Part VI: Summary of the risk management plan

Summary of risk management plan for CUVITRU (Immune Globulin Subcutaneous [Human], 20% Solution)

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

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

I. The medicine and what it is used for

CUVITRU is authorised for Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production.
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contraindicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients.
- Hypogammaglobulinaemia in patients pre- and post- allogeneic haematopoietic stem cell transplantation (HSCT).

Kindly refer SmPC for the full indication. It contains human normal immunoglobulin (IG) as the active substance, and it is given by subcutaneous (SC) route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of CUVITRU, together with measures to minimise such risks and the proposed studies for learning more about CUVITRU'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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - include PSUR statement only if product has PSUR requirements 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 CUVITRU is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of CUVITRU 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 CUVITRU. 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).

List of important risks and missing information	
Important identified risks	Interference with serological tests after infusion of immunoglobulin
	Altered immune response and implications for laboratory testing; Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella
	Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies
	Thromboembolic events (TEE)
	Aseptic meningitis syndrome (AMS)
Important potential risks	Haemolysis/Haemolytic anaemia
	Medication error: incorrect route of administration
	Transmission of infectious agents
	Severe renal adverse reactions including renal failure
Missing information	Lack of information on safety in pregnant and lactating women
	Limited information on safety in neonates or infants <2 years old
	Limited information in patients with organ impairment (e.g., kidney, liver, or cardiac)
	Limited information on safety in elderly patients 65 and older
	Overdose

II.B Summary of important risks

Important Identified Risk: Interference with serological tests after infusion of immunoglobulin	
Evidence for linking the risk to the medicine	On the basis of clinical study results and medical literature there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	All patients who receive IG therapy.

Important Identified Risk: Interference with serological tests after infusion of immunoglobulin	
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.4 SmPC section 4.8 **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	None.

Important Identified Risk: Altered immune response to live attenuated vaccines, and implications for laboratory testing: Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella	
Evidence for linking the risk to the medicine	On the basis of medical literature there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	All patients who receive IG therapy are potentially at risk for altered immune response.
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.5 where advice is given to wait for up to 3 months before vaccination with live attenuated virus vaccines and patients receiving measles vaccine should have their antibody status checked. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	None.

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies	
Evidence for linking the risk to the medicine	On the basis of post-marketing safety data and medical literature there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	Patients with antibodies to IgA potentially have a greater risk of developing severe hypersensitivity or anaphylactic reactions.
Risk minimisation measures	**Routine risk minimisation measures**

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies	
	SmPC section 4.3 SmPC section 4.4 mention that patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with CUVITRU only under close medical supervision. SmPC section 4.8 **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	None.

Important Identified Risk: Thromboembolic events	
Evidence for linking the risk to the medicine	On the basis of post-marketing safety data and medical literature there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	Patients at increased risk for thrombotic events include those with: • a history of atherosclerosis • multiple cardiovascular risk factors • advanced age • impaired cardiac output • hypercoagulable disorders • prolonged periods of immobilization • obesity • diabetes mellitus • acquired or inherited thrombophilic disorder • a history of vascular disease • a history of a previous thrombotic or thromboembolic event
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 where advice is given to use drug with caution in patients with preexisting risk factors for thrombotic events and adequate hydration should be ensure in patients before administration.

Important Identified Risk: Thromboembolic events	
	Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Important Identified Risk: Aseptic meningitis syndrome	
Evidence for linking the risk to the medicine	On the basis of post-marketing events and medical literature, there is evidence to suspect the possibility of a causal relationship between these events and CUVITRU.
Risk factors and risk groups	AMS has been reported to occur in association with immune globulin treatment including CUVITRU. AMS may occur more frequently in female patients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 where advice is given to inform the patients about first symptoms of AMS which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Proposed SmPC section 4.8 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Potential Risk: Hemolysis/Hemolytic anemia	
Evidence for linking the risk to the medicine	On the basis of post-marketing safety data and medical literature there is sufficient evidence demonstrating potential causal association.
Risk factors and risk groups	Patients with blood groups A, B, or AB receiving immune globulin therapy are potentially at risk.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 SmPC section 4.8 **Additional risk minimisation measures:** None.

Important Potential Risk: Hemolysis/Hemolytic anemia	
Additional pharmacovigilance activities	None.

Important Potential Risk: Medication error: Incorrect route of administration	
Evidence for linking the risk to the medicine	On the basis of post-marketing events and medical literature, there is evidence to suspect the possibility of a causal relationship between these events and CUVITRU.
Risk factors and risk groups	Medication errors are inherent risks associated with the therapeutic use of drugs and the administration process.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 mention that the patient or caregiver must be instructed in the use of a syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions. SmPC section 4.3 SmPC section 4.4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Potential Risk: Transmission of infectious agents	
Evidence for linking the risk to the medicine	On the basis of post-marketing events and medical literature, there is evidence to suspect the possibility of a causal relationship between these events and CUVITRU.
Risk factors and risk groups	Any patient who is administered a blood or plasma derived medicinal product is potentially at risk for transmission of infectious agents.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 contains the standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. **Additional risk minimisation measures:** None.

Important Potential Risk: Transmission of infectious agents	
Additional pharmacovigilance activities	None.

Important Potential Risk: Severe renal adverse reactions including renal failure	
Evidence for linking the risk to the medicine	On the basis of post-marketing events and medical literature, there is evidence to suspect the possibility of a causal relationship between these events and CUVITRU.
Risk factors and risk groups	Cases of acute renal failure have been reported in patients receiving intravenously administered IGs, and in most cases, other risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant use of nephrotoxic medicinal products, or age over 65 years.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing information: Lack of information on safety in pregnant and lactating women	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing information: Limited information on safety in neonates or infants <2 years old	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4

Missing information: Limited information on safety in neonates or infants <2 years old	
	SmPC Section 4.5 SmPC Section 4.8 SmPC Section 5.1 SmPC Section 5.2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing information: Limited information in patients with organ impairment (e.g., kidney, liver, or cardiac)	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing information: Limited information on safety in elderly patients 65 and older	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing information: Overdose	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.9 **Additional risk minimisation measures:** None.

Missing information: Overdose	
Additional pharmacovigilance activities	None.

II.C. Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of CUVITRU.

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

There are no studies required for CUVITRU.