HELP THEM DISCOVER PrCRYSVITA®

CRYSVITA (burosumab injection) is indicated for the treatment of:

- FGF23-related hypophosphatemia in tumour-induced osteomalacia (TIO) associated with tumours that cannot be curatively resected or localized in adult patients.
- X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

TIO=tumour-induced osteomalacia.

WHEN MANAGING PATIENTS WITH TIO

Kyowa Kirin

Important safety information

Clinical use:

Treatment should be initiated and monitored by a health professional experienced in the management of patients with metabolic bone diseases.

- Safety and efficacy in geriatric patients (≥65 years) has not been established
- No clinical trial efficacy and safety experience with CRYSVITA in patients <1 year of age

Contraindications:

CRYSVITA is contraindicated:

- In use with oral phosphate and/or active vitamin D analogues (calcitriol or alfacalcidol)
- If serum phosphorus is within or above the normal range for age
- In patients with severe renal impairment or end-stage renal disease

Relevant warnings and precautions:

- Hyperphosphatemia and risk of ectopic mineralization, most commonly nephrocalcinosis
- Hypercalcemia and hyperparathyroidism
- Injection site reactions, especially in pediatric patients
- Vitamin D decrease
- Driving and operating machinery
- Hypersensitivity reactions such as rash, urticaria, and facial swelling
- Fertility
- Pregnancy and use of effective contraception in women of childbearing potential
- Breastfeeding

For more information:

Please consult the CRYSVITA Product Monograph at https://www.kkna.kyowakirin.com/wp-content/uploads/Crysvita-PM-English.pdf for important information relating to adverse reactions and drug interactions that has not been discussed in this piece. The Product Monograph is also available by calling us at 1-866-590-9508.

TIO is an acquired and often misdiagnosed disorder of renal phosphate wasting[2,3]

TIO can be difficult to recognize, which often results in patients facing a significant delay in their diagnosis.[2]

95%

misdiagnosis rate

In a retrospective study conducted in China, 95% (137/144) of patients with TIO were initially misdiagnosed[4]

1.9–7.0 per 1,000,000

estimated prevalence

The global prevalence of TIO is unknown, but two studies (one conducted in Germany, the other in Denmark), have estimated the prevalence to be 0.19–0.70 per 100,000 persons[2,5,6]

TIO can be challenging to diagnose due to the following factors:[2]

- The clinical presentation is not well-recognized due to the rarity of disease.
- Serum phosphate is not often included in blood chemistry panels.
- The association between low serum phosphate and presenting clinical symptoms is not always recognized.
- The differential diagnosis of other conditions of hypophosphatemia must be considered.
- Tumour localization may be difficult.

TIO is typically caused by the secretion of fibroblast growth factor 23 (FGF23) from benign, phosphaturic mesenchymal tumours.[2]

IN A SINGLE-ARM, OPEN-LABEL STUDY OF 14 ADULT PATIENTS WITH TIO (TUMOUR-PRODUCED, FGF23-RELATED HYPOPHOSPHATEMIA NOT AMENABLE TO SURGICAL EXCISION OR NOT ABLE TO BE LOCATED),[1†]

CRYSVITA demonstrated an increase in mean serum phosphorus levels from baseline through Week 24[1]

Mean (SD) serum phosphate increased from 1.60 (0.47) mg/dL at baseline to 2.64 (0.76) mg/dL averaged across the midpoint of dose intervals through Week 24.[1]

50%

of patients (7/14) achieved a mean serum phosphorus level above the LLN, averaged across the midpoint of dose intervals through Week 24 (95% CI:[‡] 26.8, 73.2)

LLN=lower limit of normal; SD=standard deviation.
† A Phase 2, open-label, single-arm study in 14 adults with TIO (age 33–68 years). Patients had a confirmed diagnosis of FGF-23 related hypophosphatemia produced by an underlying tumour that was not amenable to surgical excision or could not be located. Patients received CRYSVITA every 4 weeks at a starting dose of 0.3 mg/kg that was titrated to achieve a fasting serum phosphorus level of 2.5 to 4.0 mg/dL. Oral phosphate and active vitamin D analogues were discontinued two weeks prior to study enrolment. The co-primary endpoints were i) the proportion of patients with mean fasting serum phosphorus >2.5 mg/dL (0.81 mmol/L) at the midpoint of the dosing interval between baseline and Week 24; and ii) change from baseline in parameters of osteomalacia at Week 48 (osteoid thickness, osteoid surface/bone surface, osteoid volume/bone volume, and mineralization lag time).[1,5,9]
‡ Calculated using the Wilson score method.

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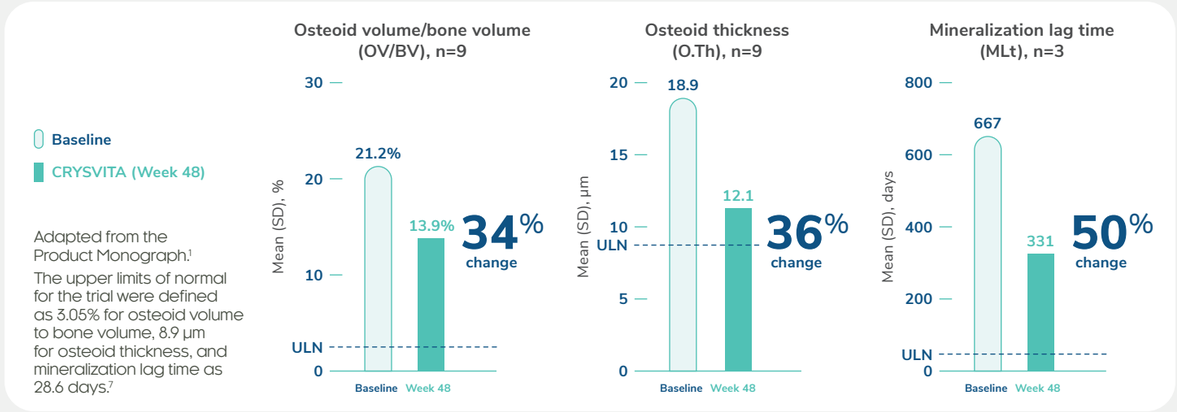
CRYSVITA: Bone histomorphometry at Week 48[1]

