CRYSVITA®
burosumab-twza
Injection 10, 20, 30 mg/mL

What to expect when starting your **patients with XLH** on CRYSVITA

Monitoring fasting serum phosphorus levels and following recommended dosing are essential to assessing and managing your **pediatric** and **adult** patients' treatment with CRYSVITA.[1]

Indication

CRYSVITA® (burosumab-twza) is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

Important Safety Information

CONTRAINDICATIONS

CRYSVITA is contraindicated:

- In concomitant use with oral phosphate and/or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol) due to the risk of hyperphosphatemia.
- When serum phosphorus is within or above the normal range for age.
- In patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.

Please see Important Safety Information throughout and on pages 14-15. For important risk and use information, please see the full Prescribing Information for CRYSVITA in pocket.

XLH=X-linked hypophosphatemia.

Starting your patients on CRYSVITA®

Initiate treatment with the recommended starting dose based on the Prescribing Information (PI)

DOSING FOR PEDIATRIC PATIENTS

CRYSVITA dosed every

2

weeks[1]

CRYSVITA is administered by an HCP every 2 weeks, and its dose is based on the patient's body weight.[1]

Recommended starting dose
(6 months to <18 years of age)[1]

Patients who weigh **<10 kg**

Starting dose regimen is 1 mg/kg of body weight, rounded to the nearest 1 mg, administered every 2 weeks.

Patients who weigh **≥10 kg**

Starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every 2 weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg.

The maximum volume of CRYSVITA per injection is 1.5 mL. If multiple injections are required, administer at different injection sites.

DOSING FOR ADULT PATIENTS

CRYSVITA dosed every

4

weeks[1]

CRYSVITA is administered by an HCP every 4 weeks, and its dose is based on the patient's body weight.[1]

Recommended starting dose
(≥18 years of age)[1]

1 mg/kg body weight, rounded to the nearest 10 mg, every 4 weeks

Doses may be increased up to 90 mg, administered every 4 weeks

The maximum volume of CRYSVITA per injection is 1.5 mL. If multiple injections are required, administer at different injection sites.

Testing fasting serum phosphorus levels throughout treatment is necessary to determine if dose adjustment is needed to maintain levels within the reference range.[1]

Important Safety Information

WARNINGS AND PRECAUTIONS

Hypersensitivity

- Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients with CRYSVITA. Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment.

Hyperphosphatemia and Risk of Nephrocalcinosis

- Increases in serum phosphorus to above the upper limit of normal may be associated with an increased risk of nephrocalcinosis. For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels.

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WHEN TO ASSESS FOR CHILDREN AND ADULTS

Measuring fasting serum phosphorus

For the first 3 months of treatment, follow these time intervals to assess fasting serum phosphorus levels in pediatric and adult patients:

PEDIATRIC ASSESSMENT SCHEDULE[1]

Dose 1
Day 1

Dose 2
Day 14

Assessment
Day 28

ADULT ASSESSMENT SCHEDULE[1]

Dose 1
Day 1

Assessment
Day 14

Dose 2
Day 28

After 3 months, continue to assess serum phosphorus levels as appropriate.[1]

Assessing serum phosphorus levels during treatment[1]

After initiation of treatment with CRYSVITA®, measure fasting serum phosphorus levels for the first 3 months of treatment at the times specified in the PI for pediatric and adult patients, and thereafter as appropriate.

- It is critical to test serum phosphorus levels at the time intervals specified in the PI to accurately monitor your patients' dosage

Pharmacokinetic characteristics of CRYSVITA[1]

- The mean T_{max} values ranged from 8 to 11 days
- The half-life of CRYSVITA is approximately 19 days
- Clearance and volume of distribution of CRYSVITA increases with body weight

Important Safety Information

WARNINGS AND PRECAUTIONS (cont'd)

Injection Site Reactions

- Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment.

