VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Indications related to replacement therapy

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.

Indications related to immunomodulation

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 have 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 have 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 have Kawasaki disease than girls.

VI.2.2 Summary of treatment benefits

Panzyga 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 first study, 51 children and adults suffering from primary immunodeficiency (PID) received Panzyga every 3 or 4 weeks. Subjects participated in the study for a mean of 360 days. The primary endpoint was the number of episodes of serious bacterial infections per patient per year which was 0.08 (4 infections over 50 patient-years). Since this is below ≤1, the result indicates that Panzyga is effective as replacement therapy in PID diseases.

Immunomodulation

In the second study, 36 patients with chronic immune thrombocytopenia received Panzyga given on 2 consecutive days.

The primary endpoint was the response rate defined as the percentage of subjects with a predefined increase in platelet count within 7 days after the first infusion. Overall, 29 patients (81%) responded to Panzyga with a rise in platelet counts. In 18 of the 23 subjects (78%) who had bleeding at baseline, the bleeds had completely resolved by Day 7.

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 Panzyga is efficacious in the approved indications.

VI.2.3 Unknowns relating to treatment benefits

The safety of Panzyga in elderly patients and patients with an impaired function of the kidney or liver has not been established.

There is no experience using Panzyga in pregnant or breastfeeding women.

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	Healthcare professionals should monitor patients at risk who receive Panzyga for early signs of thrombosis. Where appropriate, preventive anti-thrombotic

Risk	What is known	Preventability
	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.	medicines may be given.
Inflammation of the membranes that cover the brain and spinal cord not caused by bacteria or viruses (Aseptic meningitis)	Certain drugs including intravenous human normal immunoglobulins like Panzyga have been implicated in causing 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.	Healthcare professionals should • use a slow initial infusion rate, • 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	Healthcare professionals should ask patients to watch out for early signs of hypersensitivity reactions including hives, generalised urticaria (itchy rash), tightness of

Risk	What is known	Preventability
	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 Panzyga.	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.
Acute 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 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.	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 (Panzyga does not contain sucrose) • take care of sufficient fluid intake before and throughout the treatment • monitor kidney function measures • use slow infusion rates • discontinue intravenous immunoglobulin infusion if kidney function deteriorates
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	Healthcare professionals should • monitor blood parameters like haemoglobin and haematocrit. • monitor for symptoms of anaemia (shortness of breath, looking pale).

Risk	What is known	Preventability
	resulting in haemolytic 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
Transmission of infectious agents	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 passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. The measures taken are considered effective for encapsulated viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped viruses 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.
Interaction with live attenuated virus vaccines and serological testing	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 Panzyga, 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.

Missing information

Risk	What is known
Safety in pregnant or breast feeding women	The safety of Panzyga for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant and breast-feeding women. Immunoglobulin preparations have been shown to cross the placenta, increasingly during 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 the transfer of protective antibodies to the newborn.
Safety in elderly patients	The safety of Panzyga in elderly patients has not been established in controlled clinical trials.
Safety in patients with an impaired function of the kidney or liver (renal or hepatic impairment)	The safety of Panzyga 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 Panzyga.

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 Panzyga can be found on the website of national health authorities where Panzyga is approved.

Panzyga 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
None	Not applicable	Not applicable	Not applicable	Not applicable

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

Version	Date	Safety Concerns	Comment
01	23-Mar-2015	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity reactions, including anaphylactic reactions • Acute renal failure • Haemolysis **Potential Risks** • Virus safety **Missing information** • Safety in elderly patients • Safety in pregnant or breast feeding women • Safety in patients with renal or hepatic impairment	First edition of RMP
02	12-Oct-2015	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity reactions, including anaphylactic reactions • Acute renal failure • Haemolysis **Potential Risks** • Transmission of infectious agents • Interaction with live attenuated virus vaccines and serological testing **Missing information** • Safety in elderly patients • Safety in pregnant or breast feeding women • Safety in patients with renal or hepatic impairment	The indications MMN and CIDP were deleted. The potential risk “Interaction with live attenuated virus vaccines and serological testing” was added. The term “virus safety” was changed to “transmission of infectious agents” Section VI.2.4 was updated Section SIII.2 was updated to include additional information on each clinical trial. Section SVII.3 was updated with number of total infusions and additional information on the potential risk Interaction with live attenuated virus vaccines and serological testing Appendix 12 was updated to include the EMA decision (P/0138/2012) and Opinion PDCO (EMEA-001110-PIP01-10-M01).

03	26-Nov-2015	**Identified Risks** • Thromboembolic events • Aseptic meningitis • Hypersensitivity reactions, including anaphylactic reactions • Acute renal failure • Haemolysis **Potential Risks** • Transmission of infectious agents • Interaction with live attenuated virus vaccines and serological testing **Missing information** • Safety in elderly patients • Safety in pregnant or breast feeding women • Safety in patients with renal or hepatic impairment	Section SVII.3 was updated with characteristics on serological testing. Appendix 12 was updated to include the EMA/PDCO Modification Summary Report.