SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for CRYSVITA (burosumab)
This is a summary of the risk management plan (RMP) for CRYSVITA. The RMP details important risks of CRYSVITA, how these risks can be minimised, and how more information will be obtained about CRYSVITA's risks and uncertainties (missing information).

CRYSVITA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CRYSVITA should be used.

This summary of the RMP for CRYSVITA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CRYSVITA's RMP.

I The Medicine and What it is Used For

CRYSVITA is authorised for the treatment of X-linked hypophosphataemia in children 1 year of age and older when there is radiographic evidence of bone disease, and in adults. It contains burosumab as the active substance and it is given by subcutaneous injection.
CRYSVITA is authorised for the treatment of FGF23-related tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over.
Further information about the evaluation of CRYSVITA's benefits can be found in CRYSVITA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004275/human_med_002224.jsp&mid=WC0b01ac058001d124.

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of CRYSVITA together with measures to minimise such risks and the proposed studies for learning more about CRYSVITA's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of CRYSVITA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of CRYSVITA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CRYSVITA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

A summary of the important risks and missing information for CRYSVITA is provided in Table 1.

Table 1: Summary of important risks and missing information for CRYSVITA

List of important risks and missing information	
Important identified risks	None
Important potential risks	Hyperphosphataemia Ectopic mineralisation Female reproductive toxicity Increased parathyroid hormone levels
Missing information	Elderly patients ≥65 years Patients with mild to moderate renal impairment Long term use

II.B Summary of Important Risks

Further information about the important risks and missing information for CRYSVITA is provided in Table 2.

Table 2: Summary of important risks for CRYSVITA

Important potential risk — hyperphosphataemia	
Evidence for linking the risk to the medicine	Potential risk highlighted in non-clinical and clinical development programmes.
Risk factors and risk groups	Data are currently insufficient to determine risk groups/factors for potential hyperphosphataemia related to burosumab therapy. This will be monitored as part of ongoing routine pharmacovigilance for this product; it will be further assessed in Phase 3 studies, planned longer term extension studies and the proposed Post-Authorisation Safety Study.

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8, 4.9, 5.3 PL sections 2 and 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: XLH PASS in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk – ectopic mineralisation	
Evidence for linking the risk to the medicine	Potential risk highlighted in non-clinical and clinical development programmes.
Risk factors and risk groups	With conventional therapy, ectopic mineralisation is driven by urinary phosphate wasting, hyperparathyroidism, hypercalcaemia, and hypercalciuria, resulting from excess oral phosphate and $1,25(OH)_2D$ dosing. In earlier literature, the prevalence of nephrocalcinosis was up to 100% with conventional therapy and related to aggressive treatment. Even with new treatment guidelines, up to 26% of adult subjects entering the burosumab development programme, who were naïve to burosumab treatment and who were previously exposed to oral phosphate and/or $1,25(OH)_2D$ therapy, were noted to have ectopic mineralisation on kidney ultrasound at baseline. Cardiac valve or aortic calcifications have been reported in XLH subjects on phosphate therapy with secondary or tertiary hyperparathyroidism (Moltz et al. 2001), (Sun et al. 2013). Hyperphosphataemia is also invariably present in end-stage renal disease. Qunibi reported complications of hyperphosphataemia in this population, which can be directly applicable to XLH patients. These complications included secondary hyperparathyroidism and cardiovascular calcifications including haemodynamic disturbances (e.g. increased cardiac stroke index, increased systolic and decreased diastolic blood pressure, increased pulse pressure, and increased pulse wave velocity) and widespread cardiovascular calcifications (e.g. coronary artery, cardiac valves, myocardium, etc.). He further stated that cardiovascular calcification has been linked to an increased risk of cardiovascular events, including myocardial infarction, fatal arrhythmia, congestive heart failure, and valvular heart disease (Qunibi 2004).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 5.3 PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: XLH PASS in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk – female reproductive toxicity	
Evidence for linking the risk to the medicine	Potential risk highlighted in non-clinical and clinical development programmes.
Risk factors and risk groups	Females of child-bearing potential; pregnant females; breast-feeding females.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6, 5.3 PL Section 2 No additional risk minimisation measures

Additional pharmacovigilance activities	Additional pharmacovigilance activities: XLH PASS in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk – increased parathyroid hormone levels	
Evidence for linking the risk to the medicine	Clinical development programme.
Risk factors and risk groups	• Treatment of hypophosphataemia with conventional therapies (vitamin D and phosphate replacement) is believed to lead to sharp increases in plasma phosphate levels and rebound effects on PTH secretion • There are reports of elevated PTH levels in untreated patients with XLH (Schmitt et al. 2004) • Chronic kidney disease is associated with hyperparathyroidism
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: XLH PASS in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information – elderly patients ≥65 years	
Risk minimisation measures	None
Additional pharmacovigilance activities	Routine pharmacovigilance activities only
Missing information – patients with mild to moderate renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4 PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: XLH PASS in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information – long-term use	
Risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: XLH PASS in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no planned or on-going imposed post-authorisation efficacy studies.

II.C.2 Other studies in post-authorisation development plan

One category 3 PASS has been planned and details are summarised in Table 3.

Table 3: Other studies in the post-authorisation development plan of CRYSVITA

Study name	Rationale	Study objectives
Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children and Adults with X linked Hypophosphataemia	X-linked hypophosphataemia (XLH) is a rare, chronic deforming bone disease characterised by excess levels of circulating Fibroblast Growth Factor-23 (FGF23) leading to increased urinary phosphate excretion, reduced $1,25(OH)_2D$ synthesis, and subsequent hypophosphataemia. Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the excess biological activity of FGF23 thereby minimizing the clinical consequences of XLH by restoring normal serum phosphate levels. The Marketing Authorisation Holder (MAH) for burosumab has worked with XLH specialists to establish a European XLH registry to characterise the treatment, progression and long-term outcomes of XLH in the paediatric and adult settings. The PASS will be conducted using data collected in the registry.	<u>Primary objectives:</u> 2) To evaluate the frequency and severity of safety outcomes in children aged >1 year with radiographic evidence of bone disease, adolescents with growing skeletons and radiographic evidence of bone disease, and adults, treated with burosumab, including but not limited to: death, hospitalizations, cardiovascular disease, cancer, hyperphosphataemia and its complications, ectopic mineralisation and increased parathyroid hormone levels; 2) To prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab; 2) To prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate chronic kidney disease at baseline treated with burosumab <u>Secondary objectives:</u> 1) To perform a retrospective cohort study using data from the registry to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH