Washington State Health Care Authority

Endocrine and Metabolic Agents : Metabolic Modifiers – X-Linked Hypophosphatemia (XLH) Agents burosumab-twza (Crysvita®)

Medical policy no. 30.90.95-2 Effective Date: July 1, 2020

Note: New-to-market drugs in this class are non-preferred and subject to this prior authorization (PA) policy. Non-preferred agents in this class, require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed.

Background:

X-linked hypophosphatemia (XLH) is an inherited disorder associated with PHEX gene sequence mutation and subsequent inactivity of the PHEX protein. Symptoms of X-linked hypophosphatemia can include rickets, bone softening, and bone pain, among other serious manifestations. The diagnosis is made based on slow growth rate and bowing of legs or other skeletal abnormalities, low levels of phosphate, high levels of FGF23 in the blood, lack of response of phosphate levels to vitamin D treatment, and/or phosphate wasting in the kidneys. Genetic testing is available and may confirm diagnosis. Burosumab-twza is an antibody that restores renal reabsorption of phosphate and increases serum 1, 25 dihydroxyvitamin D levels by binding to and inhibiting fibroblast growth factor 23 (FGF23). Burosumab-twza is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

Medical necessity:

Drug	Medical Necessity
Burosumab-twza (Crysvita®)	Burosumab-twza may be considered medically necessary when used to treat X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

Clinical policy:

Drug	Clinical Criteria (Initial Approval)
X-Linked Hypophosphatemia (XLH) Burosumab-twza (Crysvita®)	Burosumab-twza may be covered when ALL of the following are met: 1) Patient is 6 months of age or older; **AND** 2) Diagnosis of X-linked hypophosphatemia confirmed by **ONE** of the following: a) Genetic testing results confirming a PHEX-gene mutation**; OR** b) Genetic testing results confirming a PHEX-gene mutation in a directly related family member with a low serum phosphate and increased alkaline phosphatase activity; **OR** c) Baseline lab values with **ALL** of the following to demonstrate the diagnosis of XLH: a. Elevated serum Fibroblast Growth Factor 23 (e.g. greater than 52pg/mL); **AND** b. Normal serum calcium (e.g. 8.6 to 10.0mg/dL for adults and 8.7 to 10.6mg/dL for children); **AND** **c.** Elevated serum alkaline phosphatase (e.g. Greater than 104U/L for adults and greater than 335U/L for children); **AND** d. Low to normal 1,25 dihydroxyvitamin D levels (e.g. less than 86pg/mL); **AND** e. Serum phosphorus is below normal range (e.g. Less than 2.5mg/dL for adults and less than 4.3mg/dL for children); **AND** 3) Most recent renal function labs (within 90 days) show creatinine clearance (CrCl) is greater than or equal to 30mL/min; **AND** 4) Client has an intolerance, contraindication, or inadequate response to oral phosphate and vitamin D treatment for at least 6 months; **AND** 5) Oral phosphate and/or active vitamin D analogs are stopped within 1 week prior to initiation of burosumab-twza; **AND** 6) Documentation of clinical signs or symptoms of disease (e.g., rickets, growth retardation, musculoskeletal pain, bone fractures) for patients greater than or equal to 18 years old; **AND** 7) Prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders. If ALL criteria are met, the request will be **approved for 6 months**
	Criteria (Reauthorization)
	Burosumab-twza may be continued when ALL of the following are met: 1) Current serum phosphorus level (within 90 days) is below the upper limit of lab normal range (e.g. Less than 4.5mg/dL for adults and less than 5.4mg/dL for children); **AND** 2) Documented positive clinical response defined by any **ONE** of the following; a) Increase in serum phosphorus levels (from baseline); **OR**

	b) Improvement in symptoms (e.g., skeletal pain, linear growth, improvement in skeletal deformities, reduction of fractures); **OR** c) Reduction in serum alkaline phosphatase activity from baseline; **OR** d) Improvement in radiographic imaging of rickets/osteomalacia; **AND** 3) Client is not taking an oral phosphate; **AND** 4) Client is not taking vitamin D; **AND** 5) Prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders. If ALL criteria are met, the request will be **approved for 12 months**

Dosage and quantity limits:

Drug Name	Dose and Quantity Limits
Dosing	1mg/kg, rounded to the nearest 10mg. Max of 90mg per administration
Dosing Frequency	Adults: 1 subcutaneous injection every 4 weeks Pediatric: 1 subcutaneous injection every 2 weeks

Coding:

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

Definitions:

Term	Description
Thacher Rickets Severity Score (RSS)	A 10-point score for radiographs of wrists and knees to assess the degree of metaphyseal fraying and cupping and the proportion of growth plate affected. Total points progress in half point increments from 0-10: wrists (0-4) plus knees (0-6) Higher scores indicate a more severe state of rickets; a reduction indicates an improvement in severity.
Radiographic Global Impression of Change (RGI-C)	A 7-point scale (-3= severe worsening; 0=no change; +3= near/complete healing) designed for comprehensive evaluation of skeletal health. RGI-C scores assess changes in the severity of rickets using the disease-specific qualitative RGI-C scoring system. An RGI-C score ≥ +2.0 indicates substantial healing of rickets.