Osteomalacia was present at baseline in 9 out of 11 patients with paired biopsies and healing was observed after 48 weeks of treatment.[1]



Radiographic evaluation of osteomalacia (exploratory endpoint)[1]

The number of areas of tracer uptake on bone scans decreased from Week 48 through Week 144, suggesting healing of bone abnormalities, as demonstrated by ^{99m}technetium-labelled whole body bone scans.[1]

- Bone scans allow for assessment of sites of increased tracer uptake in a wide range of bone conditions, including osteomalacia.
- In patients with TIO, increased tracer uptake on bone scan is presumed to be nontraumatic fractures and pseudofractures.
- At baseline, all patients had areas of tracer uptake with a total of 249 bone abnormalities across 14 patients.

Administer by subcutaneous injection according to the following instructions[1]

Treatment should be initiated and monitored by a health professional experienced in the management of patients with metabolic bone diseases.

FOR PATIENTS AGED 18 YEARS AND OLDER

RECOMMENDED STARTING DOSE: **0.5** mg/kg of body weight **(every 4 weeks)**

Round to the nearest 10 mg
Maximum dose: 2 mg/kg every 2 weeks

Monitoring for dose adjustments:

After initiating CRYSVITA, assess fasting serum phosphorus on a monthly basis, measured 2 weeks post-dose, for the first 3 months of treatment and thereafter as appropriate.

If serum phosphorus is within the normal range:

Continue treatment with the same dose.

If serum phosphorus is below the normal range:

Increase dose† stepwise up to a maximum dose of 2 mg/kg administered every 2 weeks, as per the table that follows.

- Dose should not be adjusted more frequently than every 4 weeks.
- For patients who do not reach a serum phosphorus greater than the lower limit of the normal range, consider dividing total dose administered every 4 weeks and administering every 2 weeks.

	1st dose increase‡	2nd dose increase‡	3rd dose increase‡	4th dose increase	5th dose increase (max. dose)
If serum phosphorus 2 weeks post-dose adjustment is below lower limit of normal	1 mg/kg every 4 weeks OR 0.5 mg/kg every 2 weeks	1.5 mg/kg every 4 weeks§ OR 0.75 mg/kg every 2 weeks	2 mg/kg every 4 weeks§ OR 1 mg/kg every 2 weeks	1.5 mg/kg every 2 weeks	2 mg/kg every 2 weeks

Adapted from the CRYSVITA Product Monograph.[1]

If serum phosphorus is above the normal range:

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

Once serum phosphorus is below the normal range, **restart CRYSVITA at approximately half the initial starting dose administered every 2 weeks**.

Reassess serum phosphorus **2 weeks after the dose adjustment**. If the level remains below the normal range after the re-initiation dose, the dose can be adjusted.

*See CRYSVITA Product Monograph for complete dosing and administration instructions.

If the patient undergoes treatment of the underlying tumour (excision or radiation):

Interrupt treatment with CRYSVITA and reassess the serum phosphorus level after treatment of the tumour has been completed.

If serum phosphorus remains below the normal range, restart CRYSVITA at the patient's starting dose.

TIO=tumour-induced osteomalacia.
†Rounded to the nearest 10 mg.

‡For those individuals not reaching a serum phosphorus greater than the lower limit of the normal range, physicians may consider dividing total dose administered every 4 weeks and administering every 2 weeks.
§In patients with high body weight, if the calculated dose is greater than 180 mg every 4 weeks, move to a divided dose every 2 weeks.

For more information and resources,
visit CRYSVITAHCP.ca

References: 1. CRYSVITA (burosumab injection) Product Monograph. Kyowa Kirin Inc. **2.** Bilezikian, JP. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Wiley-Blackwell, 2019. **3.** Jan de Beur SM, *et al.* Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia. *J Intern Med.* 2023;293(3):309-328. **4.** Feng J, *et al.* The diagnostic dilemma of tumor induced osteomalacia: A retrospective analysis of 144 cases. *Endocr J.* 2017;64(7):675-683. **5.** May M, *et al.* Epidemiology of tumor-induced osteomalacia in Germany based on real world data. *Calcif Tissue Int.* 2023;113:630-639. **6.** Abrahamsen B, *et al.* Epidemiology of tumor-induced osteomalacia in Denmark. *Calcif Tissue Int.* 2021;109(2):147-156. **7.** Jan de Beur SM, *et al.* Burosumab for the treatment of tumor-induced osteomalacia. *J Bone Miner Res.* 2021;36(4):627-635. **8.** Jan de Beur SM, *et al.* Supplementary appendix to: Burosumab for the treatment of tumor-induced osteomalacia. *J Bone Miner Res.* 2021;36(4):627-635. **9.** Ultragenyx Pharmaceutical Inc. UX023T-CL201 Protocol Clinical Study Protocol Amendment 6. September 26, 2019.

Pr CRYSVITA® burosumab injection Solution for Subcutaneous Injection 10, 20, 30 mg/mL

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KYOWA KIRIN

REVIEWED BY PAAB