PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN

Summary of risk management plan for *panzyga*

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

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

I. The medicine and what it is used for

panzyga is authorised for

Replacement therapy in adults, and children and adolescents (0-18 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 <4g/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 (0-18 years) in whom active immunisation is contraindicated or not advised.

Immunomodulation in adults, and children and adolescents (0-18 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; see 4.2)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

panzyga contains human normal immunoglobulin (IgG) as the active substance and is given by intravenous infusion.

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

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

II.A List of important risks and missing information

Important risks of *panzyga* 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 *panzyga*. 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	- Thromboembolic events - Aseptic meningitis - Hypersensitivity reactions, including anaphylactic reactions - Acute renal failure - Haemolysis
Important potential risks	- Transmission of infectious agents - Interaction with live attenuated virus vaccines and serological testing - Transfusion-related acute lung injury (TRALI) - Neutropenia/leukopenia
Missing information	- None

II.B Summary of important risks

Important identified risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Blood clots (thromboembolic events) are serious adverse reactions associated with the use of human immunoglobulin products that are potentially life-threatening. Blood clots may affect the arteries or veins. Blood clots in the veins may lead to 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 factors include obesity, age (elderly), hypertension, diabetes mellitus, hyperlipidaemia, history of vascular disease, history of thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, hypovolaemia, renal insufficiency, liver disease (cirrhosis, impaired liver function, etc.), atrial fibrillation, increased blood viscosity, severe muscle haemorrhage, crush injury, or orthopaedic surgery in haemophilia patients.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.8 and package leaflet sections 2 and 4

Important identified risk: Aseptic meningitis	
Evidence for linking the risk to the medicine	Certain drugs, including human normal immunoglobulins, have been implicated in causing noninfective (aseptic) meningitis. Patients with aseptic meningitis may experience persistent fatigue, lightheadedness, and asthenia which may impair daily activities. Most cases of aseptic meningitis syndrome are benign and patients recover fully.
Risk factors and risk groups	Individuals treated with drugs that potentially cause drug-induced aseptic meningitis, such as antimicrobials, non-steroidal anti-inflammatory drugs (NSAIDs), vaccines, or IVIG Patients with pre-existing migraine receiving high-dose IVIG
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.8 and package leaflet sections 2 and 4

Important identified risk: Hypersensitivity reactions, including anaphylactic reactions	
Evidence for linking the risk to the medicine	Rarely, severe and even fatal anaphylactoid reactions may occur during IVIG treatment in patients with IgA deficiency; the appearance of anaphylactic shock is correlated with the presence of anti-IgA antibodies of the IgG and IgE isotypes in the patient's serum. Patients with autoimmune diseases have an increased prevalence of selective IgA deficiency compared to normal blood donors.
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	Routine risk minimisation measures: Mentioned in SmPC sections 4.3, 4.4, and 4.8 and package leaflet sections 2 and 4

Important identified risk: Acute renal failure	
Evidence for linking the risk to the medicine	Cases of acute renal failure are usually serious. Because the kidneys are no longer able to filter waste products from the blood, waste products may accumulate and reach toxic levels. In most cases of acute renal failure, at least 1 day of renal dialysis is required. However, acute kidney failure is reversible, and patients may recover with normal renal function.
Risk factors and risk groups	Risk factors include pre-existing renal insufficiency, hypertension, dehydration or volume depletion, paraproteinaemia, sepsis, diabetes mellitus, hypovolaemia, concomitant nephrotoxic medicinal products, and age over 65 years (elderly patients)
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.8 and package leaflet sections 2 and 4

Important identified risk: Haemolysis	
Evidence for linking the risk to the medicine	IVIG administration may result in mild haemolytic reactions which are usually subclinical and self-limiting. In very rare cases, significant haemolysis may occur. Cases of haemolysis with clinically observable symptoms are usually serious. Severe haemolysis may result in renal failure, requiring haemodialysis. In some patients, blood transfusions may be required.

Important identified risk: Haemolysis	
Risk factors and risk groups	Risk factors include non-group O blood, large cumulative IVIG dose, high isoagglutinin titre in IVIG product, and underlying inflammatory state.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.8 and package leaflet sections 2 and 4

Important potential risk: Transmission of infectious agents	
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 pathogens or infection. Manufacturers also include steps in the processing of the blood or plasma that can inactivate or remove 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	Risk group for infection with any virus: immunocompromised patients Additional risk groups for parvovirus B19 infection: pregnant women (especially up to 20 weeks of gestation, with effects ranging from uncomplicated pregnancy to severe hydrops fetalis or intrauterine foetal death) and patients with haemoglobinopathies
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC section 4.4 and package leaflet section 2

Important potential risk: Interaction with live attenuated virus vaccines and serological testing	
Evidence for linking the risk to the medicine	Vaccination has been an important healthcare measure in preventing infectious diseases. The response to vaccination is reduced in immunocompromised patients, PID, and SID, but vaccination studies still demonstrated a protective effect resulting in reduced complications, hospitalization, treatment costs, and even mortality. Whereas live vaccines are contraindicated in patients with severe immune impairment, inactivated vaccines are

Important potential risk: Interaction with live attenuated virus vaccines and serological testing	
	highly recommended in PID and SID. However, because live-attenuated vaccines may be affected by circulating antibodies in immunoglobulin therapy, there are recommended intervals between immunoglobulins and administration of injected live attenuated vaccines.
Risk factors and risk groups	Patients receiving live-attenuated virus vaccines, such as measles, rubella, mumps, or varicella vaccine. Patients undergoing serological testing, with passively transferred antibodies in immunoglobulin preparations potentially confounding the test results
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.5 and package leaflet section 2

Important potential risk: Transfusion-related acute lung injury (TRALI)	
Evidence for linking the risk to the medicine	TRALI is a serious complication characterised by severe respiratory distress, collection of fluid in the lung (pulmonary oedema), and low blood oxygen level. TRALI mainly occurs as a result of transfusions of whole blood, packed red blood cells (RBCs), platelets, granulocytes, FFP and cryoprecipitate. Only few cases have been reported in connection with IVIG.
Risk factors and risk groups	Published recipient risk factors for TRALI include chronic alcohol abuse, history of heavy alcoholism, positive fluid balance pretransfusion, mechanical ventilation, shock pretransfusion, current smoker, liver surgery (transplant), [IL-8] pre-transfusion, per 10-fold increase, (end-stage) liver disease, emergency coronary artery bypass grafting (CABG), haematologic malignancy, massive transfusion, sepsis, patient age, and time on cardiopulmonary bypass.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.8 and package leaflet sections 2 and 4

Important potential risk: Neutropenia/leukopenia	
Evidence for linking the risk to the medicine	Since the introduction of IVIG therapy in various immunological diseases, neutropenia has been reported as a rare adverse event. Neutropenia after IVIG was first recognized in patients with ITP. In a 1992 report, a patient with active systemic lupus erythematosus received 2 courses of IVIG infusion, with marked neutropenia developing repeatedly after each IVIG course and so confirming the association between IVIG infusion and the neutropenic event.
Risk factors and risk groups	Risk factors for the development of neutropenia/leukopenia include blood cell or bone marrow conditions, cancer and cancer treatments, congenital problems, infectious diseases, autoimmune diseases, malnutrition and medications.
Risk minimisation measures	Routine risk minimisation measures: Mentioned in SmPC sections 4.4 and 4.8 and package leaflet sections 2 and 4

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 *panzyga*.

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

There are no studies for *panzyga.*