in each cell. Females have two X chromosomes; a mutation in either one of the two copies of the allele in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons since the son would only inherit the Y chromosome (no male-to-male transmission).

TIO is an extremely rare paraneoplastic syndrome where PMTs secrete excessive FGF23 and cause phosphate wasting and chronic hypophosphatemia. PMTs are small, and slow-growing, and can occur in soft tissue or in the bones throughout the body. Clinical manifestations include bone pain, skeletal deformities, fractures, muscle weakness, and gait disturbances. Treatments includes surgical excision when the tumor is resectable, or medical treatment for tumors that are not resectable, not completely excised, have recurred, or metastasized.

PEER-REVIEWED LITERATURE
Summary

In April 2018, based on results from the following studies, burosumab-twza (Crysvita®) was approved by the US Food and Drug Administration (FDA) in the treatment X-linked Hypophosphatemia (XLH) for individuals at least one year of age or older.

A randomized, open-label study in 52 XLH children under 12 years of age compared burosumab administered every 2 weeks versus every 4 weeks. Upon completion of a 16-week dose titration, participants were administered burosumab every 2 weeks for 48-weeks. None of the study participants discontinued burosumab and all completed at least the 64 weeks of treatment duration during the study. Dosing was individualized to achieve a target fasting serum phosphorus concentration of 3.5 to 5.0 mg/dL based on the fasting phosphorus level the day of dosing. Twenty-six of the total 52 received burosumab every 2 weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 mg/kg at week 16, 0.98 mg/kg at week 40 and 1.04 mg/kg (range: 0.4, 2.0) at week 60. The other 26 enrollees were treated with burosumab every weeks. At the beginning of the study, the average age of participants was 8.5 years with 46% male participants. Regarding treatment with oral phosphate and active vitamin D analogs, 96% of enrollees had received these for a mean (Standard Deviation [SD]) duration of 7 (2.4) years. In addition, discontinuation of oral phosphate and active vitamin D analogs occurred prior to study enrollment. 94% of study participants presented with radiographic evidence of rickets at baseline. In this study, individuals receiving burosumab experienced a mean (SD) increase in serum phosphorus levels from 2.4 (0.40) at baseline to 3.3 (0.40) and 3.4 (0.45) mg/dL at week 40 and week 64 respectively, in the trial participants who received burosumab every 2 weeks. The 10-point Thacher Rickets Severity Score (RSS) and the 7-point Radiographic Global Impression of Change (RGI-C) were used to evaluate rickets. The RGI-C score is assigned based on images of the wrist and knee from a single time point, and higher scores indicating greater rickets severity. After 40 weeks of therapy, mean total RSS decreased from 1.9 to 0.8 and the mean RGI-C Global score increased to +1.7 in individuals receiving burosumab every 2 weeks. Eighteen of the 26 achieved an RGI-C score of ≥ +2.0, which was defined as radiographical evidence of substantial healing in the study. These findings were consistent at 64 weeks.

In a phase 2 trial open-label study, researchers evaluated pediatric individuals aged 5 years or less (n=13), on serum phosphate levels at 64 weeks. Individuals in the study received burosumab at a dose of 0.8 mg/kg every 2 weeks with titration up to 1.2 mg/kg based on serum phosphorus levels. All participants completed treatment with burosumab. The average age was 2.9 years at study entry. At baseline, all study participants had radiographic evidence of rickets and had received oral phosphate and active vitamin D analogs for a average duration of 16.9 months. All participants discontinued treatment with oral phosphate and active vitamin D analogs occurred prior to study initiation. The researchers presented results of the first 40 weeks. At week 40, participants experienced serum phosphorus levels increases of an average (SD) from 2.5 (0.28) mg/dL at baseline to 3.5 (0.49) mg/d. After 40 weeks of treatment, mean total RSS decreased from 2.9 to 1.2 and the mean (SE) RGI-C Global score was +2.3 (0.08). The entire study population achieved a RGI-C global score ≥ +2.0. Lower limb deformity as assessed by RGI-C, using standing long leg radiographs, which resulted in an average increase of +1.3. This study was limited by the small sample size, although that is to be expected based on rarity of disease and age of participants.

In phase 3 randomized, double-blind, placebo-controlled study (RCT) in 134 adult individuals with XLH evaluated the proportion of participants achieving serum phosphate levels above 2.5 mg/dL at the dose interval mid-points of the dose interval between baseline and week 24 and osteomalacia related-fracture and pseudofractures. Researchers indicate that burosumab was administered at a dose of 1 mg/kg every 4 weeks. At study entry, the age of participant ranged from 16 to 66 years, with an average age of 40 years. At baseline, all participants had skeletal pain associated with XLH or osteomalacia. The baseline mean (SD) serum phosphorus concentration was below the lower

limit of normal at 1.98 (0.31) mg/dL. Oral phosphate and active vitamin D analogs were not allowed during the study with one study entrant in the burosumab group discontinued treatment. At the completion of 24 weeks, a total of 94% of participants treated with burosumab achieved a serum phosphorus level above the lower limit of normal at mid-point of the dose interval compared to 8% in the placebo group (P<0.0001). Assessment of active fracture/pseudofractures at week 24 demonstrated a higher rate of complete healing in the group receiving burosumab (44%) compared to placebo (18%). During the study, a total of 6 new fractures or pseudofractures appeared in 68 participants receiving burosumab, compared to 8 new abnormalities in 66 in the placebo treatment arm. The study comprised a 24- week placebo-controlled phase, after which point individuals in the placebo arm could cross-over into a 72-week open-label trial to be treated with 1 mg/kg burosumab. Although the strongest methodologically, as the only phase 3 RCT trial, this study had the shortest follow-up.