Evidence review:

X-linked hypophosphatemia (XLH) is an inherited disorder associated with PHEX gene sequence mutation and subsequent inactivity of the PHEX protein. With this mutation, the protein fibroblast growth factor 23 (FGF23) concentration is increased. FGF23 regulates the reabsorption of phosphate in the kidneys, and too much of FGF23 reduces the amount of phosphate reabsorbed by the kidneys leading to hypophosphatemia. The prevalence of X-linked hypophosphatemia is about 1 in 20,000.

Symptoms of X-linked hypophosphatemia can include rickets, bone softening, bone pain, muscle pain, muscle weakness, waddling gait, bowing of legs, other skeletal abnormalities, joint pain due to calcification of tendons and ligaments, short stature, abnormal tooth development, tooth abscesses, dental pain, and hearing loss. Some patients may have no signs or symptoms, and other patients may experience persistent discomfort or complications. Symptoms for many become apparent within first 18 months of life when legs begin to bear weight, but some patients do not develop symptoms until adulthood.

The diagnosis is made based on slow growth rate and bowing of legs or other skeletal abnormalities, low levels of phosphate, high levels of FGF23 in the blood, lack of response of phosphate levels to vitamin D treatment, and/or phosphate wasting in the kidneys. Genetic testing is available and may confirm diagnosis, but is not necessary for diagnosis.

The typical treatment of X-linked hypophosphatemia is phosphate supplements and high-dose calcitriol. Treatment may also include growth hormones, corrective surgery and dental treatment. Unlike other forms of rickets, ingestion of vitamin D is relatively ineffective in X-linked hypophosphatemia. Burosumab-twza is an antibody that restores renal reabsorption of phosphate and increases serum 1,25 dihydroxyvitamin D levels by binding to and inhibiting fibroblast growth factor 23 (FGF23). It is the first FDA-approved treatment indicated for the underlying cause of XLH in patients 6 months of age and older.

Adults:

A randomized, double blind, placebo-controlled trial of 24 weeks of treatment was conducted in 134 adults 19-66 years old. Patients were randomized to receive placebo or burosumab-twza 1mg/kg every 4 weeks. An increased normalized serum phosphorous was demonstrated in the treatment group (94%) compared to placebo (8%) through week 24. The number of healed active fractures and pseudofractures at week 24 in the burosumab-twza group was 50% and 41%, compared to 0.5 and 9% in the placebo group.

An open-label, single-arm study was conducted in 14 adults age 25-52. The primary endpoint of the study was to assess the impact of burosumab-twza on the symptom of osteomalacia through 48 weeks of treatment. The osteoid volume/bone volume score decreased from 26% at baseline to 11%. The osteoid thickness decreased from 17 mcm to 12 mcm. The mineralization lag time decreased from 594 days to 156 days.

There was also an open-label, quality of life study completed in 26 adults. Patients received low doses over the 4 month period: 0.05mg/kg at month1, 0.1mg/kg at month 2, 0.3mg/kg at month 3 and 0.6mg/kg at month 4. Patient perception of chronic functional limitation significantly improved with burosumab-twza. The Medical Outcomes Study Short Form health Survey version 2 (SF-36v2) was assessed after 4 months of treatment. “Role Limitations due to Physical Health” improved significantly and by more than the minimal important change. The other components of the SF-36v2 and Western Ontario and McMaster Osteoarthritis Index (WOMAC) did not improve significantly.

Pediatric:

An open-label, randomized, parallel-group study was conducted in 52 patients from 5-12 years of age. Patients were randomized to receive burosumab-twza or placebo subcutaneous injections either every 2 weeks or every 4 weeks for a 16-week dose-titration followed by a 48-week treatment period. The primary endpoints were change from baseline to week 40 in severity of rickets as measured by total Thacher Rickets Severity Score (RSS) and change in from baseline to week 40 in the Radiographic Global Impression of Change (RGI-C) scale. The mean score on the RSS scale decreased from 1.9 at baseline to 0.8 at week 40 in the every 2 week dosing group and decreased from 1.7 at baseline to 1.1 at week 40 in the every 4 week dosing group ($p<0.001$ for both groups

compared to placebo). These reductions continued through week 64. The RGI-C scores suggested reduction in the severity of rickets for both treatment groups compared to placebo. Substantial healing of rickets was demonstrated in 54% of patients based on an RGI-C change from baseline ≥ 2.0. The overall mean serum phosphorous level increased at week 40 (0.75 mg/dL) and at week 64 (0.84 mg/dL). Serum phosphorous levels within the normal range were reached by about half of the patients by week 6.

