Paul-Ehrlich-Institut

Public Assessment Report

(according sec 34 subs 1a and 1b Medicinal Products Act)

Panzyga

Human Normal Immunoglobulin G for Intravenous Administration

Octapharma GmbH
Elisabeth-Selbert-Str. 11
40764 Langenfeld
Deutschland

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ENR:	
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EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

Panzyga, 100 mg/ml solution for infusion

DE/H/1948/001/DC

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MODULE 1: INFORMATION ABOUT THE INITIAL PROCEDURE

Panzyga, 100 mg/ml solution for infusion

DE/H/1948/001/DC

1. **Type of application**:

   Full application according article 8.3 (i) Directive 2001/83/EC

2. **Active Substance**:

   Human Normal Immunoglobulin

3. **Form:**

   Solution for infusion

4. **Strength:**

   100 mg/ml

5. **Marketing Authorisation Holder:**

- Octapharma GmbH, 40764 Langenfeld, Germany
- Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, Austria
- Octapharma AB, 11275 Stockholm, Sweden
- Octapharma (IP) Limited, Manchester, UK
- Octapharma France, 92100 Boulogne Billancourt, France
- Octapharma Italy S.p.A., 56100 Pisa, Italy
- Octapharma Benelux S.A./N.V.1070 Brussels, Belgium
- Octapharma Produtos Farmeceuticous Lda, 1700-268 Lisboa, Portugal
- Octapharma S.A., 28830 Madrid, Spain

6. **Reference Member State:**

   Paul-Ehrlich-Institut, Germany

7. **Concerned Member State:**

   AT, BE, BG, CZ, DK, EE, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, Si, SK, UK

8. **Procedure-number:**

   DE/H/1948/001/DC

9. Timetable:

Start of procedure d0:	26.05.2015
Assessment report d70:	07.08.2015
Comments d100:	06.09.2015
End of procedure d210:	04.02.2016

MODULE 2: SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

 This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

NAME OF THE MEDICINAL PRODUCT

Panzyga, 100 mg/ml solution for infusion

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 %

The maximum IgA content is 300 micrograms/ml

Produced from the plasma of human donors.

For a full list of excipients, see section 6.1.

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.

CLINICAL PARTICULARS

Therapeutic Indications

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency (PID) syndromes with impaired antibody production (see section 4.4).
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
- Congenital AIDS with recurrent bacterial infections.

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.

Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen is dependent on the indication.

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency (PID) syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5-6 g/l. Three to six months are required after the initiation of therapy for equilibration 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 three to four weeks.

The dose required to achieve a trough level of 5–6 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.

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

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple

myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections

The recommended dose is 0.2–0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation

The recommended dose is 0.2–0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia (ITP)

There are two alternative treatment schedules:

- 0.8–1g/kg given on day one; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for two to five days.

The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day over 5 days.

Kawasaki Disease

1.6–2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of injection**
Replacement therapy in primary immunodeficiency	starting dose: 0.4–0.8 g/kg thereafter: 0.2–0.8 g/kg	every 3–4 weeks to obtain IgG trough level of at least 5–6 g/l
Replacement therapy in secondary immunodeficiency	0.2–0.4 g/kg	every 3–4 weeks to obtain IgG trough level of at least 5–6 g/l
Congenital AIDS	0.2–0.4 g/kg	every 3–4 weeks
Hypogammaglobulinaemia (<4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2–0.4 g/kg	every 3–4 weeks to obtain IgG trough levels above 5 g/l.
Immunomodulation: 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	1.6–2 g/kg or 2 g/kg	in divided doses over 2–5 days in association with acetylsalicylic acid; in one dose in association with

Indication	Dose	Frequency of injection
		acetylsalicylic acid

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 adjusted to the clinical outcome of the above mentioned conditions.

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. If well tolerated (see section 4.4), 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4).

Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

Special warnings and precautions for use

Certain severe adverse drug reactions 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.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- 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.

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 order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

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

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

In all patients, IVIg administration requires:

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

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

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, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IVIg discontinuation should be considered. While these 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.

In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within

several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, 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.

Haemolytic anaemia

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

Interference with serological testing

After injection 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.

It is strongly recommended that every time that Panzyga is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Sodium content

This medicinal product contains not more than 0.03 mmol (or 0.69 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Paediatric population

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

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.

Paediatric population

The listed interactions apply both to adults and children.

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 and breast-feeding mothers. 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

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Fertility

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

Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Panzyga. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely,

haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also Section 4.4).

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

For safety information with respect to transmissible agents, see section 4.4.

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), not known (cannot be estimated from the available data).

Within each Organ Class, adverse reactions are presented in order of decreasing seriousness.

Frequency of adverse drug reactions in clinical studies with Panzyga:

MedDRA System Organ Class (SOC) according to the sequence:	**Adverse Reaction**	**Frequency per Infusion**
Blood and lymphatic system disorders	Haemolysis†, anaemia, leukopenia	Uncommon
Nervous system disorders	Headache ---------- Aseptic meningitis, hypoaesthesia, dizziness	Common ---------- Uncommon
Eye disorders	Eye pruritus	Uncommon
Ear and labyrinth disorders	Ear pain	Uncommon
Cardiac disorders	Tachycardia	Uncommon
Vascular disorders	Hypertension	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon
Gastrointestinal disorders	Nausea ---------- Vomiting, abdominal pain, abdominal discomfort	Common ---------- Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, musculoskeletal pain or stiffness	Uncommon
General disorders and administration site conditions	Pyrexia ---------- Chills, chest pain, pain, feeling cold, asthenia, fatigue, infusion site pruritus	Common ---------- Uncommon
Investigations	Hepatic enzyme increased	Uncommon

† subclinical case

The following reactions have been reported to occur with IVIg treatment and can also occur after Panzyga administration:

