VI.2 SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCTELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of disease epidemiology

Primary immunodeficiency syndromes

Primary immunodeficiencies (PID) are a group of more than 180 diseases targeting different parts of the human immune system. In more than half of these diseases antibodies are not produced in sufficient amounts. As a result, patients with this kind of diseases are unable to defend themselves against bacteria causing for example pneumonia (lung infection), acute respiratory infections, or meningitis (inflammation of membranes in the brain).

Both sexes, all age groups, and all ethnic groups can be affected by PID.

Secondary immunodeficiency syndromes

Secondary immunodeficiency syndromes (SID) occur as a result of other diseases or when people have a weak immune system (e.g. in AIDS, during chemotherapeutic treatment or transplantation of blood stem cells). As in primary immunodeficiency syndromes these patients may suffer from recurrent bacterial infections.

Both sexes, all age groups and all ethnic groups can be affected by SID.

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an autoimmune disease which targets the platelets. These are blood components that help stopping bleedings. Many people with ITP have no symptoms. However, if symptoms occur, they can range from mild bruising to severe bleeding.

It is estimated that 5 in every 100,000 children and 2 in every 100,000 adults are diagnosed with ITP per year. In children, ITP is more common among boys than among girls. In adults, more women suffer from this disease.

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is a disease in which the body's immune system attacks parts of the peripheral nervous system. This leads to rapidly progressing weakness of the limbs and may result in almost total paralysation of the body. Most individuals recover even from severe cases of GBS, although in rare cases some weakness may remain.

It is estimated that 0.4 to 2.5 in every 100,000 persons are diagnosed with GBS per year. Both sexes, all age groups and all ethnic groups can be affected. Men more frequently suffer from GBS than women.

Kawasaki disease

Kawasaki disease is an acute inflammation of blood vessels throughout the body that typically occurs in children between 6 months and 5 years of age. Mainly the skin, mouth and lymph nodes are involved and in rare cases also the heart.

In Europe, it is estimated that 4.9 to 15.2 in every 100,000 children younger than 5 years are diagnosed with Kawasaki disease over a period of 5 years. In Asian countries more children are diagnosed with Kawasaki disease than in other countries. Boys more often suffer from Kawasaki disease than girls.

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disease where the body's immune system attacks the myelin sheath (fatty covering) of its own peripheral nerves. If left untreated, it results in progressive loss of strength and sensation in the legs and arms.

CIDP can occur at any age but most commonly between 40 and 60 years. Females suffer from CIDP more frequently than men.

Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a disease, where multiple motor nerves (nerves which control voluntary muscle activity) are attacked by the body's immune system. People with this disease lose strength in the lower parts of their arms and hands more than in the legs, usually without disturbing the touch sensation.

The mean age of onset of MMN is 40 years, with a range of 20-70 years. Men suffer from MMN more frequently than women.

VI.2.2 Summary of treatment benefits

Octagam is a human normal immunoglobulin solution (i.e. solution of human antibodies) for intravenous administration (i.e. infusion into a vein). Immunoglobulins are normal constituents of the human body and support the immune defence of the body. The medicine has been shown to be effective for replacing missing antibodies and immunomodulation (adjusting the immune response to a desired level) in two main studies.

Replacement Therapy

In the study (OCTA-06), Octagam was used as replacement therapy in 46 patients with primary immune deficiency, with the medicine being infused three to six month. The main measure of effectiveness was the number of serious bacterial infections over a year's treatment: The patients had an average of ≤ 0.115 serious infections per year. Since this is below ≤ 1 (efficacy criterion of the FDA), this indicates that the medicine is effective as replacement therapy.

Immunomodulation

A second study (GAM10-02) looked at using Octagam for immunomodulation in 116 patients with idiopathic thrombocytopenic purpura. Octagam was given on day 1, and repeated once within 3 days, or daily for 2 to 5 days. The analysis of the study results confirmed that Octagam 10% was efficacious in the treatment of idiopathic thrombocytopenic purpura with an overall response rate of 80.0% in the full analysis set.

Based on the results of these studies together with the results of studies performed with other human normal immunoglobulins that are available from the scientific literature, it can be concluded that Octagam is efficacious in the approved indications.

VI.2.3 Unknowns relating to treatment benefits

There is limited information concerning the safety of Octagam in elderly patients, in pregnant or breastfeeding women and in patients with an impaired function of the kidney or liver.

There is also limited information about the safety and efficacy of Octagam in indications that have not been approved by health authorities (off-label use).

