CRYSVITA® burosumab

THE DAWN OF A NEW ERA IN XLH MANAGEMENT

The Unforgettable Role of Phosphorus in the Development of Strong Bones

A Satellite Symposium on Hypophosphatemic Rickets at the 11th Asia Pacific Paediatric Endocrine Society 2021 Scientific Meeting (APPES 2021)

This article presents key highlights from two presentations about hypophosphatemic rickets focussing on X-linked hypophosphatemia (XLH). The topics revolved around the importance of early diagnosis and treatment of hypophosphatemic rickets and introduced a new era of managing XLH with burosumab.

Professor Dr Muhammad Yazid Jalaludin
Consultant Paediatric Endocrinologist
University Malaya Medical Centre
Kuala Lumpur, Malaysia

Approach to the Diagnosis of Hypophosphatemic Rickets

Phosphorus is, more often than not, the "*forgotten mineral*" when discussing musculoskeletal health. Hypophosphatemia causes a multitude of conditions that can lead to poor bone development, such as rickets, and which affect the quality of life of children and adults. The early diagnosis of hypophosphatemia in children is crucial as it ensures that they receive early treatment for better outcomes.

In humans, 85% of phosphorus is found in the skeleton complexed with calcium to form hydroxyapatite, while the remaining have a critical role in most intracellular processes. It is important to remember that phosphate levels in adults are very different than in children, as the normal range reduces by age. Any value <1 mmol/l in children (0-12-years-old) is considered low.[1]

Regulation of phosphate homeostasis

A significant proportion of phosphorus from foods are absorbed through the gut and is incorporated into the "phosphate pool" to be utilised. Apart from being used in the bone formation-resorption cycle and other cellular processes, it is also channelled to the kidneys to be excreted via the urine.[2]

Serum phosphate is primarily regulated by the kidneys through the fibroblast growth factor (FGF23) and parathyroid hormone (PTH). Of these, FGF23 is the primary regulator of serum phosphate levels. When serum phosphate rises through a positive feedback loop, so does FGF23. It decreases phosphate reabsorption in the kidney, causing phosphate wasting in the urine, and reduces the production of vitamin D by the kidney, which decreases the absorption of dietary phosphate from the gut (Figure 1).[3,4]

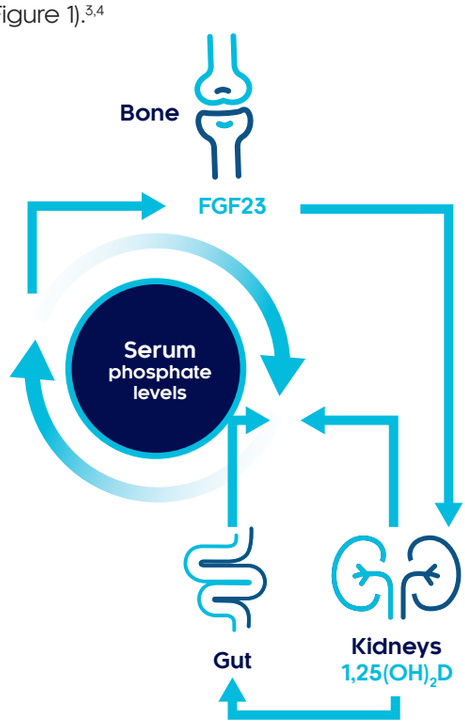

Figure 1: FGF23 is the primary regulator of serum phosphate homeostasis and exerts its action in the kidneys and, to an extent, the gut. 1,25(OH)2D, vitamin D; FGF23, fibroblast growth factor-23. Adapted from Bergwitz C, Jüppner H. Ánnu Rev Med. 2010.[5]

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Approach to hypophosphatemic rickets

The diagnostic approach to hypophosphatemic rickets is similar to other paediatric bone and mineral disorders. It should include a detailed history of presenting illness, physical examination, family history and laboratory investigations.