ADVERSE REACTIONS

Pediatric Patients

- Adverse reactions reported in 10% or more of CRYSVITA-treated pediatric XLH patients across three studies are: pyrexia (55%, 44%, and 62%), injection site reaction (52%, 67%, and 23%), cough (52%), vomiting (41%, 48%, and 46%), pain in extremity (38%, 46%, and 23%), headache (34% and 73%), tooth abscess (34%, 15%, and 23%), dental caries (31%), diarrhea (24%), vitamin D decreased (24%, 37%, and 15%), toothache (23% and 15%), constipation (17%), myalgia (17%), rash (14% and 27%), dizziness (15%), and nausea (10%).

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DOSING ADJUSTMENTS FOR CHILDREN

Adjust dosing to help maintain serum phosphorus within the reference range[1]

Directions for dose adjustments and monitoring in pediatric patients with CRYSVITA®

Reassessment after **4 weeks** is key[1]

When making dose adjustments for your patients, take note of the following[1]:

- Reassess fasting serum phosphorus level **4 weeks** after dose adjustment
- Do not adjust CRYSVITA more frequently than every **4 weeks**

INCREASING DOSES

For patients who weigh **<10 kg[1]**

If fasting serum phosphorus is **below the reference range for age:**

- The dose may be increased to 1.5 mg/kg, rounded to the nearest 1 mg, administered every 2 weeks

If additional dose increases are needed:

- The dose may be increased to the maximum dose of 2 mg/kg, rounded to the nearest 1 mg, administered every 2 weeks

For patients who weigh **≥10 kg[1]**

If fasting serum phosphorus is **below the reference range for age:**

- The dose may be increased stepwise up to approximately 2 mg/kg, administered every 2 weeks (maximum dose of 90 mg) according to the dose schedule shown to the right

XLH pediatric dose schedule for stepwise dose increase for patients ≥10 kg[1]

Body weight (kg)	Starting dose (mg)	First dose increase to (mg)	Second dose increase to (mg)
10-14	10	15	20
15-18	10	20	30
19-31	20	30	40
32-43	30	40	60
44-56	40	60	80
57-68	50	70	90
69-80	60	90	90
81-93	70	90	90
94-105	80	90	90
≥106	90	90	90

DECREASING DOSES

If fasting serum phosphorus is **>5 mg/dL[1]:**

- Withhold the next dose and reassess the serum phosphorus level in 4 weeks. The patient must have serum phosphorus below the reference range for age to reinitiate CRYSVITA
- Once serum phosphorus is below the reference range for age, treatment may be restarted

For patients who weigh **<10 kg[1]**

Restart CRYSVITA at 0.5 mg/kg of body weight, rounded to the nearest 1 mg, administered every 2 weeks.

For patients who weigh **≥10 kg[1]**

Restart CRYSVITA according to the dose schedule shown in the table to the right.

XLH pediatric dose schedule for reinitiation of therapy for patients ≥10 kg[1]

Previous dose (mg)	Reinitiation dose (mg)
10	5
15	10
20	10
30	10
40	20
50	20
60	30
70	30
80	40
90	40

After a dose decrease, reassess serum phosphorus level 4 weeks after the dose adjustment. If the level remains below the reference range for age after the reinitiation dose, the dose can be adjusted as outlined to the left under INCREASING DOSES.[1]

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DOSING ADJUSTMENTS FOR ADULTS

Adjust dosing to help maintain serum phosphorus within the normal range[1]

Directions for dose adjustments and monitoring in adult patients with CRYSVITA®

Reassess **2 weeks** after dose adjustment[1]

When making dose adjustments for your patients, take note of the following[1]:

- Reassess fasting serum phosphorus level **2 weeks** after dose adjustment
- Do not adjust CRYSVITA more frequently than every **4 weeks**

DECREASING DOSES

If fasting serum phosphorus is **above the normal range[1]:**

- Withhold the next dose and reassess the fasting serum phosphorus level after 4 weeks
- The patient must have fasting serum phosphorus below the normal range to be able to reinitiate CRYSVITA

Once fasting serum phosphorus is **below the normal range[1]:**

- Reinitiate CRYSVITA at approximately half the initial starting dose up to a maximum dose of 40 mg every 4 weeks, according to the dose schedule shown in the table to the right