However, during the long post-marketing history of Octagam, no evidence of a safety concern in these patient populations was detected.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Blood clots (Thromboembolic events)	Blood clots may affect the arteries or veins. In the veins this may lead to a painful swelling of the legs (deep vein thrombosis) and very occasionally life threatening or fatal clots may occur in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in patients who already have problems with their arteries. Known risk factors for thromboembolic events (blood clots) include: advanced age, immobility, (major) surgery, obesity, multiple trauma, hip fracture, lower extremity paralysis caused by spinal cord injury, cardiac or respiratory failure, presence of central venous lines, oestrogens, and a wide variety of inherited and acquired haematological conditions.	Healthcare professionals should monitor patients at risk who receive Octagam for early signs of thrombosis. Where appropriate, preventive anti-thrombotic medicines may be given.
Inflammation of the membranes that cover the brain and spinal cord not caused by bacteria or viruses	Certain drugs including intravenous human normal immunoglobulins like Octagam have been implicated in causing	Healthcare professionals should • use a slow initial infusion rate,

Risk	What is known	Preventability
(Aseptic meningitis)	noninfective (aseptic) meningitis. Usually, drug-induced aseptic meningitis occurs within 48 hours of the infusion but may occur later. Most cases of aseptic meningitis are benign and patients fully recover. Patients with pre-existing migraine may be at an increased risk of developing aseptic meningitis.	• take care of sufficient fluid intake before and throughout the treatment, and • consider premedication, if indicated. Recognition of aseptic meningitis is important to allow intervention and continuation of therapy.
Allergic (hypersensitivity) reactions, including severe, sudden allergic (anaphylactic) reactions	As with any intravenous protein product, allergic-type hypersensitivity reactions may occur. In very rare cases, allergic reactions may be serious. Usually, patients recover fully following treatment. Risk factors include a history of previous reactions to a human plasma-derived product or a known hypersensitivity to any of the ingredients of Octagam.	Healthcare professionals should ask patients to watch out for early signs of hypersensitivity reactions including hives, generalised urticaria (itchy rash), tightness of the chest, wheezing and hypotension (low blood pressure). Patients who are likely to develop hypersensitivity or allergic reactions may be pre-treated with corticosteroids and/or antihistamines.
Kidney (renal) failure	Cases of acute renal failure have been reported in patients receiving intravenous immunoglobulin therapy. Acute kidney failure may be reversible and patients may recover with normal function of their kidneys. Some patients may require dialysis, which is usually short term. In most cases of acute kidney failure following intravenous immunoglobulin treatment risk factors have	Healthcare professionals should • carefully evaluate the risk-benefit in patients with a history of problems with the kidney, • avoid administration of sucrose-containing intravenous immunoglobulin brands (Octagam does not contain sucrose), • take care of sufficient fluid intake before and throughout the treatment,

Risk	What is known	Preventability
	been identified, such as pre-existing insufficiency of the kidney, dehydration, diabetes mellitus, concomitant intake of medicines that are toxic for the kidneys and age greater than 65 years.	• monitor kidney function measures, • use slow infusion rates, and • discontinue intravenous immunoglobulin infusion if the kidney function deteriorates.
Interference with certain blood glucose tests	Some types of blood glucose testing systems (so called glucometers) falsely interpret the maltose contained in Octagam as glucose. This may result in falsely elevated glucose readings during an infusion and for a period of about 15 hours after the end of the infusion and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycaemia (i.e. a decreased blood sugar level). Also, cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings.	Healthcare professionals should consider and advise patients (if applicable) that the measurement of blood glucose must be done with a test system using a glucose-specific method when administering Octagam. Systems based on the glucose dehydrogenase pyrroloquinoline-quinone (GDH PQQ) or glucose-dye-oxidoreductase methods should not be used.
Loss/destruction of red blood cells (Haemolysis)	Intravenous immunoglobulin products may contain up to a certain amount antibodies against blood group A and blood group B. These antibodies may activate the immune system in recipients and lead to the destruction of red blood cells. Usually, these reactions are of mild nature and do not present with any clinical symptoms. In very rare cases significant haemolysis may occur resulting in haemolytic	Healthcare professionals should • monitor blood parameters like haemoglobin and haematocrit, and • monitor for symptoms of anaemia (shortness of breath, looking pale).

Risk	What is known	Preventability
	anaemia. In severe cases, patients may experience kidney failure and require dialysis; also blood transfusions may be necessitated.	