A randomized, active-controlled, open-label, phase 3 trial enrolled 61 patients, 1 to 12 years of age. Patients were randomized to receive either burosumab-twza every 2 weeks or conventional therapy, defined as oral phosphate and vitamin D titrated by individualized, for 64 weeks. The primary endpoint was the change in rickets severity at week 40, measured using the Radiographic Global Impression of Change (RGI-C) score. A significant difference in improvement scores of 1.9 vs 0.8 was demonstrated between burosumab-twza and conventional therapy ($p<0.0001$), respectively. This improvement continued to week 64 with mean scores of 2.1 and 1.0 for burosumab-twza and conventional therapy ($p<0.0001$). A significant proportion of patients in the burosumab-twza group achieved substantial healing of rickets, defined as a RGI-C score ≥2, compared to conventional therapy (72% vs 6%, respectively). With regards to safety, dental caries (31% vs 6%) and tooth abscess (28% vs 9%) were found to be more prevalent in the burosumab-twza group compared to conventional therapy.

References

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5. X-linked hypophosphatemia. Genetic and Rare Diseases Information Center. <https://rarediseases.info.nih.gov/diseases/12943/x-linked-hypophosphatemia>
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9. Lambert A., Zhukouskaya V., Rothenbuhler A., et al. X-linked hypophosphatemia: Management and treatment prospects. Joint Bone Spine. 2019. 86:731-738.
10. Imel E., Glorieu F., Whyte M., et al. Burosumab versus conventional therapy in children with X-linked hypophosphatemia: a randomized, active-controlled, open-label, phase 3 trial

History

Date	Action and Summary of Changes
03/24/2020	Updated clinical criteria baseline lab values to use as a guide
02/03/2020	Update policy to incorporate FDA label update and new evidence
06/12/2019	Updated initial approval clinical criteria
05/06/2019	New Policy

Washington State Health Care Authority

Endocrine and Metabolic:
X-linked hypohosphatemia (XLH) Agents

Please provide the information below, please print your answer, attach supporting documentation, sign, date, and return to our office as soon as possible to expedite this request. **Without this information, we may deny the request in seven (7) working days.**

Date of request:	Reference #:	MAS:	
Patient	Date of birth	ProviderOne ID	
Pharmacy name	Pharmacy NPI	Telephone number	Fax number
Prescriber	Prescriber NPI	Telephone number	Fax number
Medication and strength	Directions for use	Qty/Days supply	

1. Is this request for a continuation of existing therapy? ☐ Yes ☐ No
   If yes, is there improvement in symptoms (e.g. skeletal pain, linear growth, improvement in skeletal deformities, reduction of fractures) or radiographic imaging of rickets/osteomalacia? ☐ Yes ☐ No
2. Is patient's diagnosis X-linked hypophosphatemia? ☐ Yes ☐ No
   If no, specify diagnosis: _____
3. Indicate the following for patient:
   Serum Fibroblast Growth Factor 23 (FGF-23): _____ pg/mL
   Serum phosphorus: _____ mg/dL
   Serum calcium: _____ mg/dL
   Serum alkaline phosphatase: _____ U/L
   1,25 dihydroxyvitamin D level: _____ pg/mL
   CrCl: _____ mL/min
   Weight: _____ kg _____ lb
4. Has patient had an inadequate response, or has an intolerance/contraindication, to oral phosphate and vitamin D treatment for at least 6 months? ☐ Yes ☐ No
5. Will oral phosphate and/or active vitamin D analogs be stopped within 1 week prior to initiation of, and not be used in combination with the requested treatment? ☐ Yes ☐ No
6. Is this prescribed by or in consultation with a physician who is experienced in the treatment of metabolic bone disorders? ☐ Yes ☐ No
7. For patients 18 years and older, are there documented clinical signs and/or symptoms of the disease (e.g., rickets, growth retardation, musculoskeletal pain, bone fractures)? ☐ Yes ☐ No

ALL THE FOLLOWING ARE REQUIRED WITH THIS REQUEST:

- Genetic testing for PHEX-gene mutations or labs confirming diagnosis
- Chart notes

Prescriber signature	Prescriber specialty	Date