Specifically, for hypophosphatemic rickets, it is essential to determine if it is of renal or non-renal origins. Among the investigations that can point to a renal origin of hypophosphatemia is the low tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR). Low TmP/GFR and serum phosphate indicate inappropriate renal phosphate wasting. Conversely, in non-renal causes, the TmP/GFR is high.[5]

One of the causes of renal hypophosphatemia is mediated by the dysfunction of FGF23 secretion and is associated with different gene mutations and inheritance, such as XLH, which is autosomal dominant, and the less common autosomal recessive hypophosphatemic rickets.[5]

XLH – a rare inherited skeletal disorder

XLH is a rare, genetic (Figure 2), chronic and progressive skeletal disorder caused by the loss-of-function *PHEX* gene mutation that leads to excess FGF23 production. It is characterised by renal phosphate wasting and is the most common form of heritable hypophosphatemic rickets.[6,7] Though it is inherited through its X-linked dominance,[5] 20-30%[8–12] of cases arise from spontaneous mutations. Cumulatively, it affects approximately 1 in 20,000 to 1 in 60,000 people.[7,13]

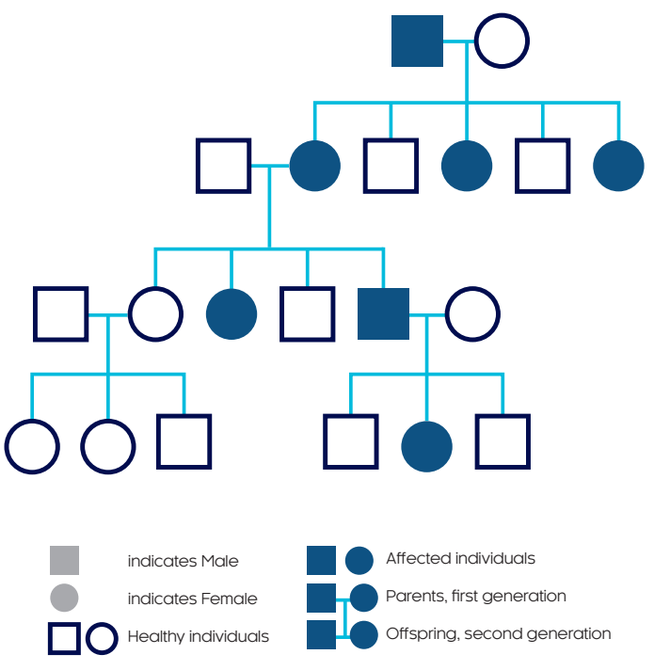


Figure 2: Pedigree analysis illustrating the X-linked dominance of XLH.

Features of XLH in children and adolescents

Patients with XLH can present with associated disease manifestations that span a wide spectrum (Figure 3) and have distinctive laboratory findings that guide diagnosis (Table 1). In children, the basic criteria for clinical diagnosis of XLH include progressive lower extremity bowing, impaired growth after the onset of weight-bearing and the characteristic signs of rickets.[14,15] XLH is also associated with functional limitations that reduce the quality of life in children and adults.[15,16]

CRANIAL
- Skull abnormalities such as craniosynostosis and Chiari malformations[14]

DENTAL
- Prone to spontaneous dental abscesses due to defects in enamel, dentin and cementum[14]

MUSCULOSKELETAL

SKELETAL
- Skeletal disease, leading to lower extremity deformity and loss of growth potential[6,14,15]

MUSCULAR
- Substantially decreased lower extremity muscle strength that contributes to functional deficits[16]

BONE AND JOINT-RELATED
- Frequent bone and joint pain, especially at the knee, upper leg and ankle[14,15]

Figure 3: Clinical manifestation of XLH in children and adults.[6,14–16]

Expected laboratory values for XLH

Serum phosphate	↓
Serum calcium	↔
Serum ALP	↑
Serum PTH	↔ , ↑
Serum 25OHD	↔
Serum 1,25(OH)$_2$D	↔ , ↓
Serum FGF23	↑
TmP/GFR	↓
Urine calcium	↔ , ↓

Table 1: Laboratory findings of patients with FGF23-mediated XLH. 1,25(OH)$_2$D; active vitamin D; 25OHD, vitamin D; ALP, alkaline phosphatase; FGF, fibroblast growth factor-23; TmP/GFR, tubular maximum phosphate reabsorption per glomerular filtration rate. Adapted from Imel EA, Econs MJ, 2012.[5]

As XLH is the most common form of heritable hypophosphatemic rickets,[6,7] evaluation of at-risk infants and children is essential for early diagnosis and treatment initiation, which have been shown to improve clinical outcomes.[17] Though molecular genetic testing to establish the *PHEX* gene mutation could help confirm a diagnosis of XLH, it is **not essential** in the presence of the characteristic biochemical findings of XLH (Table 1).