A 48-week, open-label, single-arm study was completed in 14 adult XLH individuals to determine the effects of burosumab on improvement of osteomalacia as based on histologic and histomorphometric evaluation of iliac crest bone biopsies. Treatment was 1 mg/kg burosumab every 4 weeks. At the initiation of the study, the mean age was 40 years (range 25 to 52 years) and 43% were male. Oral phosphate and active vitamin D analogs were not allowed during the study. After 48 weeks of treatment, healing of osteomalacia was observed in 10 individuals as demonstrated by decreases in Osteoid volume/Bone volume from a mean (SD) score of 26% (12.4) at baseline to 11% (6.5), a change of -57%. Osteoid thickness declined in eleven participants. Mineralization lag time declined in 6 from a mean (SD) of 594 (675) days to 156 (77) days, a change of -74%.

A Phase 2, open-label, single-arm study enrolled 14 adult individuals 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. Individuals received burosumab-twza (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 4.0 mg/dL. CRYSVITA increased mean serum phosphorus levels from 1.60 (0.47) mg/dL at baseline to 2.64 (0.76) mg/dL averaged across the midpoint of dose intervals through Week 24 with 50% of patients achieving a mean serum phosphorus level above the lower limits of normal (LLN) averaged across the midpoint of dose intervals through Week 24. Increase in the mean serum phosphorus concentrations was sustained near or above the LLN through Week 144. Treatment was associated with improved serum phosphorus levels, as well as fewer symptoms of osteomalacia. Improved mobility, reduction in fatigue and a decrease in pain levels were also seen.

A Phase 2, open-label, single-arm study with 13 adult individuals with a confirmed diagnosis of TIO received burosumab-twza (Crysvita®). Of the 13 TIO individuals who received treatment, six were male, and ranged from 41 years to 73 years of age. Individuals received burosumab-twza (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 4.0 mg/dL. Burosumab-twza (Crysvita®) increased mean 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 individuals achieving a mean serum phosphorus level above the LLN averaged across the midpoint on dose interval through Week 24. Mean serum phosphorus concentrations were sustained above LLN through Week 88. The renal phosphate reabsorptive capacity increased from a mean (SD) of 1.15 (0.43) mg/dL at baseline to 2.30 mg/dL (0.48) mg/dL at Week 48. Improved phosporus levels were noted, as well as fewer symptoms of osteomalacia. No changes in reported levels of fatigue were noted.

Safety and effectiveness in pediatric individuals 6 months to 1 year are supported by evidence from the studies in pediatric individuals with additional modeling and simulation of adult and pediatric pharmacokinetic (PK) and pharmacodynamic (PD) data to inform dosing.

SAFETY

Burosumab-twza (Crysvita®) should be interrupted if an individual's phosphorus levels above upper limit of normal, which may increase the risk of nephrocalcinosis; dose adjustment or therapy interruption may be required based on phosphorus levels. Other safety concerns that require monitoring during burosumab-twza (Crysvita®) therapy are individuals with a previous serious hypersensitivity reaction to burosumab-twza (Crysvita®).

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company’s off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

E55.0 Rickets, active
E83.31 Familial hypophosphatemia
M83.8 Other adult osteomalacia

HCPCS Level II Code Number(s)

J0584 Injection, burosumab-twza 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA09.099b:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
09/05/2023	This policy has been reissued in accordance with the Company's annual review process.
05/04/2022	This policy has been reissued in accordance with the Company's annual review process.
03/15/2021	This version of the policy will become effective 03/15/2021. This policy has been updated. The following criteria have been added to this policy: New tumor-induced osteomalacia (TIO) criterion, in considerations of revisions within the US Food and Drug Administration (FDA) labeling The following policy criteria have been revised: Age for initial and continuation therapy for X-linked hypophosphatemia (XLH) changed to 6 months

Revisions From MA09.099a:

09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
01/01/2019	This version of the policy will become effective 01/01/2019. The following HCPCS code has been **added** to the policy: J0584. The following HCPCS code has been **deleted** from this policy: J3590.

Revisions From MA09.099:

08/13/2018	This version of the policy will become effective 08/13/2018. The following new policy has been developed to communicate Company's coverage criteria for burosumab-twza (Crysvita®) injection.

Version Effective Date:
03/15/2021
Version Issued Date:
03/15/2021
Version Reissued Date:
03/28/2025