SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Panzyga 100 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:

Human normal immunoglobulin…….100 mg

(purity of at least 95 % IgG)

Each vial of 10 ml contains: 1 g of human normal immunoglobulin.
Each vial of 25 ml contains: 2.5 g of human normal immunoglobulin.
Each bottle of 50 ml contains: 5 g of human normal immunoglobulin.
Each bottle of 60 ml contains: 6 g of human normal immunoglobulin.
Each bottle of 100 ml contains: 10 g of human normal immunoglobulin.
Each bottle of 200 ml contains: 20 g of human normal immunoglobulin.
Each bottle of 300 ml contains: 30 g of human normal immunoglobulin.

Distribution of the IgG subclasses (approx. values):

IgG_1	65 %
IgG_2	28 %
IgG_3	3 %
IgG_4	4 %

Minimum level anti-measles IgG is 9 IU/ml

The maximum IgA content is 300 micrograms/ml

Produced from the plasma of human donors.

Excipient(s) with known effect
This medicinal product contains 69 mg sodium per vial of 100 ml equivalent to 3.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The solution is clear or slightly opalescent and colourless or pale yellow. The pH of the solution is 4.5 to 5.0, the osmolality is ≥ 240 mosmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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.

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, 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)

4.2 Posology and method of administration

IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

Posology

The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight and overweight patients. In overweight patients dose should be based on the physiological standard bodyweight.

The following dose regimens are given as a guidance.

Replacement therapy in primary immunodeficiency syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. 3–6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) to occur. The recommended starting dose is 0.4–0.8 g/kg given once followed by at least 0.2 g/kg given every 3–4 weeks.

The dose required to achieve a trough level of 6 g/l is of the order of 0.2–0.8 g/kg/month. The dosage interval when steady state has been reached varies from 3–4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Replacement therapy in secondary immunodeficiencies (as defined in 4.1.)

The recommended dose is 0.2–0.4 g/kg every 3–4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

Measles pre-/post exposure prophylaxis

Post-exposure prophylaxis

If a susceptible patient has been exposed to measles, a dose of 0.4 g/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 0.4 g/kg possibly to be repeated once after 2 weeks may be necessary to maintain the serum level > 240 mIU/ml.

If a PID/SID patient has been exposed to measles and regularly receives IVIg infusions, it should be considered to administer an extra dose of IVIg as soon as possible and within 6 days of exposure. A dose of 0.4 g/kg should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks.

Pre-exposure prophylaxis

If a PID/SID patient is at risk of future measles exposure and receives an IVIg maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to 0.53 g/kg. This should provide a serum level of >240 mIU/ml of measles antibodies for at least 22 days after infusion.

Immunomodulation in:

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 0.8–1g/kg given on day 1; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for 2–5 days. The treatment can be repeated, if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

Kawasaki Disease

2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Starting dose: 2g/kg divided over 2–5 consecutive days.
Maintenance doses:
1 g/kg over 1–2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient's response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN)

Starting dose: 2g/kg divided over 2–5 consecutive days
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient's response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of infusions**
<u>Replacement therapy</u>		
Primary immunodeficiency syndromes	Starting dose: 0.4–0.8 g/kg Maintenance dose: 0.2–0.8 g/kg	every 3–4 weeks
Secondary immunodeficiency (as defined in 4.1.)	0.2–0.4 g/kg	every 3–4 weeks
<u>Measles pre/post exposure prophylaxis:</u>		
Post-exposure prophylaxis in susceptible patients	0.4 g/kg	As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/mL
Post-exposure prophylaxis in PID/SID patients	0.4 g/kg	In addition to maintenance therapy, given as an extra dose within 6 days of exposure
Pre-exposure prophylaxis in PID/SID patients	0.53 g/kg	If a patient receives a maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to at least 0.53 g/kg.
<u>Immunomodulation</u>		
Primary immune thrombocytopenia	0.8–1 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2–5 days
Guillain Barré syndrome	0.4 g/kg/d	for 5 days
Kawasaki disease	2 g/kg	in one dose in association with acetylsalicylic acid

Indication	Dose	Frequency of infusions
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2g/kg Maintenance dose: 1g/kg	in divided doses over 2–5 days every 3 weeks in divided doses over 1-2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1g/kg or 2g/kg	 in divided doses 2–5 consecutive days every 2–4 weeks or every 4–8 weeks in divided doses over 2–5 days

Paediatric population

The posology in children and adolescents (0–18 years) is not different to that of adults as the posology for each indication is given by body weight and must be adjusted to the clinical outcome of the above-mentioned conditions.

Hepatic impairment

No evidence is available to require a dose adjustment.

Renal impairment

No dose adjustment unless clinically warranted, see section 4.4.

Elderly

No dose adjustment unless clinically warranted, see section 4.4.

Method of administration

For intravenous use.

Human normal immunoglobulin should be infused intravenously at an initial rate of 0.6 ml/kg/hr for 30 min. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may gradually be increased to a maximum of 4.8 ml/kg/hr.

In PID patients who have tolerated the infusion rate of 4.8 ml/kg/hr well, the rate may be further increased gradually to a maximum of 8.4 ml/kg/hr.

In CIDP patients who have tolerated the infusion rate of 4.8 ml/kg/hr well, the rate may be further increased gradually to a maximum of 7.2 ml/kg/hr.

In order to infuse any product that may remain in the infusion tubing at the end of the infusion the tubing may be flushed with either 0.9% saline or 5% dextrose solution.

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see section 4.4 and 6.1).

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially injecting the product slowly (0.6–1.2 ml/kg/hr).
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion in a controlled healthcare setting in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur. All other patients should be observed for at least 20 minutes after administration.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the IVIg infusion
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see 4.5).

In case of adverse reaction, either the infusion rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion-related reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to the rate of infusion. The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently:

- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.
- in patients with an untreated infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients

- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered. Panzyga does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis (see section 4.8).

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1–2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing

After the administration of immunoglobulin the transitory rise of various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, 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 HIV, HBV and HCV and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

Sodium content

This medicinal product contains 69 mg sodium per vial of 100 ml equivalent to 3.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products and other forms of interactions

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 this medicinal 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.

Loop diuretics

Avoidance of concomitant use of loop diuretics

Paediatric population

The listed interactions apply both to adults and children.

4.6 Fertility, pregnancy and lactation

Pregnancy

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. IVIg products 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.

Breast-feeding

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 breast-feeding mothers. Immunoglobulins are excreted into the milk. No negative effects on the breastfed newborns/infants are anticipated.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

Panzyga has no or negligible influence on the ability to drive and use machines. However, patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion.

- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), for spontaneous post-marketing ADRs, the reporting frequency is categorized as "not known". Within each Organ Class, adverse reactions are presented in order of decreasing seriousness.

The following table shows an overview of the ADRs observed in the clinical studies as well as reported spontaneously post-marketing:

MedDRA System Organ Class (SOC) according to the sequence:	**Adverse Reaction**	**Frequency per Infusion**	**Frequency per patient**
Blood and lymphatic system disorders	Anaemia, leukopenia --- Haemolysis†	Uncommon --- Rare	Common --- Uncommon
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, face oedema, angioedema, hypersensitivity	Not known	Not known
Psychiatric disorders	Confusional state, agitation, anxiety	Not known	Not known
Nervous system disorders	Headache --- Dizziness, somnolence --- Aseptic meningitis, hypoaesthesia --- Cerebrovascular accident, loss of consciousness, paraesthesia, tremor, migraine, photophobia	Common --- Uncommon --- Rare --- Not known	Very common --- Common --- Uncommon --- Not known
Eye disorders	Eye pruritus	Rare	Uncommon
Ear and labyrinth disorders	Ear pain	Rare	Uncommon
Cardiac disorders	Tachycardia --- Angina pectoris, cyanosis, bradycardia, palpitations	Uncommon --- Not known	Common --- Not known

MedDRA System Organ Class (SOC) according to the sequence:	**Adverse Reaction**	**Frequency per Infusion**	**Frequency per patient**
Vascular disorders	Hypertension --- Hypotension --- Pallor	Uncommon --- Rare --- Not known	Common --- Uncommon --- Not known
Respiratory, thoracic and mediastinal disorders	Cough --- Dyspnoea, tachypnoea --- Pulmonary oedema, hypoxia, bronchospasm, wheezing	Uncommon --- Rare --- Not known	Common --- Uncommon --- Not known
Gastrointestinal disorders	Nausea, Vomiting, abdominal pain --- Abdominal discomfort, diarrhoea	Uncommon --- Rare	Common --- Uncommon
Skin and subcutaneous tissue disorders	Dermatitis, skin exfoliation, urticaria, pruritus, rash --- Erythema	Uncommon --- Rare	Common --- Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, musculoskeletal pain or stiffness --- Muscle spasms, neck pain, pain in extremity	Rare --- Not known	Uncommon --- Not known
General disorders and administration site conditions	Pyrexia --- Chills, asthenia, flu-like illness --- chest discomfort, chest pain, fatigue, feeling cold, infusion site pruritus, pain, peripheral swelling --- Oedema, lethargy, malaise, burning sensation, feeling hot, flushing, hot flush, hyperhidrosis, injection site reaction	Common --- Uncommon --- Rare --- Not known	Very common --- Common --- Uncommon --- Not known
Investigations	Hepatic enzyme increased, blood lactate dehydrogenase increased --- Haemoglobin decreased --- Coombs' direct test positive, oxygen saturation decreased	Uncommon --- Rare --- Not known	Common --- Uncommon --- Not known