Early diagnosis of XLH is important to improve patient outcomes

As skeletal deformity and growth impairment begin in early childhood, early initiation of treatment for XLH could lead to more favourable height outcomes. In a study involving 19 XLH children, those diagnosed and treated with oral phosphate and active vitamin D analogues at <1-years-old showed improved height and biochemical outcomes, and decreased rickets severity compared to those who started treatment at ≥1 year of age (Figure 4).[17] The early diagnosis and, therefore, treatment of XLH has also demonstrated benefits in improving height outcomes in adulthood by mitigating the paediatric consequence of short stature and leg deformities,[17] and could reduce the risk of arthritis and joint replacement,[18] and improve dental health.[14]

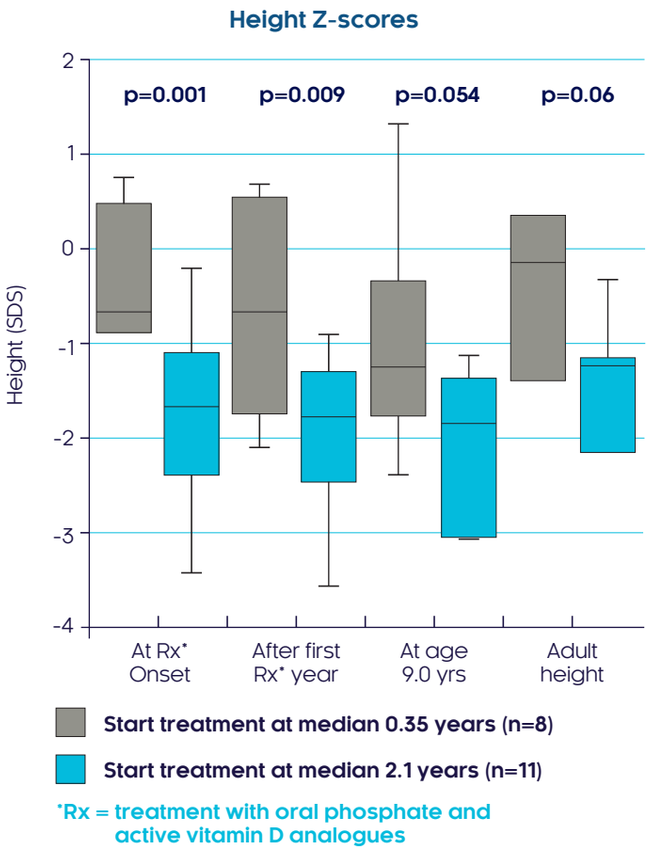


Figure 4: Treatment was with oral phosphate and active vitamin D analogues. Initiation of treatment for XLH children at median 0.35 years demonstrated significantly better height Z-scores than those who started treatment at a median age of 2.1 years. Adapted from Mäkitie O, et al. J Clin Endocrinol Metab 2003.[17]

Key messages

- Phosphate homeostasis is a major factor in the maintenance of musculoskeletal health[4]
- XLH is an inherited, chronic and progressive skeletal disorder leading to the over secretion of FGF23 and is the most common form of heritable hypophosphatemic rickets[6,7]
- Early diagnosis of XLH can be typically reached with clinical and biochemical findings, and family history[5,6,14,15]
- With early diagnosis, the initiation and optimisation of XLH treatment could have long-term benefits on clinical manifestations and complications in later life[14,17,18]

Professor Craig Munns
Paediatric Endocrinologist & Professor of Paediatric Bone and Mineral Medicine
The Children's Hospital at Westmead, University of Sydney, Australia

New Era of Management of X-linked Hypophosphatemia

XLH is the most common heritable form of hypophosphatemic rickets. Though it is conventionally treated with phosphate salts and active vitamin D (calcitriol), the treatment has its limitations. The availability of a novel antibody, burosumab, that targets the FGF23 marks a new era in the management of XLH rickets.

