BlueCross BlueShield Nebraska

CRYSVITA (REQUIRES PREAUTHORIZATION)

X.117

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POLICY

Crysvita (burosumab) may be considered **medically necessary** for the treatment of X-linked hypophosphatemia when **ALL** the following criteria are met**:**

I. **Initial Authorization**:

A. Patient has diagnosis of X-linked hypophosphatemia, confirmed by **one** of the following:

1. Genetic testing (e.g. test confirming mutation of PHEX (phosphate regulating endopeptidase homolog X-linked) gene)

OR

2. Elevated Serum fibroblast growth factor 23 (FGF23) level > 30 pg/mL

AND

B. Serum phosphorus is below the normal range for age despite use of conventional oral therapy confirmed by:

1. Compliant use of an oral calcitriol product **AND** an oral elemental phosphorus product within the last 3 months after an adequate trial as defined by **ALL** of the following:

a. The trial length was at least 12 weeks at generally accepted doses for each product **AND**

b. The patient was ≥80% adherent to the conventional agents during the trial as evidenced in patient's prescription claims history; **OR** the patient is new to BCBSNE and prescriber attests that the patient has failed an oral calcitriol product **AND** an oral elemental

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laboratory that includes the reference laboratory normal range and date of lab draw. Date of lab draw must be during timeframe patient was on conventional therapy as described above. (Baseline lab draw must be within the last 3 months to accuratley reflect serum phosphorus level on optimal conventional therapy.)

OR

2. Prescriber attests that the patient has a FDA labeled contraindication, or hypersensitivity to **BOTH** conventional agent classes

AND

C. Patient exhibits clinical signs and symptoms of the disease (e.g., rickets, slow growth rate, bowing of the legs, bone pain, bone fractures) despite use of conventional oral therapy;

AND

D. Medication is prescribed by, or in consultation with, a specialist experienced in the treatment of metabolic bone disorders;

AND

E. Prescribed dose is within the FDA approved labeling;

AND

F. If criteria are met, **initial authorization** will be for 3 months

II. **Renewal Authorization** may be considered **medically necessary** when **ALL** the following criteria are met:

A. Patient has previously been approved for Crysvita (burosumab) via BCBSNE prior authorization process.

AND

B. Patients serum phosphorus has improved and is within the normal range of age:

Documentation includes copy of results from laboratory that includes the reference laboratory normal range and date of lab draw (lab draw must be within the last 3 months to accurately reflect serum phosphorus level on Crysvita therapy).

AND

pain reduction);

AND

D. Medication is prescribed by, or in consultation with, a specialist experienced in the treatment of metabolic bone disorders;

AND

E. Prescribed dose is within the FDA approved labeling

AND

F. If criteria are met, renewal authorization will be for 12 months.

Dates

Original Effective
05-30-2018
Last Review
11-06-2024
Next Review
11-12-2025

CLINICAL RATIONALE

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

"XLH is the prototypic disorder of renal phosphate wasting, and the most common form of heritable rickets[2]. Clinical manifestations vary in severity, but patients most commonly present in childhood with bowing deformities of the legs. Progressive bowing, antero-medial rotational torsion of tibiae, and short stature represent the predominant skeletal outcomes in growing children. With medical therapy these abnormalities can be improved, but usually do not entirely resolve. Metaphyseal changes of rickets are usually evident on radiographs (we preferentially image the distal femur) when a child presents with XLH. Osteomalacia (accumulation of unmineralized osteoid) is characteristic of untreated XLH."[3]

"XLH is often misdiagnosed as nutritional rickets, metaphyseal dysplasia, and physiologic bowing. Hypophosphatemia and low-normal circulating $1,25(OH)_2D$ levels are typical biochemical findings. Serum alkaline

physiologic bowing and most skeletal dysplasias. As the diagnosis of XLH requires long-term medical therapy, definitive evidence of renal phosphate wasting is critical to obtain before committing patients to treatment. A 2-hr *fasting* urine specimen, together with a blood sample collected at the midpoint of the urine collection period is used to calculate the percent tubular reabsorption of phosphate (TRP), and to determine the tubular threshold maximum for phosphate (TMP/GFR)."[3]

