Table 32. Summary of Risk Minimization Measure

Safety Concern	Routine Risk Minimization Activities	Additional Risk Minimization Activities
Limited information on safety in elderly patients 65 and older	Discussed in SmPC section 4.4.	None
Overdose	Discussed in SmPC section 4.9	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Primary immunodeficiency diseases (PID) are disorders of the immune system that are passed down in a person's genes from one or both parents. People with PID frequently get infections, autoimmune diseases (diseases that occur when a person's immune systems attacks its own cells and tissues), and certain types of cancers. There are more than 150 types of PID that are caused by various defects in 120 different genes. About one person in every 10 000 people suffers from PID. Many studies across Europe have attempted to estimate the burden of PID and have generated inconsistent results ranging from 1.9 to 5.6 cases per 100 000 population in 2012. A US study conducted in 2005 estimated that 86 cases per 100 000 inhabitants have been diagnosed with PID, whereas earlier estimates were at 1 in 10 000. Rare immune deficiencies, such as severe combined immunodeficiency (SCID), occur 1 in every 100 000 to 500 000 births. By contrast, selective IgA deficiency may occur 1 in every 300 to 18 500 individuals, varying by ethnicity.

Patients with cancer of the blood, such as (chronic lymphocytic leukaemia; CLL), suffer with a lack of antibody production and recurrent infections when preventative antibiotics have failed. CLL is the most common leukaemia in the Western world. Globally development of CLL varies, due to the reported differences associated with ethnicity among the population. The estimated frequency of CLL in Europe is approximately 6.96 cases per 100 000 population annually, whereas a lower frequency of 4.5 cases per 100 000 population occur in the United States. CLL is 30% to 50% times more common in men than women, and is considered to be a disease of the aging population with occurrence of disease increasing around age 50 with a median age of approximately 70 years old at diagnosis. In the EU, there are approximately 46 000 individuals living with CLL.

Patients with cancer of the bone marrow (multiple myeloma) are affected by the second most common hematologic cancer in the Western world accounting for 10% to 15% of all hematologic malignancies. This hematologic cancer affects all ages; however, disease increases with each decade of life with approximately 72% of cases occurring in patients 65 years of age or older and a median age of 70 years at diagnosis. Worldwide, multiple myeloma represents 0.8% of all cancer diagnoses, with 0.4 to 6 cases occurring per 100000 person-years. Development of disease is the highest and appears to be on the rise in North America, Australia, New Zealand, and Europe unlike rates in Asian countries which have remained considerably stable. Among the general population, men are 1.5 times more likely to develop multiple myeloma than women, additionally, genetic susceptibility also may increase this risk.

VI.2.2 Summary of Treatment Benefits

Human normal immunoglobulin 20% belongs to a class of medicines called “human normal immunoglobulins”. Immunoglobulins are also known as antibodies and are found in healthy people’s blood. Antibodies are part of the immune system, which help your body to fight infections.

CUVITRU is used in patients who do not have enough antibodies in their blood and tend to get frequent infections. Regular and sufficient doses of CUVITRU can raise abnormally low immunoglobulin levels in your blood to normal levels; this is called “replacement therapy”.

CUVITRU is indicated for:

- Patients with inborn lack of antibody production (primary immunodeficiency syndromes.
- Patients with cancer of the blood (chronic lymphocytic leukaemia) that leads to a lack of antibody production and recurrent infections when preventative antibiotics have failed or cannot be given.
- Patients with cancer of the bone marrow (multiple myeloma) and lack of antibody production with recurrent infections.
- Patients before and after they receive a stem cell transplant (haematopoietic stem cell transplantation (HSCT))

CUVITRU is a benefit to paediatric patients with poor vein access and those patients interested in home-based therapy since it can be self-administrated. The higher

concentration allows for a smaller infusion volume, which may reduce the number of infusion sites and/or duration of infusion.

VI.2.3 Unknowns Relating to Treatment Benefits

It is unknown whether CUVITRU is safe to use in women who are pregnant or breast-feeding.

Clinical studies with IGSC, 20% did not include pregnant or lactating women. There is no information on the effects of CUVITRU on pregnancy, lactation, or with regards to effects on fertility.