† subclinical case

The following additional adverse reactions have been reported during post approval use of intravenous immunoglobulin products and can also occur after Panzyga administration: Cardiac arrest, acute respiratory distress syndrome, respiratory failure, coma, peripheral circulatory failure/collapse, apnoea, encephalopathy, Steven-Johnson syndrome, pancytopenia, bullous dermatitis, epidermolysis, convulsion, fluid overload, hepatic dysfunction, (pseudo)hyponatraemia, phlebitis, renal pain, falsely elevated erythrocyte sedimentation rate, nervousness, alopecia, eczema, speech disorder.

Description of selected adverse reactions

For description of selected adverse events, such as hypersensitivity reactions, thromboembolism, acute renal failure, aseptic meningitis syndrome, and haemolytic anaemia, see section 4.4.

Paediatric population

Frequency, type and severity of adverse reactions in children are the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including infants, elderly patients or patients with cardiac or renal impairment (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC Code: J06BA02.

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

The mechanism of action in indications other than replacement therapy is not fully elucidated.

Clinical Studies

A prospective, open-label, non-controlled study was done in 51 patients with primary immunodeficiency syndromes. The patients were recruited into 3 age strata (≥2 years and <12 years of age, ≥12 years and <16 years of age, and ≥16 years and ≤75 years). The primary endpoint of the study was the rate of serious bacterial infections (SBI) per person-year on treatment. Patients received a total of 17 or 13 infusions of Panzyga over the course of this study, depending on whether their regular treatment intervals were every 3 or 4 weeks,

respectively. The dose was 0.2-0.8 g/kg to be infused at increasing infusion rates up to a maximum of 0.08 ml/kg/min. Two patients experienced 4 SBIs. With altogether 50.2 patient exposure years, the result of this primary endpoint was 0.08 SBIs/patient exposure year with an upper 99% confidence interval limit of 0.5. Also the other efficacy parameters calculated by patient exposure year, such as other infections and days with use of antibiotics, absence from school or work, and hospitalised due to infection, were in line with what has been published for other IVIGs previously developed.

This study was followed by an extension study which was carried out in order to assess the tolerability of Panzyga when administered at higher infusion rates (from 0.08 ml/kg/min up to 0.14 ml/kg/min). In total, 21 patients were enrolled. The product was well tolerated and all patients completed the study as planned. Study medication related AEs were reported in 2 children and 2 adults; the most commonly reported reactions were nausea and headache.

A further prospective, open-label, non-controlled study was done in 40 patients with immune thrombocytopenic purpura of at least 12 months duration. Patients received a daily dose of 1 g/kg for 2 consecutive days. Alternative response (AR) according to the EMA Guideline was defined as an increase in platelet count to $\geq 30 \times 10^9$/L and to at least double the baseline platelet count, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding. An AR was observed in 24 patients (66.7%).

Complete response (CR) according to the EMA Guideline was defined as the achievement of platelet counts $\geq 100 \times 10^9$/L, to be fulfilled on at least 2 separate visits at least 7 days apart without new bleedings. CR was observed in 18 patients (50.0%).

Loss of AR/CR was applied if the criteria for AR/CR were fulfilled but deteriorated afterwards as a decrease in platelet count to $< 30 \times 10^9$/L (AR) or $< 100 \times 10^9$/L (CR) or a decrease in platelet count to less than double the baseline count or as occurrence of bleeding. Regarding loss of AR, 11 of 24 patients (45.8%) who fulfilled the AR criteria had a loss of response. Loss of CR was seen for 14 of 18 patients (77.8%) who fulfilled the CR criteria.

The efficacy of PANZYGA in adults with Chronic inflammatory demyelinating polyneuropathy (CIDP) was evaluated in a prospective, double-blind, randomized, multicenter study that enrolled 142 adult subjects (between 18 and 83 years of age) with CIDP who deteriorated in the 12-week Wash-out Phase, during which the current medication (immunoglobulins or corticosteroids) was reduced gradually. Of these, 124 patients (87.3%) had been on corticosteroids and 18 patients (12.7%) on IVIg before study entry. Subjects were randomized 1:2:1 to receive first a loading dose of 2 g/kg, and then maintenance doses of 0.5 g/kg, 1.0 g/kg or 2.0 g/kg PANZYGA every 3 weeks for 24 weeks.