MedDRA System Organ Class	**Adverse Reactions**
Blood and lymphatic system disorders	Pancytopenia
Immune system disorders	Hypersensitivity, anaphylactic reaction, anaphylactoid reaction, angioneurotic oedema, face oedema
Metabolic and nutritional disorders	Fluid overload, (pseudo)hyponatraemia
Psychiatric disorders	Agitation, confusional state, anxiety, nervousness
Nervous system disorders	Cerebrovascular accident, coma, loss of consciousness, convulsion,encephalopathy, migraine, speech disorder, photophobia, paraesthesia, tremor
Cardiac disorders	Cardiac arrest, angina pectoris, bradycardia, palpitations, cyanosis
Vascular disorders	Peripheral circulatory failure or collapse, phlebitis, pallor
Respiratory, thoracic and mediastinal disorders	Respiratory failure, apnoea, acute respiratory distress syndrome, pulmonary oedema, bronchospasm, dyspnoea, hypoxia, wheezing
Gastrointestinal disorders	Diarrhoea
Hepatobiliary disorders	Hepatic dysfunction
Skin and subcutaneous tissue disorders	Steven-Johnson syndrome, epidermolysis, skin exfoliation, erythema (multiforme), eczema, urticaria, rash (erythematous), (bullous) dermatitis, pruritus, alopecia
Musculoskeletal and connective tissue disorders	Pain in extremity, neck pain, muscle spasm
Renal and urinary disorders	Osmotic nephropathy, renal pain
General disorders and administration site conditions	Injection site reaction, chest discomfort, hot flush, flu-like illness, feeling hot, flushing, oedema, lethargy, burning sensation, hyperhidrosis, malaise
Investigations	Coombs' direct test positive, falsely elevated erythrocyte sedimentation rate, oxygen saturation decreased
Injury, poisoning and procedural complications	Transfusion related acute lung injury (TRALI)

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 were 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.

Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC-Code: J06B A02.

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 donations. 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, but includes immunomodulatory effects.

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 49.2 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 $\geq 100x10^9$/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 $<30x10^9$/L (AR) or $<100x10^9$/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.

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

Paediatric Population

There were no major differences in the proportion of children or adolescent patients with AEs compared with adults. AEs related to the system organ class "infections and infestations" were the most commonly AEs met in all age groups; however, they were reported in a higher percentage of children and adolescent patients. The same difference was noted for gastrointestinal disorders AEs. It was also noticed a higher percentage of patients in children age group having AEs from the system organ class "skin and subcutaneous tissue disorders".

Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3–5 days equilibrium is reached between the intra- and extravascular compartments.

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

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.

PHARMACEUTICAL PARTICULARS

List of excipients

Glycine, Water for injections

Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf-life

2 years

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 6 months, without being refrigerated again during this period, and it must be discarded if not used after this.

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.

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.

Due to the possibility of bacterial contamination, any remaining contents must be discarded.

MARKETING AUTHORISATION HOLDER

To be completed nationally

MARKETING AUTHORISATION NUMBER(S)

DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

Date of last renewal:

DATE OF REVISION OF THE TEXT

LEGAL CATEGORY

For prescription only.

MODULE 3: PACKAGE LEAFLET

Package leaflet: Information for the user

Panzyga, 100 mg/ml solution for infusion
Human Normal Immunoglobulin (IVIg)

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Panzyga is and what it is used for

What Panzyga is
Panzyga is a human normal immunoglobulin (IgG) solution (i.e. solution of human antibodies) for intravenous administration (i.e. infusion into a vein). Immunoglobulins are normal constituents of the human blood and support the immune defence of your body. Panzyga contains all IgG which are present in the human blood of healthy people. Adequate doses of Panzyga may restore abnormally low IgG levels to the normal range.
Panzyga has a broad spectrum of antibodies against various infectious agents.

What Panzyga is used for
Panzyga is used for the treatment of children and adults (replacement therapy). There are 4 groups of patients where replacement therapy is used:

- Patients with inborn deficiency of antibodies (primary immunodeficiency syndromes, such as: congenital agammaglobulinaemia and hypogammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiencies)
- Patients with diseases of the blood that lead to a lack of antibodies and to recurrent infections (Myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections)
- Patients who have low levels of immunoglobulins after the transplantation of stem cells
- Patients with congenital AIDS who have repeated bacterial infections

Panzyga can be further used in the treatment of inflammatory disorders (immunomodulation). There are 3 groups of patients:

- In patients with immune thrombocytopenia (ITP), a condition where the platelets get destroyed and are therefore reduced in number, and who have a high risk of bleeding or need to correct the platelet count prior to surgery
- In patients with Kawasaki disease, a condition that leads to inflammation of various organs
- In patients with Guillain Barré syndrome, a condition that leads to inflammation of certain parts of the nervous system

2. What you need to know before you use Panzyga

Do NOT use Panzyga:

- if you are allergic to human normal immunoglobulin or any of the other ingredients contained in Panzyga (listed in section 6).
- if you have a deficiency of immunoglobulin A (IgA deficiency) and if you have developed antibodies against immunoglobulins of the type IgA.

Warnings and precautions

Talk to your doctor or pharmacist before using Panzyga.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- when you receive Panzyga for the first time or, in rare cases, when there has been a long interval since the previous infusion.

In the case of an adverse reaction, your doctor will either reduce the rate of administration or stop the infusion. The treatment of the adverse event required will depend on the nature and severity of the adverse event.

Circumstances and conditions increasing the risk of having side effects

- If you had kidney problems in the past or if you have certain risk factors like diabetes, overweight, or age over 65, Panzyga should be administered as slow as possible because cases of acute kidney failure have been reported in patients with such risk factors. Tell your doctor, even when any of the above-mentioned circumstances had happened to you in the past.
- Thromboembolic events such as heart attack, stroke, and obstructions of a deep vein for example in the calves or of a blood vessel in the lung may occur very rarely after administration of Panzyga. These types of events occur more commonly in patients with risk factors, such as obesity, advanced age, high blood pressure, diabetes, previous occurrences of such events, prolonged periods of immobilisations, and intake of certain hormones (e.g. the pill). Ensure a balanced fluid intake; moreover Panzyga should be administered as slow as possible.
- Allergic reactions are rare, but can induce an anaphylactic shock, even in patients who had tolerated the previous treatments.
- Strong headaches and neck stiffness may rarely occur several hours to 2 days following Panzyga treatment.
- Patients with blood group A, B or AB as well as patients with certain inflammatory conditions have a higher risk of red blood cells being destroyed by the administered immunoglobulins (called haemolysis).

Effects on blood tests

Panzyga contains a wide variety of different antibodies, some of which can affect blood tests. If you have a blood test after receiving Panzyga, please inform the person taking your blood or your doctor that you have received the human normal immunoglobulin.

Virus safety

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 medicines 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 and for the non-encapsulated viruses such as hepatitis A virus 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.

It is strongly recommended that every time you receive a dose of Panzyga the name and batch number of the product are recorded in order to maintain a record of the batches used.

Children and adolescents

There are no specific or additional warnings or precautions applicable for children and adolescents.

Other medicines and Panzyga

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, or if you have received a vaccination in the last three months.

Panzyga may impair the effect of live attenuated virus vaccines such as

- measles
- rubella
- mumps
- 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.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to become pregnant, ask your doctor or pharmacist if you can get or continue with Panzyga.