VI.2.4 Summary of Safety Concerns

Table 33. Important Identified Risks

Risk	What is Known	Preventability
Interference with laboratory blood test	CUVITRU contains many different antibodies, some of which can affect blood tests (serological tests).	Patients and their doctors should be aware that the results of certain types of blood tests may not be accurate if a person has received treatment with CUVITRU due to the transfer antibodies from the medicine.
Changes in the body's immune system response, including: • Decreased effectiveness of live virus vaccines, such as the vaccines for measles, German measles, mumps, and chicken pox (Altered immune response and implications for laboratory testing; Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella)	For six weeks to three months after treatment with immunoglobulins, the effectiveness of live virus vaccines can be decreased. This includes vaccines that prevent measles, mumps, German measles, and Chicken pox. For the measles vaccine, this effect can last up to a full year.	Healthcare professionals should be aware of vaccination status of patients.
Allergic reactions (including severe allergic reactions in which a person stops breathing or their heart stops beating), especially in patients who have a deficiency in immunoglobulin A (IgA)	True allergic reactions to immunoglobulins are rare, but can occur, especially in people with IgA deficiency. Although it is rare, medicines that contain human immunoglobulins can sometimes cause a fall in blood pressure with anaphylaxis (a severe allergic reaction in which a person stops breathing or their heart stops beating, and is potentially fatal). This can	Allergic reactions (including severe allergic reactions in which a person stops breathing or their heart stops beating), especially in patients who have a deficiency in immunoglobulin A (IgA). Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with CUVITRU only

Table 33. Important Identified Risks

Risk	What is Known	Preventability
	happen even in patients who have previously received immunoglobulin treatment without negative side effects.	under close medical supervision.
Blood clots (Thromboembolic events)	Blood clots have occurred in patients who were given immunoglobulin treatment, either intravenously (infused into the vein) or subcutaneously (infused under the skin). Certain risk factors make it more likely for a person to develop a blood clot, including old age, high blood pressure, diabetes, heart disease, previous blood clots, blood clotting disorders, lack of physical activity, dehydration, or a thick consistency of the blood.	Patients should be informed about the first symptoms of a blood clot, including shortness of breath, pain a swelling in an arm or leg, chest pain, or nervous system problems and should be instructed to contact their physician immediately if they experience any of these symptoms. Patients should be well hydrated before beginning treatment with immunoglobulins.

Table 34. Important Potential Risks

Risk	What is Known
Breakdown of red blood cells, and/or a deficiency in the amount of red blood cells due to this breakdown (Haemolysis/Haemolytic anaemia)	Immunoglobulin medicines may contain antibodies to certain blood groups which can cause the red blood cells to be attacked and broken down by these antibodies. If too many red blood cells are broken down, a person can develop a special type of anaemia, called haemolytic anaemia.
Medication error: incorrect route of drug administration	A medication error can occur with the use of and drug. For example, the wrong dose can be given or the drug can be given IV (through the vein) instead of subcutaneously (under the skin).
Transmission of infectious agents	Since CUVITRU is made from pools of human plasma, it is possible that it could contain organisms that cause infection, which can be passed on through the medication. Several preventative measures are used when making CUVITRU in order to remove infectious organisms, but the possibility of this occurring cannot be completely ruled out.
Severe kidney adverse reactions including kidney failure	Some people who have received immunoglobulins through the vein (intravenous or IV) have experienced kidney failure. In most of these cases, the person had other health issues which could lead to kidney failure.
Inflammation of the layers lining	Some people who have received immunoglobulins through the vein

Table 34. Important Potential Risks

Risk	What is Known
the brain (Aseptic meningitis syndrome)	(intravenous or IV) have experienced AMS. It may be more likely to happen with high doses of immunoglobulin treatment.

Table 35. Missing Information

Risk	What is Known
Lack of information on safety in pregnant and lactating women	No clinical studies with CUVITRU have been done in women who are pregnant or breast-feeding. Studies with immunoglobulins suggest that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from harmful microorganisms which enter through the mucous.
Limited information on safety in neonates or infants <2 years old	No clinical studies with CUVITRU have been done in children under the age of 2 years. Experience with immunoglobulins suggests that no harmful effects on the treatment of children <2 years with CUVITRU are to be expected.
Limited information in patients with organ impairment (e.g., kidney, liver, or cardiac)	There is limited CUVITRU clinical trial data in patients with organ impairment (e.g., kidney, liver, or cardiac).
Limited information on safety in elderly populations 65 and older.	Only a small number of elderly people 65 and older were studied in CUVITRU clinical studies.
Overdose	The result of being given too much of CUVITRU is not known.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and the Package Leaflet for CUVITRUcan be found in the EPAR page after approval.

There are no additional risk minimization measures for CUVITRU.

VI.2.6. Planned Post-Authorization Development Plan

Not Applicable.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Major Changes to the Risk Management Plan Over Time

Table 36. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	04 May 2015	*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 *Important Potential Risks:* Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies Haemolysis/Haemolytic anaemia Thromboembolic events Transmission of infectious agents Severe renal adverse reactions including renal failure Aseptic meningitis syndrome (AMS) *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	-
Version 1.0 update	20 November 2015	Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies and Thromboembolic events were upgraded to important identified risks Medication error was added as an important potential risk	

Table 36. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		Overdose was added as missing information.	
Version 1.1	07 March 2016	Data from the completed clinical study 170904 was integrated.	