SWISS Summary of the Risk Management Plan (RMP) for Crysvita® (burosumab)

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Swiss RMP Summary dated 13 March 2020
Swiss RMP Version 1.0 (dated 19 July 2018)

The Risk Management Plan (RMP) summary of Crysvita® is a concise and comprehensive document submitted as part of the application dossier for market approval of a medicine, and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation. Please note that the reference document which is valid and relevant for the effective and safe use of Crysvita® in Switzerland is the "Arzneimittelinformation" (see www.swissmedicinfo.ch) approved and authorised by Swissmedic.

The RMP summary for Crysvita, contains information on the medicine's safety profile and details the measures to be taken in order to ensure that Crysvita is used as safely as possible e.g. by investigating the measures to be taken in order to further investigate and follow the risk as well as to prevent or minimize them.

Kyowa Kirin Saŕl is fully responsible for the accuracy and correctness of the content of the here published summary RMP for Crysvita®.

1. Overview of disease epidemiology

X-linked hypophosphataemia (XLH) is a genetic disorder that affects about 1 in 20,000 people. It is caused by a defect in the PHEX gene, which results in increased levels of a phosphate-regulating hormone and leads to reduced phosphate uptake in the kidneys. This causes low levels of phosphate in the blood. Phosphate is a mineral that is required for the normal formation of bones and teeth.

Patients with XLH are typically born with low to normal phosphorus in their blood, but over time, the amount decreases, leading to bone deformities including bowing of the legs (rickets) and knocked knees. Children can have slow growth and are shorter than their peers. They develop bone abnormalities that can affect movement and cause bone pain, early closure of the skull bones, and problems with teeth. In adults, increased blood phosphorus leads to softening of the bones, known as osteomalacia.

2. Summary of treatment benefits

Conventional therapy for XLH involves oral replacement of phosphate and supplementation with active vitamin D, which can improve some aspects of the disease, but is often associated with poor compliance.

The effectiveness and safety of burosumab have been investigated in 10 clinical studies that include a broad age range of subjects (aged from 1 to 66 years) with XLH. In total, more than 200 adults and children with XLH have received burosumab at doses up to 1 mg/kg every 4 weeks (adults) or 2mg/kg every 2 weeks (children), and for durations up to 184 weeks.

The results from these studies demonstrate the effectiveness of burosumab in addressing the underlying mechanism of disease, improving phosphate reuptake in the kidney, and normalizing blood phosphorus levels with consequent improvements in rickets, bone health, and other outcomes, beyond those achievable with conventional therapy.

Studies have demonstrated that burosumab, by restoring phosphate regulation, improves mineralization, normalizes the bone remodeling process, heals the underlying bone loss, and by this means heals rickets (in children) and progressively repairs fractures and pseudofractures (in adults). Accompanying the improvements in bone health were reductions in patient-reported pain (children and adults), patient-reported stiffness (adults), substantial reductions in the use of pain medications (adults), and increases in mobility (children and adults). These improvements are expected to have a substantial impact on the course of XLH disease and life-long disability.

Burosumab in single and repeated monthly doses up to 1.0 mg/kg had an acceptable safety profile in adults with XLH. Studies suggest that burosumab in doses up to 2.0 mg/kg given every two weeks had an acceptable safety profile also.

3. Unknowns relating to treatment benefits

Patients not studied in clinical trials included: pregnant and lactating women, patients with kidney disease, or patients with a history of active hepatitis B/C were; thus, the use of burosumab in these patients is unknown. How well burosumab works in non-Caucasians and the long term effects of burosumab are also unknowns.

4. Summary of safety concerns

4.1 Important identified risks

None

4.2 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)	Preventability
Abnormally increased level of phosphate in the blood (serum)	Due to how burosumab works, hyperphosphataemia is an important potential risk. The clinical consequences of hyperphosphataemia depend on the peak serum phosphorous value and for how long serum phosphorous is increased. In general, a sharp rise in blood phosphorus resolves within a few hours if the kidneys are working normally. If kidney function is below normal, the kidneys' ability to remove excess phosphorus from the bloodstream could be exceeded leading to increased blood phosphorus levels. This can potentially cause symptom of low calcium levels in the blood, such as: tetany (e.g. locked jaw), seizures, and deposits of minerals in the soft tissue.	Yes, by periodically measuring blood phosphorus levels and monitoring for symptoms
Ectopic mineralization	Some patients with XLH treated with conventional treatments (oral phosphorous replacement and vitamin D analogues) have developed calcium deposits in their organs, mainly in the kidney. This is believed to be due to the presence of high serum phosphorous levels. Although this effect has not been seen in clinical trials of burosumab in XLH patients, where blood phosphorous levels were maintained within the normal range, patients receiving burosumab should be monitored for ectopic mineralization using renal ultrasound scans and blood tests.	Yes, by stopping all oral phosphorous and vitamin D analogues prior to starting burosumab and by burosumab dose interruption or discontinuation on detection of hyperphosphataemia
Ability to provoke an immune response, like an allergic reaction	Although burosumab is a human antibody, there is a potential risk to cause an allergic type reaction. These	No, as everyone's body reacts differently to an antibody drug, this is not predictable