Driving and using machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Panzyga. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Panzyga contains sodium
This medicinal product contains not more than 0.03 mmol (or 0.69 mg) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Panzyga

Your doctor will decide if you need Panzyga and at what dose. Panzyga is administered as an intravenous infusion (infusion into a vein) by healthcare personnel. The dose and dosage regimen is dependent on the indication and may need to be individualised for each patient.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Use in children and adolescents
The administration of Panzyga in children and adolescents (intravenously) does not differ from the administration in adults.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor as soon as possible if you suffer from any of the serious side effects listed below (**all are very rare** and may affect up to 1 in 10,000 infusions). In some cases your doctor may need to interrupt treatment and reduce your dose or stop treatment:

- **Swelling of the face, tongue and windpipe** that can cause great difficulty in breathing
- **A sudden allergic reaction** with shortness of breath, rash, wheezing and drop of blood pressure
- **Stroke** that may cause weakness and / or loss of sensation down one side of the body
- **Heart attack** causing chest pain
- **Blood clot** causing pain and swelling of limbs
- **Blood clot in lung** causing chest pain and breathlessness
- **Anaemia** causing shortness of breath or looking pale
- **Severe kidney disorder** that may cause you to not pass urine
- **Meningitis** causing strong headache

If you experience any of the symptoms above, contact your doctor as soon as possible.

The following other side effects have also been reported:

Common side effects (may affect up to 1 in 10 infusions):
Headache, nausea, fever

Uncommon side effects (may affect up to 1 in 100 infusions):
Skin rash, back pain, chest pain, chills, dizziness, feeling tired, cough, vomiting, belly pain, joint pain, muscle pain, infusion site itching, reduced sense of touch or sensation, reduction of red blood cells, reduction of white blood cells, aseptic meningitis, eye itching, fast beating of the heart, increased blood pressure, ear pain, stiffness, feeling cold, changes in blood tests that report on how the liver is working.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Panzyga

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of the month.

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

The product may be removed from the refrigerator for a period of 6 months (without exceeding the expiry date) and stored above +8°C and below +25°C. At the end of this period, the product should not be refrigerated again and should be disposed of. The date at which the product was taken out of the refrigerator should be recorded on the outer carton.

Do not use this medicine if you notice that the solution is cloudy, has deposits or is coloured intensively.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Panzyga contains

- The active substance is human normal immunoglobulin. Panzyga contains 100 mg/ml human protein of which at least 95% is immunoglobulin G (IgG).
- The other ingredients are glycine and water for injections.

What Panzyga looks like and contents of the pack

Panzyga is a solution for infusion and is available in vials (1 g/10 ml, 2.5 g/25 ml) or bottles (5 g/50 ml, 6 g/60 ml, 10 g/100 ml, 20 g/200 ml, 30 g/300 ml).

Pack sizes:
1 vial (1 g/10 ml; 2.5 g/25 ml)
1 bottle (5 g/50 ml; 6 g/60 ml; 10 g/100 ml; 20 g/200 ml; 30 g/300 ml)
3 bottles (10 g/100 ml; 20 g/200 ml)

The solution is clear or slightly opalescent, colourless or slightly yellow.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

To be completed nationally

Manufacturers

Octapharma

72 rue du Maréchal Foch, 67380 Lingolsheim, France

Octapharma Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

This medicinal product is authorised in the member states of the EEA under the following names:

Austria:

Belgium:

Bulgaria:

Croatia

Czech Republic:

Denmark:

Estonia:

Finland:

France:

Germany:

Hungary:

Iceland:

Ireland

Italy:

Latvia :

Lithuania:

Luxembourg:

Malta:

Norway:

Poland:

Portugal:

Romania:

Slovakia:

Slovenia:

Spain:

Sweden:

The Netherlands:

United Kingdom:

This leaflet was last approved in MM/YYYY.

The following information is intended for medical or healthcare professionals only:

- The product should be brought to room or body temperature before use.
- The solution should be clear to slightly opalescent and colourless to slightly yellow.
- Solutions that are cloudy or have deposits should not be used.
- Any unused product or waste material should be disposed of in accordance with local requirements.
- This medicinal product should not be mixed with other medicinal products.
- 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% (9 mg/ml) saline or 5% (50 mg/ml) dextrose solution.

MODULE 4: LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Label of vials
(1 g)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

panzyga® 100 mg/ml solution for infusion
Human Normal Immunoglobulin (IVIg)
Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT; BY VOLUME OR BY UNIT

1 g/10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Label of vials and bottles
(2.5 g, 5 g, 6 g, 10 g, 20 g, 30 g)

1. NAME OF THE MEDICINAL PRODUCT

panzyga® 100 mg/ml solution for infusion
Human Normal Immunoglobulin (IVIg)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Human normal immunoglobulin 100 mg

IgG ≥ 95%. IgA ≤ 300 micrograms/ml.

3. LIST OF EXCIPIENTS

Glycine, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

2.5 g/25 ml
5 g/50 ml
6 g/60 ml
10 g/100 ml
20 g/200 ml
30 g/300 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use cloudy solutions.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.
or: Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma LTD.
The Zenith Building
26 Spring Gardens
Manchester
M2 1AB
U.K.

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton of vials and bottles

1. NAME OF THE MEDICINAL PRODUCT

panzyga® 100 mg/ml solution for infusion
Human Normal Immunoglobulin (IVIg)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:

Human normal immunoglobulin 100 mg

IgG ≥ 95%

IgA ≤ 300 micrograms/ml

1 g/10 ml

2.5 g/25 ml

5 g/50 ml

6 g/60 ml

10 g/100 ml

20 g/200 ml

30 g/300 ml

3. LIST OF EXCIPIENTS

glycine, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 x 10 ml
1 x 25 ml
1 x 50 ml
1 x 60 ml
1 x 100 ml
3 x 100 ml
1 x 200 ml
3 x 200 ml
1 x 300 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use cloudy solutions.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
text on cartons of vials:
Keep the vial in the outer carton in order to protect from light.
text on cartons of bottles:
Keep the bottle in the outer carton in order to protect from light.

Removed from the fridge:
..../..../....

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma LTD.
The Zenith Building
26 Spring Gardens
Manchester
M2 1AB
U.K.

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MODULE 5: SCIENTIFIC DISCUSSION

Panzyga, 100 mg/ml solution for infusion

DE/H/1948/001/DC

I. INTRODUCTION

Panzyga is a 10% (100 mg/mL) human normal immunoglobulin G (IgG) for intravenous administration (IVIg), formulated in a liquid presentation. Panzyga complies with the Ph. Eur. "monograph on Human Normal Immunoglobulin for Intravenous Administration" (0918)

Mode of action

Humoral immunodeficiencies diseases are caused by a qualitative and/or quantitative deficit of Immunoglobulins, thus, the main mechanism of action of therapeutic IgG is to replace the absent, decreased level or functionally deficient IgGs. Human normal immunoglobulin contains mainly IgG with a broad spectrum of antibodies against infectious agents. As it is usually prepared from pooled plasma from not fewer than 1000 donations, it contains IgG antibodies present in the normal population and also 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, but includes immunomodulatory effects.

Pharmacological classification

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

Indications

Panzyga was developed according to FDA Guidance and to the EMA guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94033/2007 rev. 2) in order to claim for the following indications, according to the Core SmPC guideline for IVIg (EMA/CHMP/BPWP/94038/2007 Rev. 4):

- Replacement therapy in adults, and children and adolescents (0 – 18 years) in:
  - Primary immunodeficiency (PID) syndromes with impaired antibody production,
  - Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed,
  - Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation,
  - Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT),
  - Congenital AIDS with recurrent bacterial infections.
- 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

Posology

Patients requiring replacement therapy with immunoglobulin products receive maintenance doses in the range of 0.2 to 0.8 g/kg body weight every 3 to 4 weeks.
Patients requiring immunomodulation therapy for ITP are dosed in the range 0.4 g/kg/day over 2-5 days or 0.8 – 1g/kg given on day one (this dose may be repeated once within 3 days), for GBS 0.4 g/kg/day should be given over 5 days and for Kawasaki 1.6 – 2.0 g/kg should be administered in

divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

II. QUALITY ASPECTS

II.1 Introduction

Panzyga is a solution of the normal immunoglobulin G fraction from human blood containing 100 mg of protein per ml. The pH of the preparation is 4.5 – 5.0 and contains glycine as a stabilizer.

II.2 Drug substance

The manufacturer of the Drug substance (final bulk solution) is Octapharma, 72 rue du Marechal Foch, 67380 Lingolsheim, France. The starting material is human plasma. All plasma used for the manufacture of Panzyga complies with Octapharma's Plasma Master File (EMA PMF Certificate no. EMEA/H/PMF/000008/05).
Mass capture of vitamin K dependent factors is foreseen as optional steps. The next step is the ethanol precipitation of fraction I+II+III. This fraction is the starting material for the manufacturing process, which includes protein precipitation, ion-exchange chromatography, solvent/detergent (S/D) treatment, subsequent S/D removal and nanofiltration. Removal of accompanying plasma proteins such as IgA, oligomers of IgG, potentially present procoagulant activity and process related impurities is achieved by protein precipitation and ion-exchange chromatography. Ultra/diafiltration is used to concentrate the IgG solution and to remove residual traces of ethanol. In the downstream process UF/DF is employed to adjust the final protein concentration. The final formulation is performed with the addition of glycine as a solid to a concentration of 230 mM in the product. The solution is passed over a sterilizing grade membrane filter and this filtered bulk solution (intermediate II) is defined as drug substance. Three intermediates were defined Fraction I+II+III, Intermediate I and Intermediate II (drug substance). On basis of stability studies the specific storage times were confirmed. The concerned specifications for the intermediates were provided.
Pathogen safety is assured by two dedicated orthogonal reduction steps, supplemented by validated ion-exchange chromatography. S/D (TNBP and Octoxynol) treatment at a validated pH is used ensuring safety with respect to enveloped viruses. A filter cascade including a 20 nm filter removes both lipid-enveloped and non-enveloped viruses.
The following critical steps were defined in the manufacturing process: protein precipitation, ultrafiltration, ion- exchange chromatography, S/D treatment, removal S/D reagent, nanofiltration, and formulation / filling. They are controlled via in process controls and limits for process parameter.
The process validation of Panzyga was performed using 18 batches fraction I+II+III resulting in three final bulks and 12 filled final product batches. All manufacturing variants have been included in the process validation. The presented process validation demonstrates that each validated step performed within defined justified limits, all of the results of the quality attributes and process control parameter are conforming to the acceptance criteria.
The contents of co-purified plasma proteins IgA, IgM, albumin, transferrin, fibrinogen, proteolytic activity and procoagulant activity are very low in the purified immunoglobulin. The monitoring of FXIa during the production process including precipitation and chromatography showed the ability of the process to remove procoagulant factors. For all batches, no procoagulant activity was detected in the final drug product, neither by using a specific assay for the detection of FXIa like activity nor the general tests for procoagulant activities (NATEM). The Panzyga manufacturing process complies with the Ph. Eur monograph (0918). Furthermore, process validation demonstrates the elimination during the production process of process-related impurities like TNBP, Octoxynol, castor oil and the protein precipitating agent. Overall the manufacturing process of Panzyga is considered adequately validated.

The description of product development was provided. All results of the biochemical parameters reveal that the upscale and transfer of Panzyga from Octapharma Vienna to Octapharma Lingolsheim leads to a product complying with all specifications within each development stage.
The presented analytical methods for the drug substance and in process controls are acceptable.

