OVERVIEW
Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients ≥ 1 year of age. Crysvita is a recombinant human immunoglobulin G subclass 1 (IgG1) anti-FGF antibody. FGF23 reduces renal tubular phosphate reabsorption and suppresses renal production of 1,24 dihydroxyvitamin D. Via inhibition of FGF23 activity, Crysvita restores renal phosphate reabsorption and increases serum concentrations of 1,25 dihydroxyvitamin D. Crysvita is administered as a subcutaneous (SC) injection by a healthcare provider. It is given once every 2 weeks (Q2W) in pediatric patients 1 to < 18 years of age and once every 4 weeks (Q4W) in patients ≥ 18 years of age.

Disease Overview
XLH is a dominant inherited disease of renal phosphate wasting. While it is rare, it is the most common form of hereditary rickets and is estimated to occur in one out of every 20,000 live births. The pathogenesis of XLH is not fully understood; however, an inactivating genetic mutation in phosphate regulating endopeptidase on the X chromosome (PHEX) leads to elevated FGF23. Increased levels of FGF23 increased renal excretion of phosphate and abnormal regulation of vitamin D metabolism. Patients with XLH experience hypophosphatemic rickets (or osteomalacia [i.e., accumulation of unmineralized osteoid/softening of the bones]). The majority of patients present in the first 2 years of life with bowing deformities of the lower extremities and short stature. In adults, the primary symptom in adults is enthesopathy (i.e., calcification of tendons, ligaments, and joint capsules), which is associated with joint pain and impaired mobility. These patients may also experience spontaneous dental abscesses, stress fractures, and sensorineural hearing loss. The XLH diagnosis can be established in patients with a low serum phosphate concentration, a reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR), an inappropriate calcitriol level for the severity of hypophosphatemia, and/or by identification on molecular genetic testing of a hemizygous PHEX pathogenic variant in a male patient or a heterozygous PHEX pathogenic variant in a female patient. Genetic testing is estimated to identify mutations in the PHEX gene in approximately 70% of patients with hypophosphatemic rickets and 85% to 90% of patients who have familial hypophosphatemic rickets.

Prior to the approval of Crysvita, medical therapy for adults and children with XLH consisted of oral phosphate and activated vitamin D (calcitriol). This therapy is cumbersome and can result in adverse events (AEs) such as hypercalcemia, hyperparathyroidism, hypercalciuria, nephrolithiasis, nephrocalcinosis, and possibly chronic kidney disease. This therapy often leads to suboptimal response and skeletal abnormalities persist.

Clinical Efficacy
The efficacy of Crysvita was established in three pivotal trials, including two open-label, 64-week studies in pediatric patients and one double-blind, 24-week study in adult patients with XLH. In pivotal studies, patients had baseline serum phosphorus levels less than the lower limit of normal for age. Across the studies, Crysvita was found to increase mean serum phosphorus levels significantly from baseline. Radiographic improvements and healing of fractures/pseudofractures were also observed.
**POLICY STATEMENT**

Prior authorization is recommended for medical benefit coverage of Crysvita. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Crysvita, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Crysvita to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the durations noted below.

**RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Crysvita is recommended in those who meet the following criteria:

**FDA-Approved Indications**

1. **X-Linked Hypophosphatemia (XLH).** Approve Crysvita for 1 year if the patient meets ONE of the following criteria (A or B):
   
   A) **Initial Therapy.** Approve if the patient meets ALL of the following criteria (i, ii, and iii):
      
      i. The medication is prescribed by or in consultation with an endocrinologist or nephrologist; AND
      
      ii. The patient has had a baseline (i.e., prior to any XLH treatment [e.g., Crysvita, oral phosphate/vitamin D therapy]) serum phosphorus level that was below the normal range for age; AND
      
      iii. The patient meets ONE of the following (a or b):
         
         a) The patient has had a baseline (i.e., prior to any XLH treatment [e.g., Crysvita, oral phosphate/vitamin D]) tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; OR
         
         b) The patient has had a genetic test confirming the diagnosis of X-linked hypophosphatemia via identification of a PHEX mutation.
   
   B) **Patients Currently Receiving Crysvita.** Approve if the patient is continuing to derive benefit from Crysvita as determined by the prescribing physician (e.g., increased phosphorus levels, radiographic improvement in deformities, healing of fractures/pseudofractures, reduction in the incidence of new fractures/pseudofractures).

   **Dosing.** Approve one of the following dosing regimens (A or B):

   A) For adult patients (≥ 18 years of age), approve up to a maximum dose of 90 mg administered subcutaneously (SC) not more frequently than once every 4 weeks; OR
   
   B) For pediatric patients (< 18 years of age), approve up to a maximum dose of 90 mg administered SC not more frequently than once every 2 weeks.
CONDITIONS NOT RECOMMENDED FOR APPROVAL

Crysvita has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Chronic Kidney Disease (CKD), Severe Renal Impairment or End Stage Renal Disease.**
   Crysvita is contraindicated in patients with severe renal impairment or end stage renal disease (ESRD).¹ These patients often have abnormal mineral metabolism which may be associated with FGF23. However, Crysvita has not been studied for the treatment of patients with CKD who have elevations of FGF23 impacting phosphate regulation.¹⁸

2. **Epidermal Nevus Syndrome (ENS).** A Phase II single-arm, open-label, dose-finding study (unpublished) included 16 adults with tumor induced osteomalacia (TIO) [n = 15] or ENS (n = 1) with hypophosphatemia and an elevated FGF23.¹⁰ Crysvita Q4W improved mean serum phosphorus levels and increased markers of bone turnover (as measured by biopsy) at Weeks 16 and 24. More data are necessary to establish the efficacy and safety of Crysvita in patients with ENS.

3. **Tumor-Induced Osteomalacia (TIO).** A Phase II single-arm, open-label, dose-finding study (unpublished) included 16 adults with TIO (n = 15) or ENS (n = 1) with hypophosphatemia and an elevated FGF23.¹⁰ Crysvita Q4W improved mean serum phosphorus levels and increased markers of bone turnover (as measured by biopsy) at Weeks 16 and 24. More data are necessary to establish the efficacy and safety of Crysvita in patients with TIO.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

**OTHER REFERENCES UTILIZED**

**HISTORY**

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
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<tbody>
<tr>
<td>New Policy</td>
<td>---</td>
<td>05/02/2018</td>
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<tr>
<td>Annual Revision</td>
<td><strong>X-Linked Hypophosphatemia</strong>: Added criteria for patients currently receiving Crysvita to approve if the patient is continuing to derive benefit from Crysvita as determined by the prescribing physician. Updated dosing section to approve up to 90 mg once every 4 weeks (for adult patients) or once every 2 weeks (for pediatric patients).</td>
<td>05/15/2019</td>
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<tr>
<td>Selected Revision</td>
<td><strong>X-Linked Hypophosphatemia (XLH)</strong>: Added criteria to allow for genetic confirmation of XLH.</td>
<td>08/14/2019</td>
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