XLH adult dose schedule for reinitiation of therapy[1]

Previous dose (mg)	Reinitiation dose (mg)
40	20
50	20
60	30
70	30
≥80	40

Reassess fasting serum phosphorus 2 weeks after any change in dose.[1]

Risk of nephrocalcinosis[1]

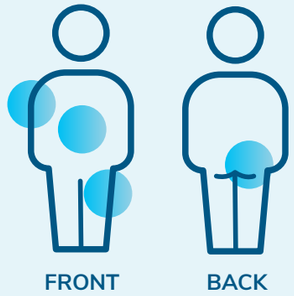
- When serum phosphorus increases above the upper limit of normal, there is an increased risk of nephrocalcinosis
- For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's fasting serum phosphorus levels

ADDITIONAL CONSIDERATIONS

Additional considerations for dosing and administration

When treating your patients with CRYSVITA, consider the following[1]:

- Patients should fast before serum phosphorus tests when specified in the PI
- If a patient misses a dose, resume CRYSVITA as soon as possible at the prescribed dose. To avoid missed doses, treatments may be administered 3 days on either side of the scheduled treatment date
- CRYSVITA should be administered by an HCP and via subcutaneous injection only



Injection sites should be rotated with each injection, administered at a different anatomic location than the previous injection. Injection site locations include[1]:

- Upper arms
- Upper thighs
- Buttocks
- Any quadrant of the abdomen

Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.[1]

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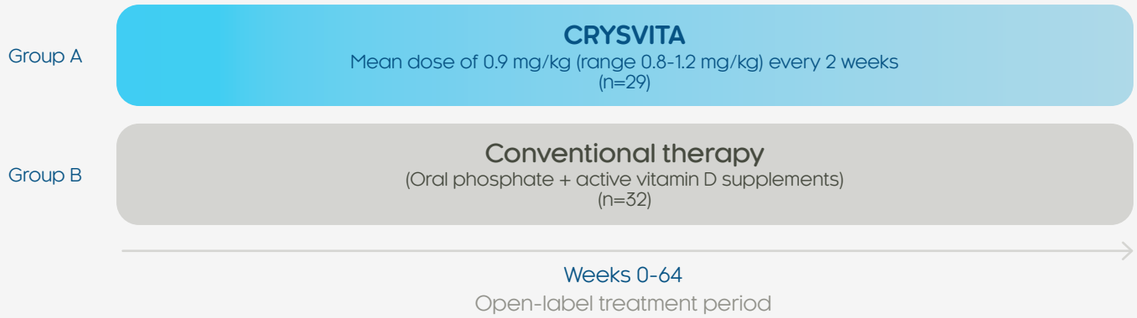
EFFICACY FOR CHILDREN

CRYSVITA® was effective in treating XLH[1]

Study 1[1] | Phase 3, a randomized study with patients aged 1-12 years



Primary endpoint[2]

- Healing of rickets at week 40, as assessed by Radiographic Global Impression of Change (RGI-C) score

Secondary endpoints[2,3]

- Lower extremity skeletal abnormalities, as assessed by RGI-C long leg score
- Severity of rickets, as measured by total Thacher Rickets Severity Score (RSS)
- Growth, as measured by standing height z-score
- Fasting serum phosphorus levels
- Alkaline phosphatase (ALP) activity
- Assessment of RGI-C at week 64
- Proportion of patients with mean RGI-C score ≥+2.0

Safety endpoint[3]

- Number of patients with adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation

CRYSVITA was evaluated in 2 other phase 2 studies. To learn more about Study 2 and Study 3, please see the full PI.[1]

Study 1 showed that CRYSVITA[1]:

Increased and sustained serum phosphorus levels

Helped heal rickets and reduce rickets severity

Increased growth

The most common adverse reactions (≥25% in the CRYSVITA group and greater than active control) in pediatric patients with XLH were pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, and dental caries.

No pediatric patients discontinued CRYSVITA treatment in Study 1.