II.3 Drug Product

In the drug product the active substance is the human normal immunoglobulin (10% immunoglobulin solution for infusion), the excipients are glycine and water. The solution contains ≥ 95 % IgG, whereas the IgA content is ≤ 0.3 mg/ml. The product contains ≤ 3 % polymers. The monomer and dimer content is ≥ 90 %.
Panzyga belongs to the well-known and characterized biological product family of immunoglobulins. A biological and physico-chemical comparison of Panzyga final container from the different development stages was provided. The presented data confirmed comparability of Panzyga batches produced (pilot batches – conformance batches– consistency batches) regarding biological, functional and physico-chemical characteristics. In addition to the Fab function (binding to 12 different antigens) also Fc function was demonstrated according to Ph. Eur. Monograph and additionally employing opsonophagocytosis assays. Fc receptor binding was analyzed by flow cytometry. These results confirm the functional integrity of the product and comparability of clinical, conformance and consistency batches. Anticomplementary activity is below the defined limit and complement fixation properties are comparable with the BRP IgG standard. Additionally different sizing methods were used and demonstrate comparable results. Furthermore, IgG subclass distributions were found well in correspondence with ranges reported for human plasma.
Two manufacturers of the Drug product (filling of final bulk solution into final container) are defined Octapharma, 72 rue du Marechal Foch, 67380 Lingolsheim, France and Octapharma Pharmazeutika Productionsges.m.b.H, Oberlaaer Straße 235, 100 Vienna, Austria. The manufacturing of the Drug product includes pooling of intermediate II, sterile filtration of the bulk and filling of sterile final bulk solution into final container. The excipients of Panzyga are glycine and water for injection and comply with Ph. Eur. requirements. The batch formula was provided and the raw material specifications of the materials not described in a pharmacopoeia were provided.
The manufacturing process of the Drug product was validated at both sites. The Drug Product specifications generally follow the relevant Ph Eur monograph (Ph. Eur. 0918) and are acceptable. Detailed descriptions of each analytical procedure and the corresponding validations were provided.
Under section batch analysis final product data of 19 conformance batches (resulting from 8 drug substance batches), 18 process validation batches (resulting from 8 drug substance batches) and 40 pilot scale batches of which 25 batches were used in clinical studies were presented. The batch analysis results show that the finished products meet the proposed acceptance criteria and specifications.
The impurity profiles of the Panzyga batches from consistency (process validation) batch production were analyzed. Product related impurities and process related impurities met all limits defined.
Primary packaging material specifications and drawings were provided for all stoppers and glass vials used.
The shelf life of 24 months at +2°C to +8°C together with the claim that the product may be stored at temperatures above +8°C and below +25°C for up to 6 months is supported by data of the conformance batches. In addition the proposed specification of the product includes a phrase to allow transport conditions between 8°C and 25°C during first three months.
The stability indicating parameters were identified during a forced degradation study and reveal fragments, polymers and anti-HBS antibody titer as sensitive parameter. To cover temporary storage at higher temperatures, temperature excursion studies were started.
The process validation batches were also placed on stability but no real time data available yet. Based on the demonstrated comparability between the conformance batches and the consistency batches the stability can be evaluated also on the stability data of the conformance batches.

TSE Safety

The TSE safety of Panzyga is assured by the exclusion of donors with an increased risk for sporadic or variant Creutzfelt-Jakob-Disease. Validation studies have demonstrated reduction of TSEs during the ion- exchange chromatography and virus filtration steps of the Panzyga manufacturing process.

Virus safety

The overall virus safety strategy for Panzyga includes selection of qualified donors and testing of plasma donations. For virus reduction, three steps of the manufacturing process have been evaluated. Virus inactivation is performed using solvent/detergent treatment and virus removal is carried out by ion- exchange chromatography and retentive virus filtration (nanofiltration). Other purification steps in the manufacturing process may also contribute to virus safety in combination with the presence of neutralizing antibodies present in the final immunoglobulin preparation.

III. NON-CLINICAL ASPECTS

Panzyga can be defined as belonging to the well-known and characterized biological product family of human normal immunogloblunins. Several standard nonclinical studies were performed as acute toxicity, pharmacokinetics, local tolerance, and safety pharmacology and efficacy studies.

Pharmacology

The pharmacodynamic properties of Panzyga were evaluated with a dose response study in mice against Streptococcus pneumoniae (Mouse Sepsis Model). Safety pharmacology studies, performed in spontaneously hypertensive (SH) rats and guinea pigs, showed that Panzyga had no relevant effect on cardiovascular and respiratory parameters, excluding thereby anaphylactoid reactions. Finally a Wessler venous stasis model was used to evaluate thrombogenic potential in rabbits and showed no thrombogenic activity. Functional integrity was demonstrated sufficiently on process validation batches, conformance batches and pilot batches. In addition to the Fab function (binding to 12 different antigens) also Fc function was demonstrated.

Pharmacokinetics

To determine pharmacokinetic parameters, a serum pharmacokinetic study in rabbits was conducted with two batches of Panzyga. The investigated pharmacokinetics parameters are acceptable. No further studies are required to gain more information.
The production of Panzyga leads to residual amounts of TNBP and Octoxynol (max 1 µg/ml and 5 µg/ml) in the product. The results of study in rats reflect the pharmacokinetic profile of TNBP and Octoxynol which is already known in the literature and revealed no risk for accumulation. Nevertheless Tri-n-butyl-phosphate (TNBP) and Octoxynol are widely used for the viral inactivation of immunoglobulin preparations but in general will be removed from the product throughout the manufacturing process. No further studies are required to gain more information. For the protein precipitating agent literature data were discussed.

Toxicology

Two single dose toxicity studies (mice and rats) gave no indications for negative effects. Two local tolerance studies in rabbits were performed and confirmed that Panzyga was locally well tolerated. Given the vast experience with immunoglobulin products and the proteinous nature of the product the presented pre-clinical program is considered as acceptable and supports the clinical use.
The toxicity of TNBP + Octoxynol was experimentally determined (single dose and repeat dose) Animal and in vitro experiments presented demonstrate no toxic adverse reactions are to be expected in patients with the concentration of TNBP and Octoxynol present in Panzyga. The protein precipitating agent is listed by the FDA as substance affirmed as generally safe. Moreover TNPB, Octoxynol and protein precipitating agent are widely used in the field of immunoglobulin manufacturing.
Glycine as excipient has a target concentration of 15.0 - 19.5 mg/mL Panzyga, which is a well-established concentration in IVIGs with marketing authorizations for years and widely used without any adverse effects.
Based on the protein nature of Panzyga, no repeat-dose toxicity testing, no mutagenicity or carcinogenicity studies, no reproductive and developmental toxicity studies were performed in animals. For a human immunoglobulin preparation this approach is considered acceptable and in line with ICH S6R1.
The mutagenicity studies with TNBP + Octoxynol in combination, as well as TNBP alone, revealed no indications of gene or chromosomal damage. For glycine and the protein precipitating agent no mutagenic activity is known from literature. TNBP revealed in diet studies oncogenic effects possibly induced by nongenotoxic mechanism but the NOEL determined are far behind any therapeutic regime in patients. For glycine, Octoxynol and the protein precipitating agent also no evidence for carcinogenicity is known. High doses TNBP and Octoxynol were used in the embryo-fetal development studies in rats and rabbits conducted by the applicant and confirm the absence of a teratogenic potential. According to literature the protein precipitating agent is non-teratogenic except in a frog embryo teratogenesis assay.

IV. CLINICAL ASPECTS

Pharmacokinetics

Pharmacokinetics in PID Study NGAM01

Study NGAM-01 investigated the efficacy, safety and PK in Primary Immunodeficiency Diseases (PID) patients. The PK assessment fulfills the EMA Guideline (EMA/CHMP/BPWP/94033/2007 rev. 2) requirements.