Risk	What is known (Including reason why it is considered a potential risk)	Preventability
	reactions tend to mostly be injection site reactions and rashes and generally last a few days.	or preventable. Worsening or recurrence of the side effect can be prevented by stopping treatment with burosumab if serious hypersensitivity occurs.
Female reproductive toxicity	Patients who were pregnant, planned on becoming pregnant or breastfeeding were not included in clinical studies. There are limited data from the use of burosumab in pregnant women. Studies in pregnant animals without XLH showed expected increases in serum phosphorus and other biologic markers; it also showed mineral deposits of the placenta at a blood burosumab level 64 times greater than the level associated with the prescribed dose in humans. These animals also experienced an increased incidence of premature births. A clear reproductive and developmental toxicity risk was not established in animal studies; however, it cannot be ruled out given the known limitations of these studies in non-humans.	Yes –if already pregnant, women should undergo serum phosphorous monitoring throughout pregnancy. Patients who are thinking about breastfeeding while on burosumab should discuss the benefits and risks of breastfeeding during treatment with their physicians.
Raised blood levels of parathyroid hormone	Raised parathyroid hormone (PTH) levels occur in the presence of diseases which disrupt normal regulation of phosphate and calcium levels in the blood, such as XLH and chronic kidney disease. Patients with XLH are at additional risk of raised PTH levels if they have received treatment with vitamin D and calcium supplements prior to starting burosumab treatment. Increased PTH can cause heart, kidney and bone disease. Studies of burosumab in patients with XLH showed asymptomatic fluctuations in PTH levels in some subjects. The long-term significance of this is not known.	No specific action is recommended in relation to burosumab treatment. Patients with XLH usually undergo periodic monitoring of plasma PTH levels as part of their routine care.

4.3 Missing information

Risk	What is known	Preventability
Use in patients over 65 years	Safety data in patients 65 years old are limited.	No.
Use in patients with underlying kidney impairment	Patients with kidney impairment were excluded from clinical trials, as they may be prone to increases in serum phosphorus and calcium.	Yes, burosumab should not be taken by patients with severe kidney impairment or end stage kidney disease.
Long term use	Safety data are limited in patients who have received burosumab for a long time in clinical trials.	No.

5. Summary of risk minimisation measures by safety concern

Details of the routine risk minimisation measures are given in the Information for Professionals. This medicine has no additional risk minimisation measures.

6. Planned post authorisation development plan

6.1 List of studies in post authorisation development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns / Efficacy issues addressed	Status (planned/ ongoing)	Date for submission of interim or final reports (planned or actual)
Paediatric Studies				
UX023-CL201 A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)	**Primary/secondary objectives:** PD (Serum phosphorus, Urinary phosphorus, TRP, TmP/GFR, Serum 1,25(OH)2D, Bone markers (ALP, BALP, CTx and P1NP), Bone Health (Growth, Severity of rickets, lower extremity deformity, BMD), physical function (6MWT, BOT 2, HHD, POSNA PODCI, SF 10), PK (serum KRN23), Safety	**Safety** Frequency and severity of adverse events in XLH children between 5 and 12 years old **Efficacy** • Bone health and deformities • Growth • Motor function • Pain	Ongoing	CSR for 64 week analysis submitted August 2017 CSR for 160 week analysis available July 2019
UX023-CL205 An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH)	**Primary Objectives**: Safety, pharmacodynamic profile **Secondary Objectives**: rickets, growth, lower extremity deformity; PK (predose drug concentration)	**Safety** **Efficacy** • Bone health and deformities • Growth • Phosphate homeostasis	Ongoing	Synopsis CSR from 4 week data in 5 patients provided with initial 2MAA. CSR for 24 week analysis submitted at D121 CSR for 40 week analysis submitted 31 October 2017 CSR for 64 week analysis available Q2 2018 CSR for 160 week analysis available May 2020
UX023-CL301	**Primary Objective**: Improvement in	**Safety**	Ongoing	CSR from 40 week analysis

