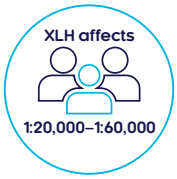
Key Facts about XLH (X-linked hypophosphataemia) and CRYSVITA® ▼ (burosumab)

XLH

What is XLH?

XLH is a rare, hereditary, progressive and lifelong renal phosphate wasting disorder, caused by mutations in the *PHEX* (phosphate-regulating endopeptidase homolog, X-linked) gene that leads to excess activity of fibroblast growth factor 23 (FGF23)[1–4]

What is the prevalence of XLH?



XLH is a rare disease that affects approximately 1 in 20,000–60,000 people[1,5]

How is XLH inherited?

XLH is inherited in an X-linked dominant pattern; however, 20–30% of cases arise from spontaneous mutations[6,7]

What causes XLH?

XLH is caused by mutations in the *PHEX* gene,[4,5] which is located on the X chromosome

What does it mean for patients with XLH?

Excess FGF23:

- Decreases renal phosphate reabsorption, which increases urinary phosphate excretion[8]
- Decreases active vitamin D ($1,25[OH]_2D$) production, which reduces intestinal phosphate absorption[8]

The resulting chronic hypophosphataemia impairs bone mineralisation, leading to a variety of clinical manifestations that can impair patients' physical function and quality of life[9]

XLH is **not** just a bone disease – it is a multisystemic disease that impacts muscles and dentition as well[4,10]

CRYSVITA®

What is CRYSVITA®?

- CRYSVITA® is a recombinant, fully human monoclonal antibody IgG1 (immunoglobulin G1) that binds to and inhibits excess FGF23 activity[11]
- It is the first and only disease-modifying biologic treatment that targets the pathophysiology of XLH[11]

How does CRYSVITA® work?

By inhibiting excess FGF23 activity, CRYSVITA® helps restore phosphate homeostasis in people with XLH to improve bone mineralisation, mobility and pain[11–14]

Who can receive CRYSVITA®?

CRYSVITA® is indicated for the treatment of XLH, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults[11]

Why use CRYSVITA®?

The efficacy and safety of CRYSVITA® in children aged 1–12 years and adults with XLH have been investigated in a global clinical development programme[12–16]

A phase 3 clinical study in children with XLH showed that compared with continuing conventional therapy, switching children to CRYSVITA®:[12]

- Improved phosphate homeostasis
- Significantly improved rickets healing and reduced its severity up to Week 64
- Significantly improved growth and mobility outcomes up to Week 64
- Significantly improved biochemical markers of phosphate regulation and bone health up to Week 64

In this phase 3 clinical study, CRYSVITA® had an acceptable safety profile over 64 weeks in children with XLH[12]

Phase 3 clinical studies in adults with XLH:

- Phosphate homeostasis, fracture healing, bone mineralisation and remodelling improved, and stiffness were reduced in the CRYSVITA® group compared with the placebo group in a double-blind placebo-controlled study[16]
- Phosphate homeostasis improved, and bone quality, mineralisation and remodelling increased in patients treated with CRYSVITA® by Week 48 when compared with that at baseline in a single-arm study[14]
- There was more healing of baseline fractures/pseudofractures in patients who continued CRYSVITA® compared with those who received CRYSVITA® after placebo at Week 48 in an open-label study[13]
- When placebo-treated patients started CRYSVITA® treatment at Week 24, the healing of fractures/pseudofractures at Week 48 was similar to the healing at Week 24 in those who received CRYSVITA® therapy from the beginning of the study[13]
- CRYSVITA® led to sustained improvements in pain, stiffness and physical function and mobility at Week 48 when compared with that at baseline in a double-blind placebo-controlled study[13]

In these phase 3 studies, CRYSVITA® had an acceptable safety profile up to 48 weeks in adults with XLH[13,14]

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system found under Section 4.8 of the Summary of Product Characteristics.

1. Beck-Nielsen SS, et al. *Eur J Endocrinol.* 2009;160:491–7. **2.** Endo I, et al. *Endocr J.* 2015;62:811–6. **3.** Carpenter TO, et al. *J Bone Miner Res.* 2011;26:1381–8. **4.** Haffner D, et al. *Nat Rev Nephrol.* 2019;15:435–55. **5.** Rafaelsen S, et al. *Eur J Endocrinol.* 2016;174:125–36. **6.** Rajah J, et al. *Eur J Pediatr.* 2011;170:1089–96. **7.** Raimann A, et al. *Wien Med Wochenschr.* 2020;170:116–23. **8.** Razzaque MS. *Nat Rev Endocrinol.* 2009;5:611–9. **9.** Linglart A, et al. *Endocr Connect.* 2014;3:R13–30. **10.** Beck-Nielsen SS, et al. *Orphanet J Rare Dis.* 2019;14:58. **11.** Kyowa Kirin Limited. CRYSVITA® (burosumab). Summary of Product Characteristics. **12.** Imel EA, et al. *Lancet.* 2019;393:2416–27. **13.** Portale AA, et al. *Calcif Tissue Int.* 2019;105:271–84. **14.** Insogna KL, et al. *J Bone Miner Res.* 2019;34:2183–91. **15.** Carpenter TO, et al. *N Eng J Med.* 2018;378:1987–98. **16.** Insogna KL, et al. *J Bone Miner Res.* 2018;33:1383–93.