"XLH was initially referred to as "vitamin D resistant rickets" due to the lack of therapeutic response to vitamin D in dosages that would cure nutritional rickets. Subsequent recognition that renal phosphate wasting was the principal pathophysiologic abnormality led to the use of phosphate replacement regimens, which resulted in partial correction of skeletal lesions but led to hyperparathyroidism. Combining active vitamin D metabolites with a balanced dose of phosphate has since become the mainstay of therapy. Careful monitoring to avoid toxicity is required. Most affected children and symptomatic or severely affected adults are candidates for treatment."[3]

The genetic basis for XLH (and in Hyp mice) is loss-of-function of PHEX (**P**hosphate regulating gene with **H**omology to **E**ndopeptidases located on the **X** chromosome).[4,5] PHEX is a member of the M13 family of neutral endopeptidases, which activate or degrade peptides, is expressed in bones and teeth, and localizes to the cell surface. PHEX is expressed in late embryonic development as skeletal mineralization begins.[6] FGF23 does not appear to be a physiologic substrate for PHEX and the mechanism by which PHEX disruption results in elevated circulating FGF23 levels remains unclear, however both are products of the osteocyte.[3] FGF23 mediates several inherited phosphate wasting disorders, of which XLH is the most common.[3] "Another direct consequence of elevated FGF23 levels is the abnormally regulated vitamin D axis. FGF23 can down-regulate CYP271B (which encodes 25-OHD- 1α-hydroxylase), and up-regulate CYP24A1 (encoding the 24-hydroxylase)[7], thereby resulting in inappropriate (low to normal) levels of $1,25(OH)_2D$ -- due to decreased synthesis and increased catabolism."[3]

Treatment of pediatric patients[3]

Calcitriol and Phosphate - The disease spectrum is variable -- some individuals are minimally affected even without treatment. Hypophosphatemia and low to low-normal serum $1,25(OH)_2D$ levels result from increased FGF23 levels . Current treatment with activated vitamin D metabolites and phosphate salts attempts to correct these

We recommend a calcitriol dosage of 20 to 30 ng/kg/day in 2-3 divided doses, and an elemental phosphorus dose of 20-40 mg/kg/day (in 3-5 divided doses), acknowledging that some children require more, while some do well with less. We often titrate to the target doses over several days to weeks to minimize gastrointestinal side effects. Alternatively, some initially employ higher calcitriol doses (50-70 ng/kg/day) for several months to accelerate the skeletal response, then reduce the dose to avoid hypercalciuria or hypercalcemia. Changes in body size, growth velocity, and skeletal mineralization will necessitate periodic dose adjustments.

Monitoring and dose adjustment - The primary goals of treatment are to correct or minimize rickets/osteomalacia, radiographic abnormalities, and skeletal deformities. A common misconception is that successful treatment requires normalization of the serum phosphate concentration, which is not a practical goal in children with XLH (29). In fact, this strategy is likely to do harm, leading to overtreatment with phosphorus and resultant secondary hyperparathyroidism. Rather, important endpoints of therapeutic efficacy include height, degree of skeletal deformity, and radiographic evidence for epiphyseal healing. Decreased height velocity or increased bowing call for reviewing adherence to treatment and dose adjustment if necessary. Maintenance of acceptable height velocity and improvement in skeletal deformities generally indicate satisfactory dosing.

To avoid complications such as hypercalcemia, hypercalciuria or hyperparathyroidism, laboratory monitoring at 3 month intervals is suggested.

Radiographs - Are indicated during the initial evaluation of XLH, for assessment of healing of rickets, and for evaluating skeletal deformities when considering surgical management. We routinely assess distal femoral/proximal tibial sites every 2 years to insure optimal epiphyseal correction. Radiographs are also used to evaluate focal bone pain.

