CRYSVITA® (burosumab-twza)

Product Fact Sheet

Indication[1]

CRYSVITA® (burosumab-twza) is the first and only FDA-approved therapy for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients one year of age and older that addresses the underlying cause of the disease. CRYSVITA is a fibroblast growth factor 23 (FGF23) blocking antibody and is administered via subcutaneous injection.

About XLH [2,3,4]

XLH, or X-Linked hypophosphatemia, is a rare, hereditary, progressive and lifelong disorder occurring in an estimated 12,000 people in the U.S. (approximately 3,000 children and 9,000 adults).

People with XLH have low levels of phosphate in the blood. Phosphate is required for healthy bones, muscles and teeth. In XLH, the body produces too much of a protein called fibroblast growth factor 23 (FGF23), causing decreased intestinal absorption of phosphate and large amounts of phosphate to pass out of the body through urine. Chronic low serum phosphate levels lead to rickets and osteomalacia (softening of the bones).

XLH is typically diagnosed during childhood when the legs start supporting weight. However, the disease progresses with time and adults can continue to experience symptoms, particularly if they are mis- or undiagnosed.

Dosing[1]

CRYSVITA is administered by subcutaneous injection and should be administered by a healthcare provider. Oral phosphate and active vitamin D analogs should be discontinued one week prior to initiation of treatment. Fasting serum phosphorus concentration should be below the reference range for age prior to initiation of treatment.

In pediatric patients with XLH (1 to less than 18 years of age), the recommended starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg.

In adult patients with XLH, the recommended dose regimen is 1 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every four weeks.

Contraindications[1]

- Do not use CRYSVITA with oral phosphate and active vitamin D analogs.
- Do not initiate CRYSVITA if serum phosphorus is within or above the normal range for age.
- CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.

Please see full Prescribing Information for additional Important Safety Information.
Please see pages 3 and 4 for Important Safety Information.

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Clinical Studies[1]

The clinical program supporting CRYSVITA approval was comprised of four clinical studies, two in pediatric XLH patients and two in the adult XLH patients. Approximately 200 patients have participated in the development program.

Pediatric Studies

- CL201 – A Phase 2, 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 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, 20.) at week 60. The remaining 26 patients received CRYSVITA every four weeks.
- CL205 – A Phase 2, 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 two weeks with titration up to 1.2 mg/kg based on serum phosphorus measurements.

Adult Studies

- CL303 – A Phase 3, randomized, double-blind, placebo-controlled study in 134 adult XLH patients with a 24-week placebo-controlled treatment phase. Patients received 1 mg/kg of CRYSVITA every four weeks.
- CL304 – A Phase 3, 48-week, open-label, single-arm study in 14 adult XLH patients. The study assessed the effects of CRYSVITA on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received 1 mg/kg of CRYSVITA every four weeks.

Pharmacodynamics[1]

Following SC administration in XLH patients, higher burosumab-twza concentrations were associated with greater increase of serum phosphorus levels. The increase in serum phosphorus was reversible and returned to baseline with elimination of systemic burosumab-twza. Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) showed dose-dependent increases from baseline. Elevation in serum total FGF23 was observed after initiation of burosumab-twza treatment however, the clinical implication is unknown.

Proposed Mechanism of Action[5]

CRYSVITA binds to and thereby inhibits the excess biological activity of FGF23. This restores normal phosphate reabsorption from the kidney, in turn increasing the production of vitamin D and the intestinal absorption of phosphate and calcium.

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Important Safety Information[1]

You should not take CRYSVITA if:

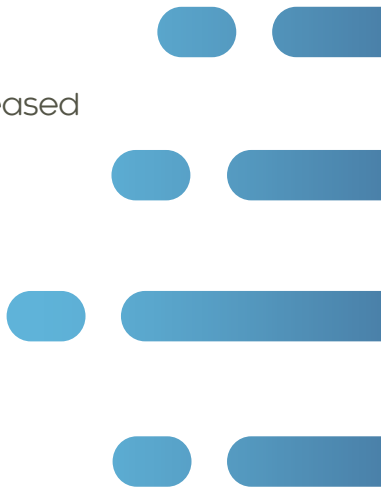
- You take an oral phosphate supplement and a specific form of vitamin D supplement.
- Your phosphorus levels from a blood sample are within or above the normal range for age.
- You have kidney problems.

What is the most important information you should know about CRYSVITA?

- Some patients developed allergic reactions (rash and hives) while taking CRYSVITA. Your doctor will monitor you for symptoms of an allergic reaction while you are taking CRYSVITA.
- High levels of phosphorus in the blood have been reported in some patients taking CRYSVITA. This may be related to a risk of high calcium levels in the kidneys. Your doctor will collect samples to monitor your levels.
- Administration of CRYSVITA may result in reactions at the injection site, such as hives, reddening of the skin, rash, swelling, bruising, pain, severe itching of the skin, and collection of blood outside of a blood vessel (hematoma).

What are the possible side effects of CRYSVITA?

- The most common adverse reactions that were seen in children with XLH are:
  - Headache
  - Injection site reaction
  - Vomiting
  - Fever
  - Pain in arms and legs
  - Decreased vitamin D levels
  - Rash
  - Toothache
  - Muscle pain
  - Tooth infection
  - Dizziness
- The most common adverse reactions that were seen in adults with XLH are:
  - Back pain
  - Headache
  - Tooth infection
  - Restless leg syndrome
  - Decreased vitamin D levels
  - Dizziness
  - Constipation
  - Phosphorus levels increased in the blood
- Narrowing of the spaces within the spine is common in adults with XLH and pressure on the spinal cord has been reported in adults taking CRYSVITA. It is not known if taking CRYSVITA worsens the narrowing of the spaces within the spine or the pressure on the spinal cord.



Please see full Prescribing Information for additional Important Safety Information.

Before taking CRYSVITA, tell your doctor about all of your medical conditions, including if you:

- are pregnant, think you may be pregnant, or plan to become pregnant. There is not enough experience to know if CRYSVITA may harm your unborn baby. Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-800-756-8657.
- are breastfeeding or plan to breastfeed. There is not enough experience to know if CRYSVITA passes into your breast milk. Talk with your doctor about the best way to feed your baby while you receive CRYSVITA.

While taking CRYSVITA, tell your doctor if you experience:

- An allergic reaction such as rash or hives
- A rash, swelling, bruising or other reaction at the injection site
- New or worsening restless leg syndrome

These are not all the possible side effects of CRYSVITA. Call your doctor for medical advice about side effects.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ultragenyx at 1-888-756-8657.

References

1. CRYSVITA (burosumab-twza) [package insert]. Novato, CA: Ultragenyx Pharmaceutical Inc.; April 2018.
2. Ruppe MD. X-linked hypophosphatemia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®* [Internet]. Seattle, University of Washington, Seattle; 1993-2017.
3. Linglart A. Biosse-Duplan M. Briot K. et al. Therapetuic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014 March 1; 3(1):R13-R30.
4. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: Endocrine Society's 97th Annual Meeting and Expo; March 5-8, 2015; San Diego, CA.
5. Ultragenyx Pharmaceutical. Data on file.

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