LEARN MORE ABOUT
Study 1

Testing fasting serum phosphorus can help you monitor your patients' treatment with CRYSVITA.[1]

Important Safety Information

ADVERSE REACTIONS (cont'd)

Pediatric Patients (cont'd)

- Postmarketing experience reported in CRYSVITA-treated pediatric XLH patients: blood phosphorus increased.

Adult Patients

- Adverse reactions reported in more than 5% of CRYSVITA-treated adult XLH patients and in at least 2 patients more than placebo in one study are: back pain (15%), headache (13%), tooth infection (13%), restless legs syndrome (12%), vitamin D decreased (12%), dizziness (10%), constipation (9%), muscle spasms (7%), and blood phosphorus increased (6%).

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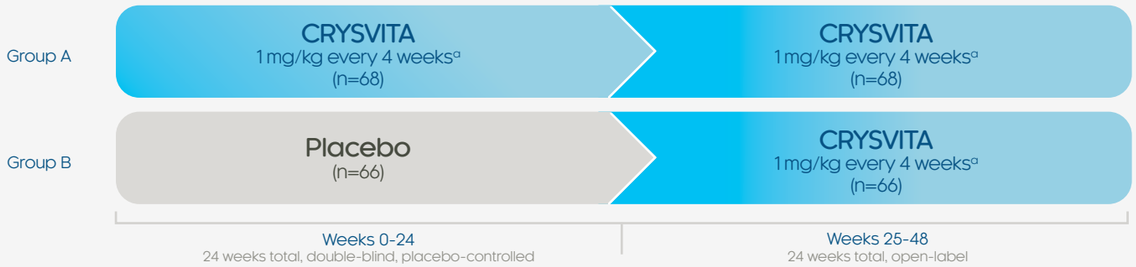
EFFICACY FOR ADULTS

In clinical trials, CRYSVITA® increased serum phosphorus levels[1]

Study 4[1] | Phase 3, a randomized study with patients aged 19-66 years



Primary endpoint[4]
- Proportion of patients achieving mean serum phosphorus levels above the lower limit of normal at the midpoint of dosing interval, averaged across dose cycles from baseline to week 24

Secondary endpoints[4,5]
- Change from baseline to week 24 in joint stiffness and physical function (as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) and pain (as assessed by Brief Pain Inventory)
- Change from baseline in serum phosphorus concentration at each study visit

Additional endpoints[5]
- Resolution of preexisting active pseudofractures and/or fractures at postbaseline visits, as defined by skeletal survey
- Number of patients with adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation

[a]Maximum dose was 90 mg total.[4]

Study 5[6] | Phase 3

Primary endpoint[6]
- Percent change from baseline to week 48 in osteoid volume to bone volume as determined by iliac crest biopsies

Secondary endpoint[6]
- Percent change from baseline in additional histomorphometric parameters, including:
  - Osteoid thickness
  - Mineralization lag time

Safety endpoint[7]
- Number of patients with AEs, SAEs, and AEs leading to discontinuation

In both studies of adult patients with XLH, oral phosphate and active vitamin D analogs were not allowed.[1]

[b]Maximum dose was 90 mg total.[7]
[c]Second biopsy was only performed if osteomalacia was present in baseline biopsy.[6]

Study 4 showed that CRYSVITA[1]:

Increased and maintained serum phosphorus levels

Study 5 showed that CRYSVITA[1]:

Helped heal osteomalacia

The most common adverse reactions (in >5% of CRYSVITA-treated patients and in at least 2 patients more than placebo) in patients with XLH were back pain, headache, tooth infection, restless legs syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, and blood phosphorus increased.

LEARN MORE ABOUT
Studies 4 and 5

Testing fasting serum phosphorus can help you monitor your patients' treatment with CRYSVITA.[1]

Important Safety Information

ADVERSE REACTIONS (cont'd)

Adult Patients (cont'd)

- Spinal stenosis is prevalent in adults with XLH, and spinal cord compression has been reported. It is unknown if CRYSVITA therapy exacerbates spinal stenosis or spinal cord compression.