In total, 51 patients were enrolled in 11 study centres; 1 patient was excluded from PP analysis population; 50 patients completed the study. The total study duration per patient was approximately 13 months (including the screening period). 26/51 were adults (> 16 – < 75 y) and 13/51 were children (2-<12 years) and 12/51 were adolescents (> 12-<16 years). The baseline characteristics corresponded to those commonly seen in the PID population. Twenty-one patients were on a 3-week schedule and 30 on a 4-week schedule.

Median serum IgG trough levels in the 3-week treatment group (n=21) was 13.20 g/L and in the 4-week treatment group (n=29) it 9.00 g/L; the lowest average levels achieved were 7.70 g/L and 6.80 g/L respectively. Apart from Patient 2006 (who missed 2 infusions) no patient had IgG levels below 5 g/L. Trough levels of IgG subclasses were congruent to their distribution.

Maximum IgG concentration ranging between 17.4 and 21.8 g/L was reached by the end of the IVIG infusion, median IgG half-life values were 26 days (mean values were higher: 38.5 d). AUCtau parameter for the total IgG were very similar between the 3-weekly and 4 weekly schedules (~7580 h*g/L or 315 d*g/L). These PK values fall within the range seen with other IVIG products

The PK profile of Panzyga is consistent with that reported with other IVIgs

Pharmacodynamics

The pharmacodynamic activity of an IVIg results from its biological characteristics which include the content of relevant antibodies, IgG subclasses, molecular size distribution, and functional integrity of the antigen-binding fragment (Fab) and crystallisable fragment (Fc). Data shows that the manufacturing process maintains the structural and functional integrity in compliance with Ph. Eur. Requirements.

No further studies are required

Clinical efficacy

PID Study NGAM01

The 51 PID patients who were included in the PK study were also evaluated for efficacy in Study NGAM01.

Primary endpoint: Serious bacterial infections (SBIs)

The 4 SBIs (in 2 patients) resulted in a rate of 0.08 per patient/year, i.e. well below the predefined threshold of one SBI per patient/year. The upper 99% CI of the total population was 0.50 thereby making a rejection of the null hypothesis possible. This is in line with the EMA GL EMA/CHMP/BPWP/94033/2007rev2. The 2 patients with SBIs presented with 4x pneumonia (3x in the adult patient 1007 and once in the paediatric patient 2006). The mean time to resolution of the SBIs was 14.3 days.

Other infections and endpoints

Overall, 185 other infections (not SBIs) were observed in 39/51 patients (76.5% of total patients) corresponding to 101 infections in 25 paediatric patients (87.8% of paediatrics) and 84 infections in 17 adult patients (65.4% of adults). The annualised number of all infections per patient was 3.68, which is also in line with the average range reported with other IVIgs

Less than half of the enrolled patients (25 patients [49.0%]) had days missed from school/work due to infections. The overall rate of days absent from work/school per person-year was 3.6, which is in the range seen for other IVIGs. The higher rate of infections in the paediatric patients is reflected in much higher percentage of children with absence from school compared to adults absent from

work. (~76% vs 23 %)

During the course of the study, only one patient (Patient 1007, enrolled in 4-week treatment schedule and in adult age group) was hospitalised for 4 days (overall rate of days in hospital per person-year: 0.080) due to a serious bacterial infection. This is within the lower range seen with other authorized IVIGs.

A total of 11/51 patients (21.6%) had 14 episodes of fever as part of their underlying disease. The total number of episodes of fever per person-year was fairly low at 0.279. As in the general population, young children were more prone to these episodes (38.5%) than either adolescents (8.3%) or adults (19.2%)

Use of antibiotics was reported in 42/51 patients (82. 4%) whereby children (~92%) were treated more often than adults (73%), which would correspond to their higher infection rate. This rate has also been seen with other IVIGs. The total annualised number of days on antibiotics per patient was 87.3; children were also noticeably higher in this respect (98.9 days for younger children, 151.7 days for adolescents) than adults (52.6 days).

ITP Study NGAM02

Study NGAM02 was a phase III, multinational, multicenter, prospective, uncontrolled, open-label and single-arm study that included 40 patients diagnosed with chronic primary ITP who presented with a platelet count < 20 x 109/L (except for one excluded patient who had 28 x 109/L –this would have been acceptable by EMA criteria). Thirty-one patients (77.5%) completed the study and 9 (22.5%) terminated early. Of the 9 patients who terminated early, 3 were discontinued by the investigator, 2 died (1 from an unrelated cerebral haematoma and the other one from unrelated sepsis), 2 patients withdrew consent, 1 withdrew due to an AE, and 1 was lost to follow-up. Twenty patients had 19 minor and 10 major protocol violations. The most common violations concerned exclusion criteria. Mean age was 36.7 years (range 18 to 72); 36 patients were white and 4 were Asian. Twenty-three men and 17 women were enrolled.

They received 1g Panzyga/kg/day on two consecutive days (with 4 exceptions; 3 due to AEs, 1 x insufficient amount on 2nd day). Duration of study participation was 22 days, safety follow-up was on Day 63.

Response rate

As the primary endpoint response (R) was evaluated acc. to FDA requirements (increasing platelet counts to ≥50x109/L within 7 days of the first infusion); response was also evaluated as secondary endpoints acc. to the EMA revised GL (the applicant referred to this as “alternative response” AR and complete response CR; see CPMP/BPWP/94033/2007 rev.2). This approach is considered acceptable and led to overall similar outcomes.

R:

Over 80% of patients had a response. The median time to response was 2 days, with a median of 14 days until the platelet count fell below 50x109/L and 19 days until the platelet count fell below 20x109/L.

AR/CR:

AR was achieved by 24/36 patients (66.7%) in the FA set, and a CR by 18 patients (50.0%). The median time to AR was 1 day and to CR 2 days; the median duration of AR was 18.5 days and CR 12.5 days.

Just over 40% of patients (15/36) met the criterion for non-response.

Loss of AR (46%) and CR (78%) over the course of the study is expected as the platelet count decreases and similar figures have been observed for other IVIGs evaluated acc. to the EMA criteria.

Platelet count

The mean platelet count over time showed a typical pattern following IVIG, with increases in mean values from approximately 9x109/L at Baseline to just over 200x109/L at Day 7 and subsequent decreases to just over 40x109/L at Day 22/ET. In almost 80% of the patients with a response (23/29) platelet counts reached a normal level.

For the 36 patients a median maximum platelet value of 196.3x109/L (ranging from 8 to 1067x109/L) was obtained.

Bleedings

Generally, the assessment of bleeding showed an improvement over the course of the study. No bleedings were observed in 13 patients (36.1%) at Baseline; this number increased to 26 patients (72.2%) at Day 22/ET. Only 1 patient (Patient 4501) developed new sites of bleeding and had a worsening of minor bleeding at Baseline to severe at Day 15 and Day 22/ET; one patient had a recurrence of a bleed.