Case of XLH rickets

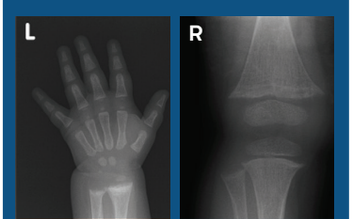
7-month old boy
History
- Full-term via elective caesarean section
- First born

Physical exam
- Normal length and weight
- Normal development
- **Frontal bossing**
- **Rachitic rosary**
- **Flaring wrists**
- Systemic exam - normal

No family history of bone or growth disorder

Lab investigations:
Normo-calcaemic rickets
- Calcium 2.31 mmol/L ↔
- Magnesium 0.94 mmol/L ↔
- **Phosphorus 0.70 mmol/l ↓**
- **Alkaline phosphatase 586 µ/l ↑**
- **PTH 6.2 pmol/l ↔**
- **Vitamin D 57 nmol/L ↔**
- ***PHEX* gene mutation +**

X-rays —
Cupping & flaring

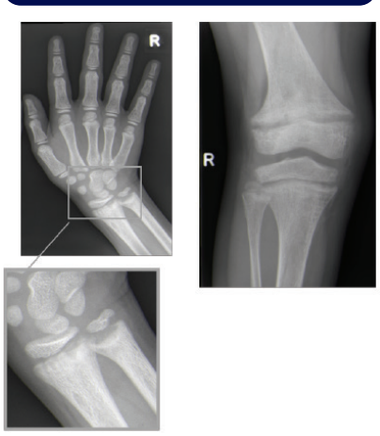


Conventional treatment
- Phosphate 20 mg/kg/day + Calcitriol 20 ng/kg/day
- Start low (1/3rd the standard dose) & slowly increase to avoid gastrointestinal effects
- Standard dose: **Phosphate 750 mg/day (4-5 divided doses) + Calcitriol 250 ng/bd**

10 years on treatment
- Genu valgum +
- Aches and pains +
- Short stature +
- Recurrent tooth abscess +
- Phosphorus 0.87 mmol/l ↓
- Alkaline phosphatase 619 µ/l ↑
- PTH 4.3 pmol/l ↔
- X-rays – persistent evidence of rickets

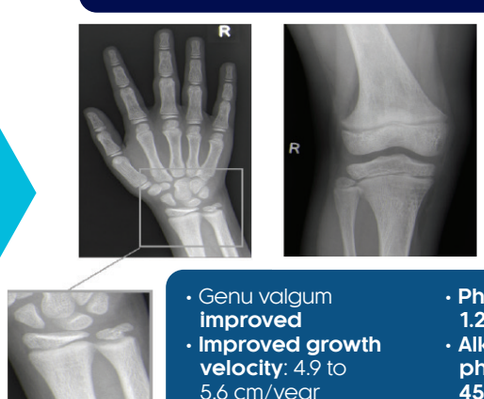
What next?
A novel treatment for XLH?

At 10 years of age, the child was included in a phase III trial and randomised to receive burosumab



Burosumab
0.8 mg/kg
second weekly
+
Cholecalciferol
400 IU daily

At 11.5 years of age
1.5 years on burosumab



- Genu valgum **improved**
- **Improved growth velocity**: 4.9 to 5.6 cm/year
- **No** tooth abscess
- **Phosphorus 1.2 mmol/l ↔**
- **Alkaline phosphatase 450 µ/l ↔**
- PTH 2.3 pmol/l ↔
- **No** limb pain

Figure 5. A case study of a patient with XLH rickets that was diagnosed at infancy and followed up to 11.5 years old. This case illustrates the importance of early diagnosis of XLH rickets and the limitations of conventional oral phosphate and active vitamin D treatment. The addition of burosumab significantly improved the clinical and radiological outcomes of the patient.

