Summary of risk management plan for Flebogamma DIF (Human normal immunoglobulin)

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

Flebogamma DIF Summary of Product Characteristics and its package information leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Flebogamma DIF should be read in 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 Flebogamma DIF's RMP.

I. The medicine and what it is used for

Flebogamma DIF is an intravenous solution for infusion that contains unmodified human immunoglobulin G (IgG). Flebogamma DIF is authorized for:

Replacement therapy in adults, children and adolescents (2-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, children and adolescents (2-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré syndrome
- Kawasaki disease (in conjunction with acetylsalicylic acid)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

The product proposed indications are:

Replacement therapy in adults, children and adolescents (2-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production.

- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l.

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (2-18 years) in whom active immunisation is contraindicated or not advised.
Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post exposure prophylaxis and active immunisation.

Immunomodulation in adults, children and adolescents (2-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease (in conjunction with acetylsalicylic acid).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Further information about the evaluation of Flebogamma DIF's benefits can be found in Flebogamma DIF's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. Flebogamma DIF (previously Flebogammadif) | European Medicines Agency (europa.eu).

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

Important risks of Flebogamma DIF, together with measures to minimize such 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 Insert and Patient Information 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 Flebogamma DIF is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Flebogamma DIF 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 Flebogamma DIF. 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.

List of important risks and missing information	
Important identified risks	• Hypersensitivity reactions including anaphylactic reactions • Haemolysis • Thromboembolic events • Renal Failure • Aseptic Meningitis • Infusion related reactions
Important potential risks	• Neutropenia • Theoretical risk of pathogen infection • Interaction with live attenuated vaccines • Transfusion Related Acute Lung Injury (TRALI) • Lupus-like syndrome • Medication error
Missing information	• Use in women who are pregnant or lactating • Use in geriatric population

II.B Summary of important risks

Important identified risk: Hypersensitivity reactions including anaphylactic reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions, including life-threatening anaphylactic reactions can occur even when a previous administration has been tolerated (including a negative test). Caution is therefore needed with every dose, even if previous tests have been made.
Risk factors and risk groups	Risk factors associated with anaphylactic reactions are IgA deficiency and history of hypersensitivity reactions. Most often, hypersensitivity reactions are associated with first-time exposure as well as with rapid infusion rate.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.3 Contraindications* - *EU SmPC section 4.4 Special warnings and precautions for use* - *EU SmPC section 4.8 Undesirable effects* Additional risk minimisation measures: None proposed.

Important identified risk: Haemolysis	
Evidence for linking the risk to the medicine	Haemolytic anaemia can develop subsequent to immune globulin products therapy due to enhanced red blood cells (RBC) sequestration. Immune globulin products recipients should be monitored for clinical signs and symptoms of haemolysis.
Risk factors and risk groups	The following risk factors are associated with the development of haemolysis: high doses, whether given as a single administration or divided over several days; non-0 blood group; and underlying inflammatory state.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.4 Special warnings and precautions for use*

Important identified risk: Haemolysis	
	- *EU SmPC section 4.8 Undesirable effects* Additional risk minimisation measures: None proposed.

Important identified risk: Thromboembolic events	
Evidence for linking the risk to the medicine	A link between the use of immune globulin products and thromboembolic events has been established and there is evidence that suggests that there are procoagulant proteins present in the medicine, in addition to other factors such as an increase in viscosity that could lead some patients to experience a thromboembolic event.
Risk factors and risk groups	Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.4 Special warnings and precautions for use* - *EU SmPC section 4.8 Undesirable effects* Additional risk minimisation measures: None proposed.

Important identified risk: Renal Failure	
Evidence for linking the risk to the medicine	Renal failure or renal insufficiency following IGIV therapy is a well-known and identified adverse event of IGIV. Approximately 90% of renal adverse events associated with IGIV in the United States have been reported with sucrose-containing IGIV preparations.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication:

Important identified risk: Renal Failure	
	- *EU SmPC section 4.4 Special warnings and precautions for use* - *EU SmPC section 4.8 Undesirable effects* Other routine risk minimisation measures beyond the Product Information: None proposed.

Important identified risk: Aseptic Meningitis	
Evidence for linking the risk to the medicine	Aseptic meningitis syndrome has been reported to occur in association with intravenous use of human immunoglobulin treatments. This may occur more frequently in association with high-dose treatments.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.4 Special warnings and precautions for use* - *EU SmPC section 4.8 Undesirable effects* Additional risk minimisation measures: None proposed.

Important identified risk: Infusion related reactions	
Evidence for linking the risk to the medicine	Infusion related reactions have been reported to occur in association with immune globulin treatments. This may occur more frequently in association with high-dose treatments.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.4 Special warnings and precautions for use* - *EU SmPC section 4.8 Undesirable effects*

Important identified risk: Infusion related reactions	
	Additional risk minimisation measures: None proposed.

Important potential risk: Neutropenia	
Evidence for linking the risk to the medicine	A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIGs. This typically occurs within hours or days after IVIG administration and resolves spontaneously within 7 to 14 days.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.8 Undesirable effects** - *New proposed EU SmPC section 4.4 Special warnings and precautions for use* Other routine risk minimisation measures beyond the Product Information: None proposed. *This applies to Flebogamma DIF 100 mg/ml SmPC only

Important potential risk: Theoretical risk of pathogen infection	
Evidence for linking the risk to the medicine	Because this product is made from human blood, it may carry a risk of transmitting infectious agents. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit infectious agent, e.g. viruses and, theoretically, the Creutzfeld-Jakob disease (CJD) agent. The possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.

Important potential risk: Theoretical risk of pathogen infection	
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.4 Special warnings and precautions for use* Other routine risk minimisation measures beyond the Product Information: None proposed.

Important potential risk: Interaction with live attenuated vaccines	
Evidence for linking the risk to the medicine	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 this product, 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.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.5 Interaction with other medicinal products and other forms of interaction* Other routine risk minimisation measures beyond the Product Information: None proposed.

Important potential risk: Transfusion Related Acute Lung Injury (TRALI)	
Evidence for linking the risk to the medicine	TRALI has been reported to occur in association with immune globulin treatments.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *Not specified in the current EU SmPC*

Important potential risk: Transfusion Related Acute Lung Injury (TRALI)	
	- *New proposed EU SmPC section 4.4 Special warnings and precautions for use* - *New proposed EU SmPC section 4.8 Undesirable effects* Additional risk minimisation measures: None proposed.

Important potential risk: Lupus-like syndrome	
Evidence for linking the risk to the medicine	Transient cutaneous reactions such as cutaneous lupus erythematosus or Lupus-like Syndrome have been reported to occur in association with immune globulin treatments.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.8 Undesirable effects* Additional risk minimisation measures: GPV should closely monitor lupus-like syndrome and present data within the next PSUSA procedure.

Important potential risk: Medication error	
Evidence for linking the risk to the medicine	Medication errors have been reported to occur in association with immune globulin treatments.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk.
Risk minimisation measures	Routine risk communication: - *Not specified in the EU SmPC* Additional risk minimisation measures: None proposed.

Missing information: Use in women who are pregnant or lactating	
Risk minimisation measures	Routine risk communication: - *EU SmPC section 4.6 Fertility, pregnancy and lactation* Other routine risk minimisation measures beyond the Product Information: None proposed.

Missing information: Use in geriatric population	
Risk minimisation measures	Routine risk communication: - *Not specified in the EU SmPC* Other routine risk minimisation measures beyond the Product Information: None proposed.

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 Flebogamma DIF.

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

There are no studies required for Flebogamma DIF.