Study/activity Type, title and category (1-3)	Objectives	Safety concerns / Efficacy issues addressed	Status (planned/ ongoing)	Date for submission of interim or final reports (planned or actual)
A Randomized, Open-Label, Phase 3 Study to Assess the Pharmacodynamics, Efficacy and Safety of the anti-FGF23 antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)	rickets compared to conventional therapy **Secondary Objectives**: Growth, lower extremity deformity, urinary phosphorus, TRP, TmP/GFR, serum $1,25(OH)_2D$, biochemical markers of bone turnover, functional and patient reported outcomes, safety	Frequency and severity of adverse events in XLH children between 3 and 17 years old **Efficacy** • Bone health and deformities • Growth • Phosphate homeostasis • Clinician and Patient reported outcomes		available Q2 2018 CSR for 64 week analysis available July 2019
PASS Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children with X-linked Hypophosphataemia **Category 3**	**Primary objectives:** Evaluate safety, pregnancy outcomes and outcomes in patients with mild to moderate kidney disease at baseline **Secondary objectives:** Compare safety outcomes of patients exposed to burosumab to those receiving alternative treatments for XLH	Long-term safety, hyperphosphatemia, ectopic mineralization, increased parathyroid hormone levels, effects on pregnancy outcomes and effects in patients with mild to moderate chronic kidney disease at baseline	Planned	Planned: First interim report – to be submitted after 50 patients have achieved at least 6 months of time in the PASS Second interim report – Dec 2023 Final report – Dec 2028
XLH Disease Monitoring Program **Category 3**	Long-term observational follow-up of adult and paediatric patients treated with burosumab in clinical trials in the US; objectives include assessments of effectiveness, pharmacodynamics and safety	Safety data to be collected include: iPTH, urinary calcium, serum calcium, renal ultrasound, anti-drug antibodies, blood pressure, serious adverse events	Planned	Final reported expected in approximately 2028 - to be confirmed

Study/activity Type, title and category (1-3)	Objectives	Safety concerns / Efficacy issues addressed	Status (planned/ ongoing)	Date for submission of interim or final reports (planned or actual)
Adult Studies				
UX023-CL203 A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH)	**Primary Objectives:** Long-term safety, serum phosphorus, long-term PD, long-term immunogenicity Secondary Objectives: Changes in skeletal disease, pain, WOMAC, HRQoL, 6MWT, TUG test, long-tern PK	**Efficacy** • Phosphate homeostasis • Skeletal pain • PD • Motor function • Patient reported outcomes	Ongoing	CSR from 48 week analysis available Q1 **2017**
UX023-CL303 A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Assess the Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia (XLH)	**Primary Objectives**: Serum phosphorus **Secondary Objectives:** Improvement in pain, additional serum phosphorus measures, serum $1,25(OH)_2D$, TmP/GFR, TRP, biochemical markers of bone remodeling; BPI, BFI, WOMAC (Stiffness and Physical Function)	Safety Frequency and severity of adverse events compared to placebo rates in XLH adults **Efficacy** • Bone health and deformities • Skeletal pain • Bone remodeling • Phosphate-calcium homeostasis and renal function • Pseudofracture healing • Motor function	Ongoing	CSR from 24 week analysis submitted at D121 CSR from 48 week analysis available Q1 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns / Efficacy issues addressed	Status (planned/ ongoing)	Date for submission of interim or final reports (planned or actual)
UX023-CL304 An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH)	**Primary Objective**: Improvement in osteomalacia **Secondary Objectives**: serum phosphorus, additional histomorphometry measurements and, TmP/GFR, TRP, biochemical markers of bone turnover	**Safety** Frequency and severity of adverse events in XLH adults **Efficacy** • Osteomalacia • Bone mineralization • Phosphate homeostasis and renal function • Bone remodeling • Pseudofracture healing • Patient reported outcomes	Ongoing	CSR from 48 week analysis available Q2 2018

6.2 Studies which are a condition of the Marketing Authorisation

There are no studies which are condition to Marketing Authorisation Application.

7. Summary of changes to the Risk Management Plan over time

Not applicable.