News release

European Medicines Agency Accepts Kyowa Kirin's Application for the Expanded Use of CRYSVITA® (burosumab) for the Treatment of Adults with X-Linked Hypophosphataemia

CRYSVITA is the first treatment for X-linked hypophosphataemia that targets the cause of the disease. Adults with XLH currently have limited treatment options.

TOKYO, Japan, November 5, 2019 – Kyowa Kirin Co., Ltd., (Kyowa Kirin) today announced that the European Medicines Agency (EMA) has accepted an application for the expanded use of CRYSVITA® (burosumab) for the treatment of X-linked hypophosphataemia (XLH) in adult patients. Acceptance of this application begins the EMA's review process of the submission.

In 2018, the European Commission granted a conditional marketing authorisation 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.[1] Currently, patients treated with CRYSVITA in the European Economic Area (EEA) who are transitioning into adult care must cease CRYSVITA therapy.[1] This application seeks to expand the current indication for CRYSVITA to include the adult population.

"As in children, adults with X-linked hypophosphataemia, the most common form of hereditary rickets, experience debilitating symptoms on a daily basis, including joint and bone pain, stiffness and fatigue, and may have trouble walking. Since XLH is a progressive disease, these adults are at an increased risk of fractures and early onset of osteoarthritis," said Abdul Mullick, President at Kyowa Kirin International PLC. "If approved, CRYSVITA® (burosumab) will be the first treatment for children and adults in the European Economic Area that targets the cause of XLH. We look forward to working with the European Medicines Agency to bring this important treatment to more patients across the EEA."

"This filing is another key milestone for Kyowa Kirin. We are one step closer to being able to provide a better solution for adult patients with XLH in the EEA," said Tomohiro Sudo, Head of Global Product Management Office of Kyowa Kirin. "We are proud that CRYSVITA® (burosumab) has helped many children with XLH in EEA and we'll keep working to broaden the treatment options for more and more patients with XLH around the world."

This submission is supported by data from two Phase 3 studies. The Phase 3 UX023-CL303 study, a randomised, double-blind, placebo-controlled trial investigating the safety and efficacy of burosumab in adults with XLH, and the Phase 3 UX023-CL304 study, an open-label, single-arm trial investigating the effects of burosumab on osteomalacia in adults with XLH.

About X-linked hypophosphataemia

X-linked hypophosphataemia (XLH) is a rare genetic disease that causes hypophosphataemia which leads to abnormalities in the bones and joints.[2,3] While XLH is not life threatening, its burden is lifelong.[4]

XLH occurs due to a defect in a gene on the X-chromosome known as PHEX (phosphate-regulating gene with homologies to endopeptidases on the X-chromosome), resulting in excess production of fibroblast growth factor 23 (FGF23) which leads to excessive loss of phosphate in the urine and poor absorption from the gut.[4,5] The low levels of phosphate in the blood lead to poor bone quality[6,7] and abnormal development of bones and joints.[2,3] XLH is the most common form of hereditary rickets.[8]

People with XLH experience reduced physical function and quality of life compared with the general population.[9] Adults with XLH typically have short statures and experience trouble walking due to lower extremity deformities such as bowed legs acquired in childhood. It is common for these individuals to experience bone and joint pain due to rickets, as well as muscle weakness and dental abnormalities. People with XLH are also at a much greater risk of pseudofractures and early onset osteoarthritis.[9,10,11]

About CRYSVITA® (burosumab)

CRYSVITA® (burosumab) is a recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Kirin Co., Ltd. against the phosphaturic hormone fibroblast growth factor 23 (FGF23). FGF23 is a hormone that reduces serum levels of phosphorus and active vitamin D by regulating phosphate excretion and active vitamin D production by the kidney. Phosphate wasting in X-linked hypophosphataemia (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 authorisation 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.[1] In the same year, CRYSVITA received approval from the US Food and Drug Administration (FDA) and Health Canada for paediatric and adult use.[12,13] In 2019, CRYSVITA received approval from Japan's Ministry of Health, Labor and Welfare for the treatment of FGF23-related hypophosphataemic rickets and osteomalacia[14].

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 commercialisation of CRYSVITA globally, based on the collaboration and license agreement between Kyowa Kirin and Ultragenyx.

Important Safety Information

Refer to the full Summary of Medicinal Product Characteristics for full safety information.

Most Common Side effects
The most common side effects reported in adult patients during clinical trials were back pain (23%), headache (21%), tooth infection (19%), restless legs syndrome (13%), muscle spasms (12%), vitamin D decrease (15%) and dizziness (11%).

Injection site side effects
The frequency of side effects at the site of the subcutaneous injections was 12% in both burosumab and placebo treatment groups (such as redness, rash and pain). These were generally mild and resolved within 1-2 days.

High plasma phosphate
In the randomised study UX023-CL303, nine (7%) of patients in the burosumab treatment group experienced high plasma phosphate and this was managed with dose reduction of 50%. A single patient (1%) required a second dose reduction for continued hyperphosphataemia.

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 high serum phosphate.

Monitoring patients
After starting burosumab treatment fasting plasma phosphate should be monitored between dosing 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 at www.kyowakirin.com

About Ultragenyx Pharmaceutical Inc.

Ultragenyx is a biopharmaceutical company committed to bringing patients novel products for the treatment of serious rare and ultra-rare genetic diseases. The company has built a diverse portfolio of approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, for which there are typically no approved therapies treating the underlying disease.

The company is led by a management team experienced in the development and commercialization of rare disease therapeutics. Ultragenyx's strategy is predicated upon time and cost-efficient drug development, with the goal of delivering safe and effective therapies to patients with the utmost urgency.

For more information on Ultragenyx, please visit the Company's website at www.ultragenyx.com.

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