Treatment goals for XLH

The goals for treating XLH in children are to,[6,14]

- improve their growth by improving the skeletal deformities in rickets
- improve osteomalacia
- reduce bone pain and tooth abscess
- avoid complications

For adults, they are to also prevent arthritis, decrease or heal pseudo-fractures and improve healing after orthopaedic surgery.[6,14] Treatment should be started early, preferably at <1-years-old for better outcomes (Figure 4).[14,17,18]

Conventional treatment for XLH in children

The conventional treatment available for XLH is the combination of phosphate salts 20-60 mg/kg/day and active vitamin D (calcitriol) 20-30 ng/kg/day. However, due to its gastrointestinal adverse events, the therapy is generally started at a lower dose and gradually increased to the standard doses of 750 mg/day in 4-5 divided doses and 250 ng twice daily.[6,14]

There are some challenges with conventional therapy. When treating XLH with conventional therapy, the aim is not to increase phosphate to normal levels. Normal serum phosphate levels indicate overtreatment with phosphate salts which can lead to hyperparathyroidism or nephrocalcinosis.[6] The primary outcome measure is height, whilst 3-monthly monitoring of biochemical markers are required during therapy to determine the need to modify the dosing strength of either phosphate salts or calcitriol.[6] Radiological monitoring of skeletal improvement and renal ultrasound to monitor for nephrocalcinosis every 1-2 years is also recommended.[6,14] Even with optimised treatment with oral phosphate and active vitamin D, stature is generally short with a significant reduction in leg length, while sitting height is maintained, indicating that spinal height is relatively normal in these children.[19]

Other than the gastrointestinal side effect of phosphate salts, conventional therapy has other risks. These include the occurrence of hyperparathyroidism (particularly in overtreatment with phosphate), hypercalciuria and hypercalcaemia and nephrocalcinosis. Long-term treatment could lead to chronic kidney disease, hypertension and ectopic calcification.[6,14]

A new era of XLH management in children

Burosumab is a recombinant human IgG1 monoclonal antibody that binds to FGF23 and inhibits its biologic activity.[7,14] A phase III study of burosumab involving 61 children with XLH was conducted to determine the efficacy and safety of burosumab against conventional therapy.[20] The children were stratified by age (<5 and ≥5 years of age) and were randomised to receive either 0.8 mg/kg subcutaneous (SC) burosumab two weekly (n=29) or oral phosphate and active vitamin D (n=32) for 64 weeks. The primary assessments were the height Z-score and Radiographic Global Impression of Change (RGI-C) based on a 7-point scale describing temporal changes at the wrist, knee and leg. All 61 subjects completed 64 weeks of treatment and were included in the efficacy and safety analyses.

Burosumab treatment resulted in a sustained increase of **fasting serum phosphorus in both age groups**, while conventional therapy showed little change.[20] Burosumab also resulted in a decrease in serum alkaline phosphatase, demonstrated rapid improvement and normalisation of the TmP/GFR resulting in a reduction of urine phosphate loss, improved rickets more than conventional therapy (Figure 6) and achieved greater height Z-score change (Figure 7) and annualised growth velocity at 64 weeks than with conventional therapy (6.65 cm vs 5.94 cm, respectively).[20] The height outcomes were better in the younger age group, suggesting again that the earlier the treatment, the better the growth outcomes.

In terms of safety, burosumab was well tolerated, with most adverse events being mild-to-moderate in severity. More than half (57%) had a transient local reaction to the SC injection, while 37.9% had hypersensitivity to the treatment,[20] which was easily managed with antihistamines before therapy. Although 55.2% of the children in this study experienced pyrexia, this is not typically observed in clinical practice.

