burosumab (Crysvita®)

Policy # 00633
Original Effective Date: 08/15/2018
Current Effective Date: 08/15/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), 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 Company may consider burosumab (Crysvita®)‡ for the treatment of X-linked hypophosphatemia (XLH) to be **eligible for coverage.**

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

- Initial therapy:
  - The patient has a diagnosis of XLH; AND
  - The patient is greater than or equal to 1 year of age; AND
  - The 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; AND
  - Crysvita will not be given concurrently with oral phosphate and active vitamin D analogs (e.g., calcitriol)
  - The patient has a serum phosphorus level that is below the normal range for age; AND
  - The patient does NOT have severe renal impairment or end stage renal disease.
- Continuation therapy:
  - The patient has previously received treatment with burosumab (Crysvita); AND
  - The patient has experienced normalization of serum phosphorus levels while on therapy; AND
    *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - The 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
    *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - The patient does NOT have severe renal impairment or end stage renal disease; AND
  - The dose requested will not exceed 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.

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When Services Are Considered Not Medically Necessary
Based on review of available data, the Company 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 Company considers the use of burosumab (Crysvita) when patient selection criteria are not met to be **investigational.***

Background/Overview

Crysvita is a monoclonal antibody indicated for the treatment of the rare condition, XLH. XLH is a genetic condition that results in excess 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 4 weeks for adults. 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.

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 1 year 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. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Crysvita was approved 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%).

References

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

Policy History

Original Effective Date: 08/15/2018
Current Effective Date: 08/15/2018
08/09/2018 Medical Policy Committee review
08/15/2018 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 08/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 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.

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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	C9399, J3590
ICD-10 Diagnosis	E83.30-E83.39

*****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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.