News release

Kyowa Kirin Announces Approval of CRYSVITA® (burosumab) in Switzerland for the Treatment of Adults and Children with X-Linked Hypophosphatemia (XLH)

CRYSVITA is the first and only treatment for XLH that targets the underlying cause of the disease

TOKYO, Japan, February 25, 2020 – Kyowa Kirin Co., Ltd., (Kyowa Kirin) today announced the approval of CRYSVITA (burosumab) by Swissmedic (dispensing category B) for the treatment of adults, adolescents and children (1 year of age and older) with X-linked hypophosphatemia (XLH), a rare genetic disease that causes abnormalities in the bones, muscles and joints.[1,2,3] The product is expected to be available for prescription in Switzerland in accordance with the provisions of Article 71 of the KVV (Verordnung über die Krankenversicherung).

“X-linked hypophosphatemia is the most common form of hereditary rickets,” said Abdul Mullick, President of Kyowa Kirin International. “Many patients experience debilitating symptoms on a daily basis, including joint and bone pain, stiffness and fatigue, and may have trouble walking. Bringing this important treatment to adults and children with XLH in Switzerland is a very important milestone for our company and for the treatment of this rare, progressive disease.”

“CRYSVITA (burosumab) is the first and only treatment available in Switzerland for patients with XLH that targets the underlying cause of the disease,” said Tomohiro Sudo, Head of Global Product Management Office of Kyowa Kirin. "We are proud that CRYSVITA is now available to patients in Switzerland and we are continuing our work to broaden the treatment options for more patients with XLH around the world."

About X-linked hypophosphatemia

X-linked hypophosphatemia (XLH) is a rare, genetic disease that causes abnormalities in the bones, muscles and joints.[1,2,3] XLH is not life threatening but its burden is lifelong, and it may reduce a person’s quality of life.[4]

People with XLH have a genetic defect on the X-chromosome, which causes an excessive loss of phosphate through the urine and poor absorption from the gut, resulting in chronically low levels of phosphate in the blood.[4,5] Phosphate is a key mineral needed for maintaining the body’s energy levels, muscle function, and the formation of healthy bones and teeth.[6,7]

XLH is the most common form of hereditary rickets.[8] It can sometimes appear in individuals with no family history of the disease but is usually passed down from a parent who carries the defective gene.[9]

About CRYSVITA (burosumab)

CRYSVITA (burosumab) was discovered by Kyowa Kirin Co., Ltd., and is a recombinant fully human monoclonal IgG1 antibody against the phosphaturic hormone fibroblast growth factor 23 (FGF23). FGF23 is a hormone that reduces serum levels of phosphate by regulating phosphate excretion and active vitamin D production by the kidney. Phosphate wasting and resulting hypophosphatemia in X-linked hypophosphatemia (XLH) is caused by excessive levels and activity of FGF23. CRYSVITA is designed to bind to, and thereby inhibit, the biological activity of FGF23. By blocking excess FGF23 in patients, CRYSVITA is intended to increase phosphate reabsorption from the kidney and increase the production of vitamin D, which enhances intestinal absorption of phosphate and calcium.

In 2018, the European Commission granted a conditional marketing authorization for CRYSVITA for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and in adolescents with growing skeletons.[10] In the same year, CRYSVITA received approval from the U.S. Food and Drug Administration (FDA) and Health Canada for pediatric and adult use.[11,12] In 2019, CRYSVITA received approval for the treatment of XLH in adult and pediatric patients one year of age and older from Brazil's National Health Surveillance Agency (ANVISA), and from Japan's Ministry of Health, Labor and Welfare for the treatment of FGF23-related hypophosphatemic rickets and osteomalacia.

In November 2019, the European Medicines Agency (EMA) accepted an application for the expanded use of CRYSVITA (burosumab) for the treatment of XLH in adult patients. Under the terms of the current conditional marketing authorization, the treatment is not approved for use in adults in the European Economic Area (EEA).[10]

Kyowa Kirin International PLC, a wholly owned subsidiary of Kyowa Kirin Co., Ltd., and Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE: Ultragenyx) have been collaborating in the development and commercialization of CRYSVITA globally, based on the collaboration and license agreement between Kyowa Kirin and Ultragenyx. Kyowa Kirin Sàrl is the MAH holder of CRYSVITA in Switzerland.