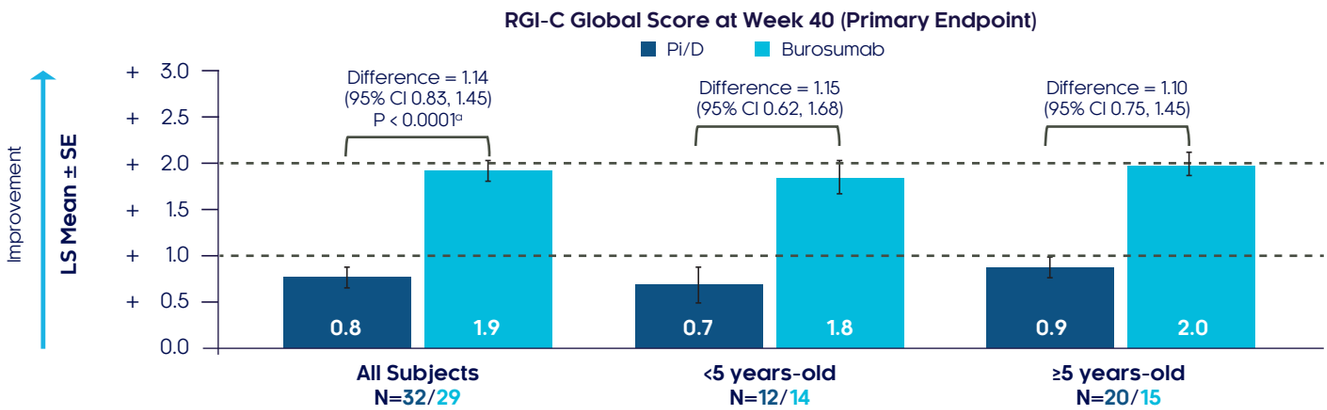


Figure 6: The radiographic changes after 40 weeks of treatment with burosumab in children <5 and ≥5-years old compared to conventional therapy. [a]ANCOVA model; P-values not calculated for age subgroups. Radiographic Global Impression of Change (RGI-C Scale: +3.0=complete healing, +2.0=substantial healing, +1.0=minimal healing, 0.0=unchanged, -1.0=minimal worsening, -2.0=moderate worsening, -3.0=severe worsening). CI, confidence interval; Pi/D, phosphate salts/calcitriol; SE, standard error. Adapted by Imel et al. Lancet 2019.[20]

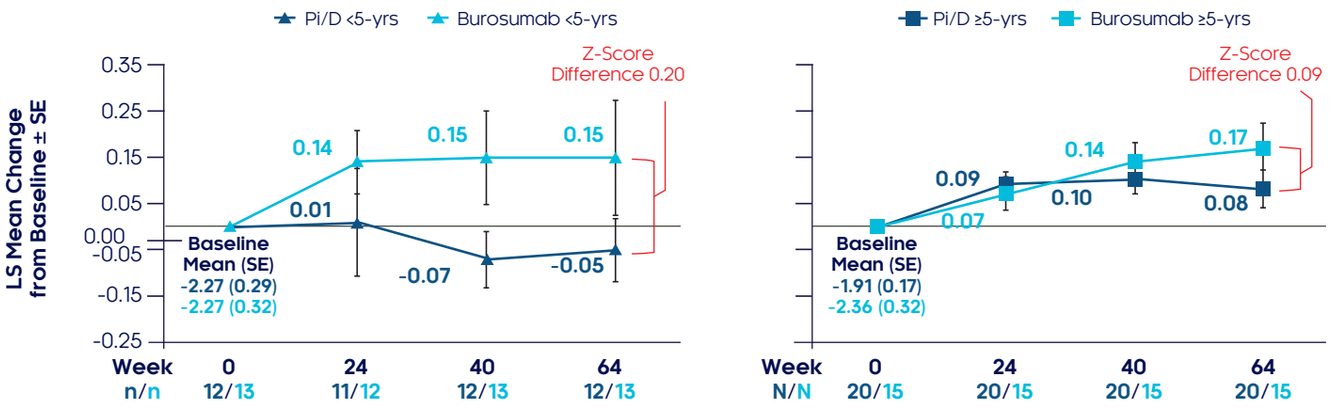


Figure 7: The difference in height z-score between treatments. Pi/D, phosphate salts/calcitriol; SE, standard error. Adapted by Imel et al. Lancet 2019.[20]

Key messages

- The available XLH conventional therapy of phosphate salts and calcitriol has its limitations[6,14,19]
- Burosumab, an FGF23-antibody, offers the opportunity for improved outcomes for patients with XLH[20]
- Burosumab showed greater improvement in height Z-score compared to conventional treatment in younger subjects, suggesting a critical developmental period for intervention[20]
- There were no concerning safety findings with burosumab[20]

