PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *octaplas*

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

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

I. The medicine and what it is used for

octaplas is authorised for complex deficiencies of coagulation factors , substitution therapy in coagulation factor deficiencies, rapid reversal of the effects of oral anticoagulants, potentially dangerous haemorrhages during fibrinolytic therapy, and therapeutic plasma exchange procedures (see SmPC for the full indication). It contains human plasma (pooled and treated for virus inactivation) as the active substance and it is given by intravenous infusion.

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

Important risks of *octaplas*, together with measures to minimise such risks and the proposed studies for learning more about *octaplas*' 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 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 *octaplas* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *octaplas* 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 *octaplas*. 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);

Table II.A.1 - Summary table of Safety concerns

List of important risks and missing information	
Important Identified Risks	- Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events - ABO-incompatible *octaplas* infusions - Transfusion-related acute lung injury (TRALI) - Hyperfibrinolysis - Citrate toxicity - Medication errors - Fluid overload and pulmonary oedema
Important Potential Risks	- Suspected transmission of pathogen infection
Missing Information	- Safety in pregnant or breastfeeding women

II.B Summary of important risks

Table II.B.1 – Important identified risk: Hypersensitivity reactions, including anaphylactic reactions

Identified risk	**Hypersensitivity reactions, including anaphylactic reactions**
Evidence source(s) and strength of evidence	As with any protein product given into a vein, allergic-type hypersensitivity reactions may occur. In some cases, allergic reactions may be life-threatening, therefore this risk is considered as important identified risk. Usually patients recover fully after treatment.
Risk factors and risk groups	Patients with a history of previous reactions to plasma-derived products or known hypersensitivity to any of the constituents of the drug. Patients presenting with anti-IgA antibodies or IgA deficiency.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Mentioned in the SmPC (section 4.3, 4.4 and 4.8) and in the package leaflet (section 2, 3 and 4) <u>Additional risk minimisation measures:</u> None

Table II.B.2 – Important identified risk: Thromboembolic events

Important identified risk	**Thromboembolic events**
Evidence for linking the risk to the medicine	Blood clots (thromboembolic events) are serious adverse reactions that are potentially life-threatening. 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.
Risk factors and risk groups	Risk groups are patients who receive continued treatment of *octaplas* with high doses and who have known clinical or laboratory risk factors. 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.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.4, 4.5 and 4.8) and in the package leaflet (section 2 and 4) Additional risk minimisation measures: None

Table II.B.3 – Important identified risk: ABO-incompatible *octaplas* infusions

Important identified risk	**ABO-incompatible *octaplas* infusions**
Evidence for linking the risk to the medicine	Administration of *octaplas* must be based on ABO-blood group specificity. In case of an incompatible transfusion by mistake ABO-antibodies in *octaplas* might bind to the antigens of recipient red blood cells and cause an immediate or delayed type of haemolytic transfusion reaction. ABO-incompatible infusions may be serious or even life-threatening.
Risk factors and risk groups	All patients except patients with blood group O (universal recipients).

Important identified risk	**ABO-incompatible *octaplas* infusions**
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.2, 4.4 and 4.8) and in the package leaflet (section 3 and 4) Additional risk minimisation measures: None

Table II.B.4 – Important identified risk: Transfusion-related acute lung injury (TRALI)

Important identified risk	**Transfusion-related acute lung injury (TRALI)**
Evidence for linking the risk to the medicine	TRALI is a serious complication and is characterised by severe respiratory distress, collection of fluid in the lung (pulmonary oedema), and low blood oxygen level. It typically occurs within 1-6 hours after transfusion. Most patients recover fully within a few days. TRALI mainly occurs as a result of transfusions of whole blood, red blood cells (RBCs), platelets, fresh-frozen plasma (FFP) and cryoprecipitate.
Risk factors and risk groups	Risk factors for TRALI include among others chronic alcohol abuse, history of heavy alcoholism, mechanical ventilation, shock pre-transfusion, smoking, liver transplantation, (end-stage) liver disease, haematologic malignancy, massive transfusion, sepsis, patient age, time on cardiopulmonary bypass.
Risk minimisation measures	Routine risk minimisation measures: Routine test for HNA- and HLA-antibodies and rejection of positive batches Additional risk minimisation measures: None

Table II.B.5 – Important identified risk: Hyperfibrinolysis

Important identified risk	**Hyperfibrinolysis**
Evidence for linking the risk to the medicine	Hyperfibrinolysis is a pathological state that often results in massive bleeding episodes, depletion of coagulation factors and platelets. Hyperfibrinolysis may be serious. Usually, patients recover following treatment.
Risk factors and risk groups	Patients with congenital or acquired deficiency of plasmin inhibitor (e.g. patients with liver disease, severe trauma and during major surgical procedures).

