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UnitedHealthcare Community Plan

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

CRYSVITA® (BUROSUMAB-TWZA)

Policy Number: CSLA2020D0071G **Effective Date**:TBD

Instructions for Use

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APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

Crysvita (burosumab) is proven and medically necessary for the treatment of X-linked hypophosphatemia (XLH) when the following criteria are met: [1]

- For initial therapy, **all** of the following:
  - Diagnosis of XLH, confirmed by **one** of the following:
    - Genetic testing (e.g., confirmed *PHEX* gene mutation in patient or first-degree relative)
    - Elevated Serum fibroblast growth factor 23 (FGF23) level > 30 pg/mL;

    and
  - Patient is greater than **6 months**~~1 year~~ of age; **and**
  - **One** of the following:
    - Patient epiphyseal plate has **not** fused; **or**
    - **All** of the following:
      - Patients' epiphyseal plate has fused; **and**
      - Patient is experiencing clinical signs and symptoms of the disease (e.g., limited mobility, musculoskeletal pain, bone fractures); **and**
      - Failure, contraindication, or intolerance to therapy with calcitriol in combination with an oral phosphate agent (e.g., K-Phos®, K-Phos Neutra®);

    and
  - Prescribed by, or in consultation with, an endocrinologist orspecialist experienced in the treatment of metabolic bone disorders; **and**
  - Fasting serum phosphorus is below the normal range for age; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 12 months.

- For continuation therapy, **all** of the following:

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- Patient has previously received treatment with burosumab; **and**
- Prescribed by, or in consultation with, an endocrinologist or specialist experienced in the treatment of metabolic bone disorders; **and**
- Patient has experienced normalization of serum phosphate while on therapy; **and**
- Patient has experienced a positive clinical response to burosumab (e.g., enhanced height velocity, improvement in skeletal deformities, reduction of fractures, reduction of generalized bone pain); **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0584	Injection, burosumab-twza, 1 mg

ICD-10 Diagnosis Code	Description
E83.31	Familial hypophosphatemia

BACKGROUND

XLH is a heritable disorder of renal phosphate transport, which results in abnormal phosphate hemostasis, resulting in hypophosphatemia and abnormal bone mineralization. Elevated serum FGF23 levels are observed in patients with XLH, and believed to be associated with phosphate level abnormalities. Burosumab inhibits excess FGF23 levels, which results in normalization of serum phosphate. [1-3] Combining active vitamin D metabolites with a balanced dose of phosphate has been the mainstay of therapy for XHL. Most affected children are candidates for treatment. In adults, the role of treatment has not been well studied; treatment is generally reserved for individuals with symptoms such as skeletal pain, upcoming orthopedic surgery, biochemical evidence of osteomalacia with an elevated serum alkaline phosphatase (ALP) level, or recurrent pseudofractures or stress fractures. The primary goals of treatment in children are to correct or minimize rickets/osteomalacia, as assessed by radiographic abnormalities and resolution of skeletal abnormalities. In contrast with children, once a patient reaches adult height and the epiphyses have fused, the goal of therapy is simply to manage generalized bone pain and enhance limited mobility, if either occurs, and to cure any non-union fractures. [6]

CLINICAL EVIDENCE

A randomized, open-label study (NCT 02163577) in 52 prepubescent XLH patients compared burosumab administered every 2 weeks versus every 4 weeks. Upon completion of a 16-week dose titration, patients were administered burosumab every 2 weeks for 48-weeks. No study patients discontinued burosumab and completed at least 64 weeks of the study. Patient 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 52 patients received burosumab every two weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 mg/kg (range: 0.3, 1.5) at week 16, 0.98 mg/kg (range: 0.4, 2.0) at week 40 and 1.04 mg/kg (range: 0.4, 2.0) at week 60. The other 26 patients received burosumab every four weeks. At the beginning of the study, the mean age of patients was 8.5 years with 46% male. Regarding treatment with oral phosphate and active vitamin D analogs, 96% of study participants had received these for a mean (SD) duration of 7 (2.4) years. In addition, discontinuation of oral phosphate and active vitamin D analogs occurred prior to study enrollment. Radiographic evidence of rickets was observed in 94% of patients at baseline. In this study, patients 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 in the patients 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. After 40 weeks of therapy, mean total RSS decreased from 1.9 to 0.8 and the mean RGI-C Global score was +1.7 in patients receiving burosumab