References: 1. Cundy T, Grey A, Reid IR. Clinical Biochemistry: Metabolic and Clinical Aspects (Third Edition). Churchill Livingstone; 2014:93-123. **2.** Shaikh A, *et al. Pediatr Nephrol.* 2008;23(8):1203-1210. **3.** Bergwitz C, Jüppner H. *Annu Rev Med.* 2010;61:91-104. **4.** Goretti Penido M, Alon US. *Pediatr Nephrol.* 2012;27(11):2039-2048. **5.** Imel EA, Econs MJ. *J Clin Endocrinol Metab.* 2012;97(3):696-706. **6.** Carpenter TO, *et al. J Bone Miner Res.* 2011;26(7):1381-1388. **7.** Padidela R, *et al. Orphanet J Rare Dis.* 2020;15(1):172. **8.** Beck-Nielsen SS, *et al. J Hum Genet.* 2012;57(7):453-458. **9.** Burnett CH, *et al. Am J Med.* 1964;36:222-232. **10.** Dahir K, *et al. J Endocr Soc.* 2020;4(12):bvaa151. **11.** Gaucher C, *et al. Hum Genet.* 2009;125(4):401-411. **12.** Whyte MP, *et al. J Clin Endocrinol Metab.* 1996;81(11):4075-4080. **13.** Hawley S, *et al. J Clin Endocrinol Metab.* 2020;105(3):e871-878. **14.** Linglart A, *et al. Endocr Connect.* 2014;3(1):R13-30. v**15.** Skrinar A, *et al. J Endocr Soc.* 2019;3(7):1321-1334. **16.** Veilleux LN, *et al. J Clin Endocrinol Metab.* 2012;97(8):E1492-1498. **17.** Mäkitie O, *et al. J Clin Endocrinol Metab.* 2003;88(8):3591-3597. **18.** Chesher *et al. J Inherit Metab Dis.* 2018;41(5):865-876. **19.** Zivičnjak M, *et al. Pediatr Nephrol.* 2011;26(2):223-231. **20.** Imel EA, *et al. The Lancet.* 2019;393(10189):2416-2427.

CRYSVITA® Abbreviated Product Information
[Based on Hong Kong package insert, version 01/2020]

Please refer to the full Prescribing Information before prescribing.

Abbreviated Package Insert of CRYSVITA® Solution for Injection 10 mg/1mL, 20 mg/1mL, or 30 mg/1mL

Composition: Burosumab. **Indication:** Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 yr of age and older. **Dosage & Administration:** Pediatric: BW<10 kg: 1 mg/kg (rounded to the nearest 1 mg), administered q2w. BW>10 kg: starting dose is 0.8 mg/kg (rounded to the nearest 10 mg), administered q2w. The starting dose should between 10 to 90 mg. Dose may be increased to ~2mg/kg (max 90 mg), administered q2w to achieve normal serum P. Adult: 1 mg/kg (rounded to the nearest 10 mg, max dose: 90 mg), administered q4w. **Contraindications:** Concomitant use with oral phosphate &/or active vit D analogs due to the risk of hyperphosphatemia; serum phosphorus is within/above the normal range for age; severe renal impairment/ESRD due to abnormal mineral metabolism. **Precautions:** Hypersensitivity; hyperphosphatemia & risk of nephrocalcinosis; injection site reactions; Pregnancy & lactation; Pediatric <1 yr of age; Elderly; Renal impairment. **Common adverse reactions:** For pediatric: pyrexia; injection site reactions, cough, vomiting; pain in extremity; headache; tooth abscess; dental caries. For adults: back pain; headache; tooth infection; restless leg syndrome; vitamin D decreased; dizziness; constipation; muscle spasms; increase serum P. Interaction: Oral phosphate and active vit D analogs. **P/P:** Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL in a single-dose vial. Approved version of package insert: Jan 2020

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CRYSVITA® burosumab

Kyowa Kirin Hong Kong Co., Limited
Unit B, 13/F., 169 Electric Road, North Point, Hong Kong
Phone : +852 29560828 | Fax : +852 29561627

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