Treatment of Adults[3]

The goals of treatment in adults are to reduce pain symptoms, the extent of osteomalacia (that is, the abundance of unmineralized osteoid present in the skeleton), and/or to improve fracture healing or surgical recovery. There are limited clinical trial data that support the efficacy of conventional therapy for these indications.

the therapeutic goal, and if not achieved within 9-12 months treatment should probably be discontinued. For some mildly symptomatic patients, treatment is unlikely to offer much benefit. Affected adults with the following presentations are considered candidates for pharmacologic therapy:

1. Spontaneous insufficiency fractures
2. Pending orthopedic procedures
3. Biochemical evidence of osteomalacia
4. Disabling skeletal pain

Like pediatric XLH, adults are treated with calcitriol and phosphate. Treatment is individualized for each patient depending on age, body weight, parathyroid status and renal function. As a general guide, a normocalcemic adult patient with a normal or only mildly elevated serum PTH, usually starts treatment with 0.50-0.75 mcg/day of calcitriol in 2 divided doses. After one week, daily phosphate (250 mg of elemental phosphorus) is begun, and titrated every 4 days to 750-1000 mg/day in 3-4 divided dosages. The reason treatment with calcitriol is begun before phosphate is to reduce the risk of exacerbating pre- existing secondary hyperparathyroidism or causing it to develop; this development may occur when phosphate supplementation is begun first and, at times, simultaneously. Patients with XLH have low to low-normal circulating levels of endogenous 1,25$(OH)_2$vitamin D, which may partly explain why they are prone to develop secondary and even tertiary hyperparathyroidism with phosphate treatment unless it is carefully managed.

Monitoring and dose adjustment -After 4-6 weeks of this regimen, serum calcium, phosphorus, creatinine, alkaline phosphatase and PTH, and 24-hour urinary excretion of calcium and creatinine are measured. If serum PTH has increased from baseline, but the serum calcium is normal and urine calcium is ≤ 3.0 mg/kg lean body weight /24 hours, the calcitriol dose is considered inadequate and increased in 0.25 mcg/day increments every 3-4 weeks until

dose. Once providing established doses of calcitriol and phosphorus that do not cause hypercalcemia, hypercalciuria or secondary hyperparathyroidism, we repeat the above biomarkers in 6-8 weeks to ensure stability. Serum alkaline phosphatase activity may transiently rise during the first few months of therapy, during the initial healing phase of the osteomalacia.

The major risks of long-term therapy with calcitriol and phosphorus in adults with XLH are similar to those in children: hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis, and potentially, chronic kidney disease. Careful monitoring is essential in order to minimize these risks. During the first year of treatment at stable doses, we repeat biochemical evaluation, every 3-4 months. Frequent monitoring in the first year is critical because the requirements for calcitriol and phosphorus may decrease abruptly as osteomalacia heals. It is important to detect this change early to avoid prolonged hypercalcemia or hypercalciuria. Beyond the first year we generally monitor treated adult patients every 6-9 months.

Efficacy[1]
FDA approval was based on the following study results:

CRYSVITA has been evaluated in 65 pediatric patients with XLH.

Study 1 (NCT 02163577) is a randomized, open-label study in 52 prepubescent XLH patients, 5 to
12 years old, which 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 CRYSVITA every 2 weeks. All 52 patients completed at least 64 weeks on study; no patient discontinued. Burosumab-twza dose was adjusted to target a 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 CRYSVITA 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 remaining 26 patients received CRYSVITA every four weeks. At study entry, the mean age of patients was 8.5 years and 46% were male. Ninety-six percent had received oral phosphate and active vitamin D analogs for a mean (SD) duration of
7 (2.4) years. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment. Ninety-four percent of patients had radiographic evidence of rickets at baseline.

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Patients received CRYSVITA at a dose of 0.8 mg/kg every two weeks with titration up to 1.2 mg/kg based on serum phosphorus measurements. All patients completed at least 40 weeks on study; no patients discontinued. At study entry, the mean age of patients was 2.9 years and 69% were male.
All patients had radiographic evidence of rickets at baseline and had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 16.9 (13.9) months. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment.

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12-01-2023

Policy reviewed at Medical Policy Committee meeting on 11/8/2023 – no changes to policy

09-01-2021

Added J0584

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