This factsheet is developed and funded by Kyowa Kirin International.
Prescribing information is available overleaf. CRYSVITA® has a conditional marketing authorisation.

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Prescribing Information:

▼CRYSVITA® (Burosumab)

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each vial contains 10/20/30 mg burosumab in 1 mL solution for injection. Contains 45.91 mg/mL sorbitol. **Indication:** Treatment of X-linked hypophosphataemia, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults. **Dosage and Administration:** At initiation, fasting serum phosphate concentration should be below the reference range for age. For subcutaneous use. Treatment should be initiated by a physician experienced in the management of patients with metabolic bone diseases. Discontinue oral phosphate and active vitamin D analogues 1 week prior to initiation of treatment. **Recommended starting dose in children and adolescents aged 1 to 17 years** is 0.8 mg/kg of bodyweight every 2 weeks. Maximum dose 90 mg. Round dose to the nearest 10 mg. **Dose conversion at age 18 years:** At 18 years of age, the patient should convert to the adult dose and dosing regimen. **Recommended starting dose in adults** is 1.0 mg/kg of bodyweight every 4 weeks. Maximum dose 90 mg. Round dose to the nearest 10 mg. Inject in upper arm, abdomen, buttock or thigh, 1.5 ml max. volume per site. If >1.5 mL is required, split total volume over two sites. Rotate sites and monitor for signs of reactions. Self/carer-administration may be suitable if no immediate dose modifications anticipated. First self-administered dose after drug initiation or dose change should be under supervision of a healthcare professional. Clinical monitoring of patient, including phosphate levels, must continue as required. **Dose Adjustments:** Measure fasting serum phosphate and adjust dose accordingly (not more frequently than every 4 weeks) (see SmPC). **Special Populations:** Safety/efficacy not established in renal impairment and age <1 year. Limited data are available in patients over 65 years of age. **Contraindications:** Hypersensitivity to ingredients (Refer to SmPC). Concurrent administration with oral phosphate, active vitamin D analogues. Fasting serum phosphate above normal range for age. Severe renal impairment or end stage renal disease. **Warnings and Precautions:** *Ectopic mineralisation:* stop oral phosphate and active vitamin D analogues at least 1 week prior to treatment. Monitor for signs and symptoms of nephrocalcinosis at the start of treatment and every 6 months for the first year and annually thereafter. Monitor plasma alkaline phosphatase (ALP), calcium, parathyroid hormone (PTH) and creatinine every 6 months (3 months for children 1 - 2 years). Monitor urine calcium and phosphate every 3 months. *Hyperphosphataemia:* monitor fasting serum phosphate. Dose interruption and/or reduction may be required. Measure post-prandial serum phosphate. *Serum PTH:* increases have been observed during treatment. Measure serum PTH periodically. *Injection site reactions:* Interrupt administration in any patient experiencing severe injection site reactions. *Hypersensitivity:* discontinue CRYSVITA® if serious reactions occur. **Drug Interactions:** Concurrent oral phosphate and active vitamin D analogues contraindicated (increased risk of hyperphosphataemia and hypercalcaemia). Caution when combining with calcimimetic medicinal products (potential to exacerbate hypocalcaemia). **Pregnancy and Lactation:** CRYSVITA is not recommended during pregnancy and in women of childbearing potential not using contraception. No or limited amount of data in pregnant women. Studies in animals have shown reproductive toxicity. It is unknown whether burosumab/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. **Undesirable effects (Refer to SmPC for full safety profile):** Mild or moderate hypersensitivity reactions (including: injection site rash, rash, urticaria, swelling face, dermatitis) were reported in 18% of paediatric patients and 6% of adult patients. The most common adverse drug effects in paediatric patients were: injection site reactions (56%), cough (56%), headache (50%), pyrexia (43%), pain in extremity (40%), vomiting (39%), tooth abscess (35%), vitamin D decrease (32%), diarrhoea (25%), rash (24%), nausea (15%), constipation (11%), dental caries (11%) and myalgia (11%). The most common adverse drug reactions in adult patients were: back pain (23%), headache (21%), tooth infection (19%), vitamin D decrease (15%), restless legs syndrome (13%), muscle spasms (12%), and dizziness (11%).

Date of Preparation of Prescribing Information: July 2021.
Legal Category: POM.
Marketing Authorisation numbers and list price:
1 x CRYSVITA 10mg; EU/1/17/1262/001, £2,992.
1 x CRYSVITA 20 mg; EU/1/17/1262/002, £5,984.
1 x CRYSVITA 30 mg; EU/1/17/1262/003, £8,976.
Marketing Authorisation holder: Kyowa Kirin Holdings B.V., Bloemlaan 2, 2132NP Hoofddorp, The Netherlands, +31 (0) 237200822.

CRYSVITA has a conditional Marketing Authorisation in Europe. A conditional authorisation in Europe is granted when a medical product meets an important medical need and when the availability and benefit to health outweighs the risk in additional data being required. The European regulatory agency will review new information on CRYSVITA annually and the Summary of Product Characteristics will be updated accordingly.

Please refer to the Summary of Product Characteristics for details on full safety profile of CRYSVITA. Adverse events should be reported to Kyowa Kirin at medinfo@kyowakirin.com or by phone:+44 (0)1896 664000.

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