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every two weeks. Eighteen out of 26 patients achieved an RGI-C score of ≥ +2.0. These findings were maintained at week 64. [1,4]

A 64-week open-label study (NCT 02750618) was conducted in 13 XLH patients age 1 to 4 years old. Study patients received burosumab at a dose of 0.8 mg/kg every two weeks with titration up to 1.2 mg/kg based on serum phosphorus. No study participants discontinued burosumab. The mean age of patients 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 mean (SD) duration of 16.9 (13.9) months. Discontinuation of oral phosphate and active vitamin D analogs occurred prior to study enrollment. At week 40, patients experienced an increased mean (SD) serum phosphorus levels 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). All 13 patients achieved a RGI-C global score ≥ +2.0. The mean (SE) lower limb deformity as assessed by RGI-C, using standing long leg radiographs, was +1.3 (0.14). [1,5]

A randomized, double-blind, placebo-controlled study (NCT 02526160) in 134 adult XLH patients was completed. Burosumab was administered at a dose of 1 mg/kg every 4 weeks. At study entry, the patient age ranged from 16 to 66 years, with a mean of 40 years. The average age of diagnosis was 9 years and 81% of patients had received conventional therapy before the age of 18, for an average of approximately 12 years. 69% of patients had used phosphate and/or active vitamin D within 2 years of study baseline. At baseline, all patients 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 patient in the burosumab group discontinued treatment. Through week 24, a total of 94% of patients receiving burosumab achieved a serum phosphorus level above the lower limit of normal compared to 8% in the placebo group. Assessment of active fracture/pseudofractures at week 24 demonstrated a higher rate of complete healing in the group receiving burosumab compared to placebo. During the study, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving burosumab, compared to 8 new abnormalities in 66 patients receiving placebo. The FDA conducted its own analysis in order to examine pain medication usage during burosumab treatment. The FDA determined that there is insufficient evidence to support that burosumab decreased use of pain medication during therapy. The FDA stated that it is possible that as longer term data is collected, a significant reduction in pain medication may become evident. [1,5]

A 48-week, open-label, single-arm study (NCT 02537431) was completed in 14 adult XLH patients 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 four weeks. At study entry, the mean age of patients 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 ten patients 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 patients. Mineralization lag time) declined in 6 patients from a mean (SD) of 594 (675) days to 156 (77) days, a change of -74%. [1,5]

The pharmacokinetics, efficacy, and safety profile of burosumab was evaluated in a Phase 3 randomized, double blind, placebo controlled trial. The primary endpoint was the proportion of subjects achieving mean serum phosphate above 2.5 mg/dL at the dose interval mid-points of the dose interval between baseline and week 24. 94.1% of burosumab-treated subjects vs 7.6% of placebo-treated subjects achieved mean serum phosphorus > the lower limit of normal at mid-point of the dose interval, averaged across dose cycles (P<0.0001). At week 24, treatment was associated with healing of active fractures as well as pseudofractures in 44% of patients in the treatment group compared to 18% in the placebo group. The overall safety profile of patients on burosumab was similar to that of placebo. [2]

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Crysvita is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients ~~1 year~~**6 months** of age and older. [1]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Crysvita® (burosumab-twza injection). Local Coverage Determinations (LCDs) do not exist at this time.

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In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.
(Accessed March 28, 2019)

REFERENCES

1. Crysvita [prescribing information]. Novato, CA: Ultragenyx Pharmaceutical; September **2019**~~2018~~.
2. Osteocyte regulation of phosphate homeostasis and bone mineralization underlies the pathophysiology of the heritable disorders of rickets and osteomalacia. Feng JQ, Clinkenbeard EL, Yuan B, White KE, Drezner MK SOBone. 2013 Jun;54(2):213-21. Epub 2013 Feb 9.
3. 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.
4. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. N Engl J Med 2018;378:1987-1998.
5. Food and Drug Administration/Center for Drug Evaluation and Research. Crysvita summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761068Orig1s000MultidisciplineR.pdf. Accessed April 8, 2019.
6. Scheinman SJ, Drezner MK. Hereditary hypophosphatemic rickets and tumor-induced osteomalacia. UpToDate Website. Updated September 26, 2017. www.uptodate.com. Accessed April 8, 2019.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	**Updated age criterion from 1 year to 6 months based on revised FDA labeling. Updated references.**

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

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