Important Safety Information

Refer to the full Product Information for human medicinal products for full safety information: Switzerland: www.swissmedicinfo.ch

Most common undesirable effects
The most common undesirable effects reported in adult patients during clinical trials were back pain (15%), headache (13%), tooth infection (13%), restless legs syndrome (12%), vitamin D decrease (12%) and dizziness (10%).

Injection site reactions
The frequency of injection site reactions was 12% in both burosumab and placebo treatment groups (such as injection site reaction, erythema, rash, bruising, pain, pruritus and hematoma, redness, rash and pain). These were generally mild and resolved within 1-3 days.

Hyperphosphatemia (high plasma phosphate)
In the randomized study UX023-CL303, nine (7%) of patients in the burosumab treatment group experienced hyperphosphatemia and this was managed with dose reduction. A single patient (1%) required a second dose reduction for continued hyperphosphatemia.

Contraindicated treatments
Administration of burosumab with oral phosphate and vitamin D analogues at the same time is contraindicated as it may cause an increased risk of hyperphosphatemia.

Monitoring patients
After starting burosumab treatment fasting plasma phosphate should be monitored between dosing (every two weeks) for the first 3 months of treatment. It is recommended that patients treated with burosumab also have monitoring through: kidney ultrasound; plasma alkaline phosphatase; calcium and parathyroid hormone.

Burosumab is not recommended during pregnancy and in women of childbearing potential not using contraception.

About Kyowa Kirin

Kyowa Kirin commits to innovative drug discovery driven by state-of-the-art technologies. The company focuses on creating new values in the four therapeutic areas: nephrology, oncology, immunology/allergy and neurology. Under the Kyowa Kirin brand, the employees from 36 group companies across North America, EMEA and Asia/Oceania unite to champion the interests of patients and their caregivers in discovering solutions wherever there are unmet medical needs.

You can learn more about the business of Kyowa Kirin Switzerland at:
http://www.international.kyowa-kirin.com/ch/index.html

Kyowa Kirin Sàrl
Rue Philippe-Plantamour 18-20 c/o Intertrust (Suisse) SA
1201 Genève

References

[1] Linglart A, Biosse-Duplan M, Briot K et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3:R13-30.

[2] Orphanet. X-linked hypophosphatemia. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=89936. Last updated: January 2012. Last accessed: February 2020.

[3] Haffner D, Emma F, Eastwood DM, et al. Consensus Statement. Evidence-based guideline. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphatemia. *Nat Rev Nephrol*. 2019;15;435-455.

[4] Skrinar A, Dvorak-Ewell M, Evins A, et al. The lifelong impact of X-linked hypophosphatemia: Results from a burden of disease survey. *J Endocr Soc*. 2019;3:1321-1334.

[5] Beck-Nielsen SS, Mughal Z, Haffner D, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis*. 2019;14:58.

[6] Unnanuntana A, Rebolledo BJ, Khair MM, et al. Diseases affecting bone quality: beyond osteoporosis. *Clin Orthop Relat Res*. 2011;469:2194-2206.

[7] Pesta D, Tsirigotis DN, Befroy DE, et al. Hypophosphatemia promotes lower rates of muscle ATP synthesis. *The FAESB Journal.* 2016;39:3378-3387.

[8] Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26:1381-8.

[9] National Center for Advancing Translational Sciences. X-linked hypophosphatemia. Available at: https://rarediseases.info.nih.gov/diseases/12943/x-linked-hypophosphatemia. Last updated: February 2019. Last accessed: February 2020.

[10] European Medicines Agency. CRYSVITA EPAR product information. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/crysvita-epar-product-information_en.pdf. Last updated: December 2019. Last accessed: February 2020.

[11] CRYSVITA Prescribing Information. Available at: https://www.ultragenyx.com/file.cfm/29/docs/Crysvita_Full_Prescribing_Information.pdf. Last updated: September 2018. Last accessed: February 2020.

[12] Health Canada. Regulatory Decision Summary – CRYSVITA. Available at: https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00463. Last updated: December 2018. Last accessed: February 2020.