Important identified risk	**Hyperfibrinolysis**
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.4) and in the package leaflet (section 2) Additional risk minimisation measures: None

Table II.B.6 – Important identified risk: Citrate toxicity

Important identified risk	**Citrate toxicity**
Evidence for linking the risk to the medicine	Citrate (anticoagulant used in blood products to keep blood liquid) is usually rapidly degraded in the liver. However rapid administration of *octaplas*, administration of *octaplas* to patients with an impaired liver function or to patients undergoing plasma exchange procedures may lead to citrate toxicity. Citrate toxicity (fall in ionised calcium) may rarely cause cardiovascular effects, especially in patients with liver function disorders. In the course of plasma exchange procedures, symptoms attributable to citrate toxicity such as fatigue, paraesthesia, tremor, and hypocalcaemia may be rarely observed.
Risk factors and risk groups	Risk groups include patients receiving *octaplas* at high infusion rates, patients with liver function disorders and patients undergoing plasma exchange procedures.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.2, 4.8 and 4.9) and in the package leaflet (section 3 and 4) Additional risk minimisation measures: None

Table II.B.7 – Important identified risk: Medication error

Important identified risk	**Medication errors**
Evidence for linking the risk to the medicine	The most commonly observed medication errors reported with *octaplas* concern ABO-incompatibility and administration of the wrong product, especially mixing-up Octapharma's *octaplas* and *octaplex*. In the reported cases of mixing-up *octaplas* and *octaplex*, no adverse drug reactions had occurred.
Risk factors and risk groups	Not applicable.

Important identified risk	**Medication errors**
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.2, 4.3, 4.4, 4.5 and 4.9) and in the package leaflet (section 2 and 3) Statement of blood group on the label Characteristic pack size, pharmaceutical form and handling. Characteristic packaging and packaging colour scheme and/or pattern. Characteristic trade name Additional risk minimisation measures: None

Table II.B.8 – Important identified risk: Fluid overload and pulmonary oedema

Important identified risk	**Fluid overload and pulmonary oedema**
Evidence for linking the risk to the medicine	Transfusion-associated circulatory overload (TACO) is a serious transfusion-related complication. It can even be fatal. TACO can occur with any blood component when patients are transfused with a large volume in a short timeframe. Symptoms include acute respiratory distress, pulmonary oedema, hypertension, and acute left ventricular failure.
Risk factors and risk groups	High plasma volume and infusion rate, renal dysfunction, elderly patients and those with compromised cardiac function especially left ventricular dysfunction.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.8 and 4.9) and in the package leaflet (section 3 and 4) Additional risk minimisation measures: None

Table II.B.9 – Important potential risk: Suspected transmission of pathogen infection

Important potential risk	**Suspected transmission of pathogen infection**
Evidence for linking the risk to the medicine	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 the blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove the viruses. Despite these measures, when medicines prepared from human blood or plasma are administrated, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
Risk factors and risk groups	Patients with a depressed immune system are regarded to be at particular risk of developing infectious diseases induced by any virus. Parvovirus B19 infection may be serious for pregnant women (infection of the baby) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or abnormal breakdown of red blood cells).
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.4) and in the package leaflet (section 2) Additional risk minimisation measures: None

Table II.B.10 – Missing information: Safety in pregnant or breastfeeding women

Missing information	**Safety in pregnant or breastfeeding women**
Risk minimisation measures	Routine risk minimisation measures: Mentioned in the SmPC (section 4.6) and in the package leaflet (section 2) Additional risk minimisation measures: 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 *octaplas*.

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

There are no studies required for *octaplas*.