Clinical safety

PID NGAM01

In this study 51 patients (25 children/adolescents and 26 adults) received a total of 740 infusions (356 infusions in 3-week schedule and 384 infusions in 4-week schedule). This amount of safety data for the PID study fulfils the requirements of the EMA GL (40 PID patients thereof 20 children of different age groups).

The average total dose of IgG received by the patients in the study per body weight at each infusion was 0.485 g/kg. The average duration of each infusion was 2.2 hours, with no significant differences among treatment schedules and age groups.

The increase of the infusion rate to the maximum allowed rate (0.080 mL/kg/min= 4.8 ml/kg/h) was permitted as per protocol starting with the 7th infusion in the study; 90.11% of these infusions were given at the maximum permitted rate. The dosing, dosing intervals, infusion times and rates are commonly seen in this patient population.

Drug-related AEs

Sixteen patients (31.4%) had a total of 60 drug-related AEs; the most frequent drug-related AEs were headaches (17.6%), nausea (7.8%), abdominal pain (9.8%), pyrexia (5.9%), vomiting (3.9%), fatigue (3.9%), chills (3.9%)%) all other drug-related AEs were only seen in 1 patient. Fewer children and adolescents experienced drug-related TEAEs compared to adults (15.4% and 25% vs. 42%). These figures have been seen with other marketed IVIGS.

Infusional AEs (during + within 72 hours post-infusion)

A total of 89/ 740 infusions (12.0%) were associated with at least one infusional AE; the most frequently occurring AE was headache (in 25 infusions, 3.4%). The ratio of infusions with infusional AEs was 0.1215 (for all patients) and the upper limit of 95%-CI was 0.1588. Study medication related infusional AEs were associated with 35 infusions (4.7%); study medication related headache was noted in 21 infusions (2.8%).

SAEs

Five patients (9.8%) (1 adolescent and 4 adults) experienced 7 unrelated SAEs (gout, pneumonia, 2x broncectasis, bronchospasm, septoplasty, thrombocytopenia). There were no related SAEs - this rate (0) is low for IVIG treatment. No deaths occurred.

Laboratory values

Most values were in the norm range. The mainly non-clinically significant (NCS) values seen for haematological, biochemistry and urine parameters compared screening and end of treatment which reflected the patterns/fluctuations seen throughout the study. The few individual clinically significant values in haematology (1x haptoglobin high, 1x neutrophil low, WBC + RBC high, 1 x neutrophils high) did not give rise to any particular safety signal. No patient changed to positive result for direct Coombs' test during the study and no positive viral test (HIV, HBV and HCV) result was observed.

Physical examination and vital signs

Fluctuations in these observations/measurements did not reveal any clear pathologies or trends.

Children vs adults

No relevant clinical signals emerged for children. Differences in AE frequencies various SOCs/PTs are more likely to reflect of the childhood situation (more prone to infections through new pathogens, more likely to vomit, more injury prone etc.) than specifically linked to differences of tolerance of the product compared to adults. No major differences were seen for infusions with infusional AEs by age group. Fewer children and adolescents experienced drug-related AEs compared to adults (15.4% and 25% vs. 42%). No children and 2 adolescent patients (16.7%) experienced severe AEs compared to 5 adults (19.2%). None of the severe AEs were related to the study drug. A higher infusional AEs rate was noticed in the adolescents group compared with children and adult age groups. Concerning treatment related infusional AEs, the highest rate was observed in adults (7.0%) compared to children (2.7%) and adolescents (2.2%). As with adults, fluctuations were seen with laboratory values, physical examination parameters and vital signs without exposing any specific trend.

Higher infusion rates (NGAM -05)

Overall, the evaluation of AEs, routine laboratory examination, vital signs and physical examination showed that administration of Panzyga up to a maximum infusion rate of 0.14 mL/kg/min was generally well tolerated and safe in both treatment schedules (trends were seen for higher AEs in the 3 weekly group) and all age groups. Study medication related AEs in this population were headache and nausea, and musculoskeletal and connective tissue disorders observed in 2 patients each (9.5%), and abdominal pain, chest pain, observed in 1 patient each (4.8%).

ITP Study NGAM02

Overall, 77 infusions were administered to 40 chronic ITP patients; all except 3 patients received 2 infusions each.

Related AEs

A total of 58 drug-related TEAEs were experienced by 23/40 patients (57.5%). The most commonly reported related AE was headache in 13 patients (17 events), followed by pyrexia in 8 patients (8 events), nausea in 5 patients (5 events) vomiting in 4 patients (4 events)), and chills in 2 patients (2 events)). This is within the range and pattern distribution seen with other IVIGs

Infusional AEs

24 patients (60.0%) experienced 71 infusional AEs (irrespective of causality). The most common infusional AEs at all time points (during and within 1 hour, 24 hours and 72 hours after the end of infusion) were headache, pyrexia, nausea and vomiting; these AEs were also the most related infusional AEs. In total 25/77 infusions (32.5%) had at least 1 related infusional AE. This is noticeably higher than in NGAM01 (4.7%) and NGAM05 (6.3%) but has also been seen in ITP studies with other IVIGs.

Severity
Most AEs were mild (85 AEs in 15 patients [37.5%]) or moderate (22 AEs in 10 patients [25%]) in intensity; 5 patients (12.5%) experienced 15 AEs of severe intensity. Of the related AEs, 38 were mild in intensity (in 19 patients)), 13 were moderate (in 9 patients), and 7 were severe. (in 2 patients). The amount of mild and moderate TEAEs is in keeping with other IVIgs, however the percentage of patients with severe AEs (12.5%) is fairly high as was also seen in the PID study.

Deaths and SAEs
Two patients died during the study, 1 from an unrelated cerebral haematoma (the patient had a major protocol violation (Evans Syndrome syndrome = autoimmune thrombocytopenia and autoimmune haemolysis) and the other from unrelated sepsis. Six patients (15%) experienced 10 SAEs, only one of which was related: a case of aseptic meningitis; this is a low occurrence of related SAEs.

Vital signs
Pyrexia, a common side-effect of IVIGs, occurred in 10 patients; otherwise vital signs did not reveal any untoward safety signals.