Important potential risks

Risk	What is known
Suspected transmission of pathogen infection	When medicines are made from human blood or plasma certain measures are put in place to prevent infections being passed on to patients. These include: • careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded • testing of each donation and pools of plasma for signs of virus/infections • steps included by the manufacturers in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.
Interference with live attenuated virus vaccines	Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of Octagam, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.
Medication errors	The two strengths of Octagam (5% and 10%) may be mixed up

Risk	What is known
	due to human error, which could lead to over- or underdosing of the product. Overdose may lead to fluid overload and an increase in the viscosity of the blood, particularly in patients at risk, including elderly patients or patients with an impaired function of the heart or kidney; this may result in the formation of blood clots (thromboembolic events). Underdose may render therapy with Octagam ineffective. The most frequently reported medication errors with Octagam include the accidental leakage of the drug into surrounding tissue (extravasation) and too high infusion rates. The locally authorised prescribing information (e.g. SmPC) clearly describes the dosing and method of administration relevant for Octagam. Additionally, information is provided in which situations Octagam must not be taken (contraindications) and details on interaction with other medicinal products are given. For preventing medication errors, the text of the packaging and the prescribing information or package leaflet must be carefully read.
Transfusion-related acute lung injury (TRALI)	There have been reports of non-cardiogenic pulmonary oedema (collection of fluid in the lung) also called transfusion-related acute lung injury (TRALI) in patients treated with intravenous immunoglobulins. TRALI is a serious complication and is characterised by severe respiratory distress, collection of fluid in the lung (pulmonary oedema), low blood oxygen level, normal function of the left heart chamber and fever. It typically occurs within 1-6 hours after transfusion. Most patients recover fully within a few days.

Missing information

Risk	What is known
Safety in elderly patients	The safety of Octagam in elderly patients has not been established in controlled clinical trials.
Safety in pregnant or breastfeeding women	<u>Pregnancy</u> The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly after the third trimester. Clinical experience with immunoglobulins suggests 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 pathogens which have a

Risk	What is known
	mucosal portal of entry. Breastfeeding Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected. Fertility Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.
Safety in patients with an impaired function of the kidney or liver (renal or hepatic impairment)	The safety of Octagam in patients with an impaired function of the kidney or liver has not been established in controlled clinical trials. Patients with an impaired function of the kidney may be at risk of acute renal failure. These patients should be monitored for early signs of kidney failure when receiving treatment with Octagam.
Use of Octagam in indications that are not approved by health authorities (Off-label use)	Intravenous immunoglobulins are also used in indications that have not been formally approved by health authorities. There is limited information concerning the efficacy and safety of Octagam in these indications.

VI.2.5 Summary of risk minimisation 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, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet for Octagam can be found on the website of national health authorities where Octagam is approved.

Octagam has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

Study/activity	Objectives	Safety concern/efficacy issue addressed	Status	Date for submission of interim or final reports
GAM5-28 Observational study	Safety of Octagam 5%, special focus on occurrence of TEEs	Thromboembolic events	Ongoing. Started in May 2013.	2020
Neurotrack Observational study	Long term efficacy and safety study of Octagam 50 mg/ml in patients with CIDP	Not applicable	Planned	Final report Q3 2017

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
09	10-Aug-2016	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity reactions, including anaphylactic reactions • Renal failure • Interference with certain blood glucose tests • Haemolysis **Potential Risks** • Suspected transmission of pathogen infection	Update according to the comments raised during procedure EMEA/H/C/PSUSA/00001633/201505.

Version	Date	Safety Concerns	Comment
		• Interference of IVIG with live attenuated virus vaccines • Medication errors • Transfusion-related acute lung injury (TRALI) **Missing information** • Safety in elderly patients • Safety in pregnant or breastfeeding women • Safety in patients with renal or hepatic impairment • Off-label use	
08	01-Oct-2015	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity reactions, including anaphylactic reactions • Acute renal failure • Interference with certain blood glucose tests • Haemolysis **Potential Risks** • Virus safety • Medication errors • Transfusion-related acute lung injury (TRALI) **Missing information** • Safety in elderly patients • Safety in pregnant or breastfeeding women • Safety in patients with renal or hepatic impairment • Off-label use	Update of RMP according to "Guidance on format of the risk management plan (RMP) in the EU – in integrated format" (EMA/465932/2013 Rev. 1). Re-classification of the safety concern "haemolysis" as identified risk. Update of missing information regarding paediatric patients as requested within the RMS PSUR final assessment report for IG PSUR 02 (reporting period 01-Jun-2013 to 30-Nov-2013). There is clinical trial information as well as sufficient post-marketing information to support that there is no more missing information with regard to "paediatric patients". The additional PV activity regarding the PISA programme is now completed. The additional PV activity regarding an additional safety evaluation for double processed batches is now completed. Update of relevant annexes. In detail, the following changes were introduced: - Part I was updated according to guideline EMA/465932/2013 Rev. 1 and the newly approved indication CIDP in France - Part II was updated in general according to guideline EMA/465932/2013 Rev. 1. Additionally, o in Module SI the newly approved indication CIDP in France was included. Some modifications in the epidemiology of indications