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Important Safety Information

CONTRAINDICATIONS

CRYSVITA is contraindicated:

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- When serum phosphorus is within or above the normal range for age.
- In patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.

WARNINGS AND PRECAUTIONS

Hypersensitivity

- Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients with CRYSVITA. Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment.

Hyperphosphatemia and Risk of Nephrocalcinosis

- Increases in serum phosphorus to above the upper limit of normal may be associated with an increased risk of nephrocalcinosis. For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels.

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- Postmarketing experience reported in CRYSVITA-treated pediatric XLH patients: blood phosphorus increased.

Adult Patients

- Adverse reactions reported in more than 5% of CRYSVITA-treated adult XLH patients and in at least 2 patients more than placebo in one study are: back pain (15%), headache (13%), tooth infection (13%), restless legs syndrome (12%), vitamin D decreased (12%), dizziness (10%), constipation (9%), muscle spasms (7%), and blood phosphorus increased (6%).
- Spinal stenosis is prevalent in adults with XLH, and spinal cord compression has been reported. It is unknown if CRYSVITA therapy exacerbates spinal stenosis or spinal cord compression.

USE IN SPECIFIC POPULATIONS

- There are no available data on CRYSVITA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Serum phosphorus levels should be monitored throughout pregnancy. Report pregnancies to the Kyowa Kirin, Inc. Adverse Event reporting line at 1-844-768-3544.
- There is no information regarding the presence of CRYSVITA in human milk or the effects of CRYSVITA on milk production or the breastfed infant. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CRYSVITA and any potential adverse effects on the breastfed infant from CRYSVITA or from the underlying maternal condition.

PATIENT COUNSELING INFORMATION

- Advise patients not to use any oral phosphate and/or active vitamin D analog products.
- Instruct patients to contact their physician if hypersensitivity reactions, injection site reactions, and restless legs syndrome induction or worsening of symptoms occur.

You may report side effects to the FDA at (800) FDA-1088 or **www.fda.gov/medwatch**. You may also report side effects to Kyowa Kirin, Inc. at 1-844-768-3544.

For important risk and use information, please see the full Prescribing Information for CRYSVITA in pocket.

References:

1. CRYSVITA (burosumab-twza). US Prescribing Information. Kyowa Kirin, Inc.; March 2023. **2.** Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet*. 2019;393(10189):2416-2427. doi:10.1016/S0140-6736(19)30654-3 **3.** Data on file. 301-Week 64 CSR. Ultragenyx Pharmaceutical Inc.; 2019. **4.** Insogna KL, Briot K, Imel EA, et al. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res*. 2018;33(8):1383-1393. doi:10.1002/jbmr.3475 **5.** Data on file. 303 CSR. Ultragenyx Pharmaceutical Inc.; 2018. **6.** Insogna KL, Rauch F, Kamenický P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. *J Bone Miner Res*. 2019;34(12):2183-2191. doi:10.1002/jbmr.3843 **7.** Data on file. 304 EOS CSR. Ultragenyx Pharmaceutical Inc.; 2019.

[BUSINESS CARD PLACEHOLDER FPO]

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PATIENT SUPPORT

Personalized support for patients with Kyowa Kirin Cares

Kyowa KIRIN cares
ACCESS • ASSISTANCE • UNDERSTANDING

From access to reimbursement assistance,[d] Kyowa Kirin Cares provides dedicated support to your patients and their caregivers throughout their treatment journey with CRYSVITA®.

- **Case managers available to answer questions**
- **Help patients understand their financial options based on their insurance coverage**
- **Address treatment onboarding inquiries**
- **Educational information (non-medical)**

ENROLL YOUR PATIENTS TODAY

Patients and their caregivers can call 833-KK-CARES (833-552-2737) Monday through Friday, 8 AM to 8 PM (ET), to speak with a Kyowa Kirin Cares Case Manager.

The information provided on this page is intended for informational purposes, and should not be considered a guarantee of treatment or coverage.

[d]For eligible patients; additional terms and conditions apply. Insurance requirements may vary. Prior results do not guarantee future results or outcomes.

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Kyowa KIRIN

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