Efficacy was based on the proportion of responders in the 1.0 g/kg PANZYGA arm at Week 24 relative to Baseline (Week 0). A responder was defined as a subject with a decrease of at least 1 point in the adjusted 10-point Inflammatory Neuropathy Cause and Treatment (INCAT) disability score at Week 24 relative to Baseline. The proportion of responders in the 1.0 g/kg arm was 79.71% (95% CI: 68.8, 87.5), with 55 out of 69 subjects classified as responders.

In patients with a documented increase in INCAT by at least 1 point prior to treatment, the proportion of responders in the 1.0 g/kg PANZYGA arm was 82.26% (95% CI: 71.0; 89.8), with 51 out of 62 subjects classified as responders.

Efficacy was supported by results of all other secondary endpoints.

For safety information derived from clinical studies please see Section 4.8.

5.2 Pharmacokinetic properties

Absorption

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution

It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3–5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination

Panzyga has an average half-life of about 26–39 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Paediatric Population

The results of the pharmacokinetic studies in the different paediatric age groups are summarized in the following table, with a comparison to adults.

Overview on Pharmacokinetic Characteristics of Total IgG for Panzyga Divided by Different Age Groups (median values)

		Paediatric Population		*Adults*	*All Age Groups*
		Children	*Adolescents*		
		≥ 2 to <12 yrs	≥ 12 to <16 yrs	≥ 16 to ≤75 yrs	
Parameter	*Unit*	*N=13*	*N=12*	*N=26*	*N=51*
C_{max}	g/L	18.6	19.3	17.1	18.2
C_{min} [range]	g/L	10.7 [7.2 – 16.8]	9.3 [7.4 – 20.4]	10.1 [6.8 – 20.6]	9.9 [6.8 – 20.6]
$AUC_{0\text{-}tau}$	h•g/L	6957	6826	7224	7182
$t_{½}$	days	36	33	37	36

Measles pre-/post exposure prophylaxis

No clinical studies have been performed in susceptible patients regarding Measles pre-/post exposure prophylaxis.

Panzyga meets the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard. The dosing is based on pharmacokinetic calculations which take body weight, blood volume and half-life of immunoglobulins into consideration. These calculations predict a:

▪ Serum titer at 13.5 days = 270 mIU/ml (dose: 0.4 g/kg) This provides a safety margin more than double that of the WHO protective titer of 120 mIU/ml

▪ Serum titer at 22 days (t1/2) = 180 mIU/ml (dose: 0.4 g/kg)

▪ Serum titer at 22 days (t1/2) = 238.5 mIU/ml (dose: 0.53 g/kg – pre-exposure prophylaxis)

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body.

The safety of Panzyga has been demonstrated in several non-clinical safety pharmacology (cardiovascular, respiratory, and bronchospastic effects, thrombogenic potential) and toxicology studies (acute toxicity, local tolerance). The non-clinical data reveal no special risk for humans based on these conventional safety pharmacology and toxicity studies. Studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction in animals are impracticable due to induction of and interference by developing antibodies to heterologous proteins. Since clinical experience provides no evidence for carcinogenic potential of immunoglobulins, no experimental genotoxicity/carcinogenicity studies in heterogeneous species were performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, Water for injections

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.

The product may be stored at temperatures above +8°C and below +25°C for up to 12 months, without being refrigerated again during this period, and it must be discarded if not used during this period or after the expiry date whichever is sooner.

The date at which the product was taken out of the refrigerator should be recorded on the outer carton.

6.5 Nature and contents of container

Pack sizes:

1 g	in	10 ml	in a 20 ml vial
2.5 g	in	25 ml	in a 30 ml vial
5 g	in	50 ml	in a 70 ml bottle
6 g	in	60 ml	in a 70 ml bottle
10 g	in	100 ml	in a 100 ml bottle
3 x 10 g	in	3 x 100 ml	in a 100 ml bottle
20 g	in	200 ml	in a 250 ml bottle
3 x 20 g	in	3 x 200 ml	in a 250 ml bottle

30 g in 300 ml in a 300 ml bottle

Not all pack sizes may be marketed.

The vials/bottles are made of type II glass closed with bromobutyl rubber stoppers and sealed with aluminium flip-off caps.

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use.

The solution should be clear or slightly opalescent and colourless or pale yellow.

Solutions that are cloudy or have deposits should be not used.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

Date of last renewal:

10 DATE OF REVISION OF THE TEXT