Version	Date	Safety Concerns	Comment
			were introduced. o Module SIII was updated with new information. o information on actions taken with regard to Octagam (double processed) were included in Module SV. Furthermore, sections SV.3 to SV.5 were updated. o more information was included in sections SVI.2, SVI.4 and SVI.5 of Module SVI. o information included in Module SVII was modified and updated. The potential risk "haemolysis" was upgraded to an identified risk. Due to harmonisation between RMPs, the identified risk "Hypersensitivity" was changed to "Hypersensitivity reactions, including anaphylactic reactions". Furthermore, additional MedDRA queries were introduced for this safety concern. For the safety concern "virus safety" the MedDRA term PT "Transmission of an infectious agent via a medicinal product" was exchanged for the HLT "Infectious transmissions". The MedDRA search terms for TRALI were changed: medical assessment concluded that the PT "Transfusion-related acute lung injury" is sufficient for the identification of suspect TRALI cases; the HLT "Transfusion related complications" will not be carried on to RMP version 08. - Part III was updated in general according to guideline EMA/465932/2013 Rev. 1. Additionally, o MedDRA queries to search for identified and potential risks were classified as routine pharmacovigilance activities. o study GAM5-28, requested by FDA, was included as category 3 additional PV activity. o stated additional PV activities were introduced. o the additional PV activity regarding the PISA programme is now completed.

Version	Date	Safety Concerns	Comment
			○ the additional PV activity regarding an additional safety evaluation for double processed batches is now completed. - In Part IV some modifications were introduced regarding the description of approved and unapproved indications. Study Neurotrack, requested by ANSM for the indication CIDP, was included as post-authorisation efficacy study. The summary of completed post-authorisation efficacy studies was updated, i.e. studies GAM-FR-003, GAM-NL-002, GAM-1-07 and GAM-05 were removed from the table as in these studies either efficacy was not the primary objective, or the study was no efficacy study or the study was not conducted in an approved indication. - Part V was updated according to guideline EMA/465932/2013 Rev. 1 and the valid CCSI for Octagam. - Part VI was updated according to guideline EMA/465932/2013 Rev. 1 and other changes introduced in RMP version 08.
07	01-Jul-2013	For safety concerns, see RMP Version 05.	Update according to the comments raised during procedure DE/H/0479/1/II/016.
06	29-May-2013	For safety concerns, see RMP Version 05.	Inclusion of additional safety monitoring for double processed batches.
05	22-Oct-2012	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity • Acute renal failure • Interference with certain blood glucose tests **Potential Risks** • Haemolytic anaemia • Viral safety • Medication error (mixing up Octagam 5% and 10% solutions) • Transfusion-related acute lung injury (TRALI) **Missing information** • Pregnant or lactating mothers	The potential risk “Transfusion-related acute lung injury” was added. Off-Label use was added as Missing information. Figures were updated.

Version	Date	Safety Concerns	Comment
		• Paediatric patients • Elderly persons • Persons with renal/hepatic failure • Off Label Use	
04	06-Aug-2012	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity • Acute renal failure • Interference with certain blood glucose tests **Potential Risks** • Haemolytic anaemia • Viral safety • Medication error (mixing up Octagam 5% and 10% solutions) **Missing information** • Pregnant or lactating mothers • Paediatric patients • Elderly persons • Persons with renal/hepatic failure	Document was restructured according the GVP requirements. Safety concerns "Paediatric Population": The sentence "However, clinical experience with Octagam 10% on paediatric patients (<18 years old) is limited." was added. Missing information concerning "paediatric patients" was added.
03	13-Mar-2012	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity • Acute renal failure • Interference with certain blood glucose tests **Potential Risks** • Haemolytic anaemia • Viral safety • Medication error (mixing up Octagam 5% and 10% solutions) **Missing information** • Pregnant or lactating mothers • Elderly persons • Persons with renal/hepatic failure	According to the request of Health Canada: Hypersensitivity was added as Important Identified Risks. Viral safety was added as Important Potential Risk. Pregnant or lactating mothers, Elderly persons, and Persons with renal/hepatic failure were added as Important missing information. The minimum number of patients in the non-interventional post-marketing study GAM5-28 was expanded to 2500.

Version	Date	Safety Concerns	Comment
02	21-Oct-2011	**Identified Risks** • Thrombogenicity • Aseptic meningitis • Acute renal failure • Interference with certain blood glucose tests **Potential Risks** • Haemolysis • Medication error (mixing up Octagam 5% and 10% solutions) **Missing information** • None	Update of the Pharmacovigilance Specification. More data on risk and epidemiology of thrombogenicity were added. Evaluation of the need for risk minimisation activities and risk minimisation plan was included. Missing sections were added and follows the EU RMP template.
01b	08-Apr-2011	**Identified Risks** • Thromboembolic events **Potential Risks** • None **Missing information** • None	The minimum number of infusions in the non-interventional post-marketing study program was expanded to 20,000.
01a	16-Feb-2011	**Identified Risks** • Thromboembolic events **Potential Risks** • None **Missing information** • None	First edition of RMP for Octagam 5% and Octagam 10%