Laboratory parameters
In general no clear signal emerged from the laboratory data. Signs for haemolysis were specifically reviewed. Six patients (15.0%) had laboratory abnormalities consistent with haemolysis, and 1 had a clinically evident (i.e., reported as an AE) haemolysis considered probably related to Panzyga. This was however mild in intensity and did not require any treatment. No clear safety signal emerges from this data.
Nevertheless, a fairly large percentage had changes to a positive Coomb's test throughout the study: 39 patients tested negative at Baseline and 15 patients (40.5%) tested positive on Day 3, and 11 patients remained positive to the final assessment – this was not seen in the PID study. Questions concerning this issue and the LDH reference ranges were solved.

Safety conclusion on PID and ITP studies
From the literature and general extensive use of IVIGs the commonly known immediate AEs include headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnoea, back pain, nausea, vomiting, diarrhoea, blood pressure changes, tachycardia and anaphylactic reactions, especially in IgA-deficient patients. Late AEs are rare and include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia, and autoimmune haemolytic anaemia, and skin reactions.
The data presented here on treatment emergent related AEs reflects the common types of adverse events (headaches, pyrexia, back pain, vomiting, chills) and their approximate incidences seen in a given PID and ITP population treated with an IVIG product. No major, clinically relevant differences appear between children and adults in the PID study. Differences in frequencies various SOCs/PTs are more likely to reflect of the childhood situation than specifically be linked to differences of tolerance of the product compared to adults.

Not unexpectedly, slight increases in infusional AEs are seen with increased flow rate of the infusion (NGAM05: maximum of 0.14 mL/kg/min in 19/21 PID patients and 46/96 infusions; treatment related AEs were observed in 4 patients), and noticeable increases were observed in the higher-dosed ITP population, which were further elucidated by the applicant. No clear signals with regard to thromboembolic events or haemolysis emerged.

Summary Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Panzyga."

The detailed assessment report regarding the risk management plan can be viewed in an extra document.

- Summary table of safety concerns as proposed in RMP

Important identified risks	Thromboembolic events Aseptic meningitis Hypersensitivity reactions, including anaphylactic reactions Acute renal failure Haemolysis
Important 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

- Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Thromboembolic events	Mentioned in the SmPC in Sections 4.4 and 4.8	None
Aseptic meningitis	Mentioned in the SmPC in Sections 4.4 and 4.8	None
Hypersensitivity reactions, including anaphylactic reactions	Mentioned in the SmPC in Sections 4.3, 4.4 and 4.8	None
Acute renal failure	Mentioned in the SmPC in Sections 4.4 and 4.8	None
Haemolysis	Mentioned in the SmPC in Sections 4.4 and 4.8	None
Important Potential Risks		
Virus safety	Mentioned in the SmPC in Sections 4.4 and 4.8	None
Missing Information		
Safety in elderly patients	Mentioned in the SmPC in Sections 4.4 and 4.9	None
Safety in pregnant or breast feeding women	Mentioned in the SmPC in Sections 4.6	None
Safety in patients with renal or hepatic impairment	Mentioned in the SmPC in Sections 4.4 and 4.9	None

No additional pharmacovigilance studies or other activities in the pharmacovigilance plan are ongoing or planned in RMP.

BENEFIT RISK ASSESSMENT

The clinical program of Panzyga included 3 international, multi-centre, prospective, open-label, uncontrolled, single-arm Phase III studies.
Study NGAM-01 investigated the efficacy, safety and PK in 51 Primary Immunodeficiency Diseases (PID) patients.
Study NGAM-05 to evaluate the safety and tolerability of Panzyga administered at high infusion rates to21 PID patients (extension of study NGAM-01).
Study NGAM-02 investigated the efficacy and safety in 40 chronic ITP patients

Dosing adhered to the recommendations of the coreSPC (EMA/CHMP/BPWP/94038/2007 Rev. 4). The dosing further reflects standard medical practice of individually adjusting dose and/or interval between infusions.

Benefits

Beneficial effects

The beneficial effect of Panzyga in patients with primary immunodeficiency (and those with secondary immunodeficiencies) is the reduction in serious bacterial infections. With an SBI rate per patient/year of 0.08 in line with the EMA guidance, this objective was met. The annualised number of all other infections per patient was 3.68, which is also within the average range reported with other IVIgs, as were the secondary endpoints antibiotic use, missing days at work/school.
In general, the very low occurrence of SBIs is of clear value to the patient and has the potential unmeasured benefit of preventing complications from recurrent infection, e.g. bronchiectasis. The resulting fuller participation in everyday life due to very few days of absence is a benefit to society as a whole.

The beneficial effect of Panzyga in chronic ITP patients is a prompt rise in platelet counts and reduction of bleeding for the majority of the patients. According to the EMA GL the immunomodulatory effects seen in the ITP trial allow for extrapolation to the auto-immune indications as listed in the core SmPC (Kawasaki, GBS).

Uncertainty in the knowledge about the beneficial effects

Neither the rates of serious bacterial infections nor the increases in platelet counts/reductions of bleeds have been obtained in an untreated population in a randomised fashion as this would be unethical. The uncertainty of the beneficial effects is regarded as low for the following reasons: the quality of the product is according to current pharmacopoeia, the results from the clinical studies are consistent to those other IVIG products, by and large for the past 50 years.

Risks

Unfavourable effects

The data presented on treatment emergent related AEs reflects the common types of adverse events (headaches, pyrexia, nausea, vomiting) and their approximate incidences seen in a given PID and ITP population treated with an IVIG product. No major, clinically relevant differences appear between children and adults in the PID study.
Differences in related AEs were seen with increased flow rate in Study NGAM 05 (in 6.3% of the infusions vs. 5.1% in NGAM01), however, noticeable increases in related infusional AEs (32.5%) were observed in the higher-dosed ITP population. No clear signals emerged with regard to thromboembolic events, hemolysis, changes in vital signs or changes in laboratory values.
The 2 deaths (intracerebral bleeding and severe sepsis**)** were not regarded to be related to the study drug.

Uncertainty in the knowledge about the unfavourable effects

The uncertainty as to the noticeable increases in infusionally related AEs in the ITP population were explained primarily by the higher dosing (4x compared to PID) and recording time after the

second infusion in ITP. In a comparatory product similar differences were seen between ADR rates in PID and ITP patients.

Benefit-risk balance
Discussion on the benefit-risk assessment
The favourable effects in the PID and ITP populations in respectively keeping SBIs and bleeds at bay have been demonstrated.

Conclusions
The overall B/R of Panzyga is positive.

MODULE 6: STEPS ARE TAKEN AFTER THE INITIAL PROCEDURE

Scope	Procedure number	Product information affected	Start	End	Approval	Assessment report attached
Second step PMF	DE/H/1948/001/IA/01/G	n	25.05.2016	24.06.2016	y	n