SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pentaglobin 50 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human immunoglobulin for intravenous use.

One ml of solution contains 50 mg human plasma proteins, of which at least 95% is immunoglobulin with

- immunoglobulin M (IgM) 6 mg
- immunoglobulin A (IgA) 6 mg
- immunoglobulin G (IgG) 38 mg

The distribution of the IgG subclasses is approximately 63% (IgG1), 26% (IgG2), 4% (IgG3), 7% (IgG4).

Produced from the plasma of human donors.

Excipients with known effect:
One ml of solution for infusion contains 25 mg glucose (equivalent to approximately 0.0021 'bread units') and 0.078 mmol (1.79 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Faintly to moderately opalescent and colourless to pale yellowish solution.
Pentaglobin has a pH of 6.4–7.2 and an osmolality of 310–340 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant therapy of severe bacterial infections additional to antibiotic therapy.

Immunoglobulin substitution in immunocompromized patients and patients suffering from severe secondary antibody deficiency syndrome (immunocompromized patients and those with a suppressed immune defence).

4.2 Posology and method of administration

Posology
The dosage is dependent on the patient's immune status and on the severity of the disease. Dose based on body weight may require adjustment in underweight or overweight patients. The following dosage suggestions may be used as reference:

Bacterial infections
Neonates, infants, children and adults:

The recommended dose is 5 ml (0.25 g)/kg body weight (bw) daily on 3 consecutive days. Further infusions may be required depending on the clinical course.

Immunoglobulin replacement therapy
Children and adults:
The recommended dose is 3–5 ml (0.15–0.25 g)/kg body weight (bw). Repetition at weekly intervals, if necessary.

The dosage recommendations are summarized in the following:

Indication	**Dose**	**Frequency of infusions**
Bacterial infections in neonates, infants, children and adults	5 ml/kg bw (0.25 g/kg bw)	Daily on 3 consecutive days. Further infusions may be required depending on the clinical course.
Immunoglobulin replacement therapy in children and adults	3–5 ml/kg bw (0.15–0.25 g/ kg bw)	Repetition every week if necessary.

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
Intravenous use.
Pentaglobin should be brought to room or body temperature before use and should be infused intravenously at the following infusion rates:

Patient group	**Infusion rate**
Neonates and infants:	1.7 ml/kg bw/hour by infusion pump
Children and adults:	0.4 ml/kg bw/hour
Alternatively: Children and adults	0.4 ml/kg bw/hour for the first 100 ml then continuously 0.2 ml/kg bw/hour until reaching target dose of 15.0 ml/kg bw within 72 hours.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

Calculation examples for dose, infusion rate and duration:

	Body weight	**Total dose on day 1**	**Infusion rate**	**Infusion period**
Neonate	3 kg	15 ml	5 ml/h	3.0 h
Child	20 kg	100 ml	8 ml/h	12.5 h
Adult	70 kg	350 ml	28 ml/h	12.5 h
Alternatively: Adult	70 kg	350 ml	28 ml/h then 14 ml/h	first 3.5 h continuously for 68 h

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 administering the product slowly (0.4 ml/kg body weight/hour).
- are carefully monitored for any symptoms throughout the whole 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 at the hospital or controlled healthcare setting during the first infusion and for the first hour after the first infusion, 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 section 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.

<u>Infusion-related reaction</u>
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 active infection or underlying chronic inflammation

<u>Hypersensitivity</u>
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.

<u>Thromboembolism</u>

There is clinical evidence of an association between intravenous immunoglobulin (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 immunoglobulins 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 hypovolemic 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.

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. Pentaglobin does not contain sucrose or maltose, but contains glucose (see section 'Pentaglobin contains glucose').

Aseptic meningitis syndrome (AMS)

AMS 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 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.

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

Intravenous immunoglobulins (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 after 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 the 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 blood 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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus (HAV) and/or parvovirus B19.

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

Pentaglobin contains glucose:
One ml of solution for infusion contains 25 mg glucose (equivalent to approximately 0.0021 'bread units'). One daily dose of the solution for infusion of approximately 350 ml for adults (70 kg body weight) contains 8.75 g glucose equivalent to approximately 0.735 'bread units'. This should be taken into account in patients with diabetes mellitus.

Pentaglobin contains sodium:
Pentaglobin contains 0.078 mmol/ml (1.79 mg/ml) sodium (main component of cooking/table salt). One daily dose of approximately 350 ml for adults (70 kg body weight) contains 27.3 mmol (627.6 mg) sodium. This is equivalent to approximately 31% of the WHO recommended maximum daily dietary sodium intake of 2 g for an adult.

Paediatric population
Clinical presentation of infusion reactions, hypersensitivity or allergic reactions in neonates and infants may vary from those in other age groups in terms of the reported signs and symptoms, see section 4.8

4.5 Interaction with other medicinal products and other forms of interaction

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
It is expected that the same interactions mentioned for the adults may also occur in the paediatric population.

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. Intravenously administered IgG has been shown to cross the placenta, increasingly during the third trimester. Pentaglobin also contains IgA and IgM. Maternal IgA has been shown to cross the placenta to a lesser extent than IgG. Usually IgM does not cross the placenta in relevant amounts. This may change in case of ascending infections of the birth canal, where transplacental transfer of all three classes of immunoglobulins increases with increasing degree of infection. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are expected.

Breastfeeding
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 human 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

Pentaglobin has minor influence on the ability to drive and use machines. 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)

Information on safety with regard to transmissible agents: see section 4.4.

Tabulated list of adverse reactions observed with the use of Pentaglobin.

Table 1 shows the adverse reactions from clinical trials of Pentaglobin and Table 2 shows the adverse reactions from post-marketing experience with Pentaglobin.

The assessment of adverse reactions is based on the following frequency categories: 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).

Table 1: Adverse reactions from clinical trials

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
Immune system disorders	Allergic reactions	Uncommon
Vascular disorders	Low blood pressure, hypotension	Common
Gastrointestinal disorders	Nausea, vomiting	Common
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
	Cutaneous reactions/allergic dermatitis	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon

Table 2: Adverse reactions from post-marketing experience (frequency not known (cannot be estimated from the available data))

MedDRA System Organ Class (SOC)	**Adverse reaction**
Infections and infestations	Aseptic meningitis
Blood and lymphatic system disorders	Haemolytic anaemia/haemolysis
Immune system disorders	Anaphylactic shock, anaphylactoid reactions, hypersensitivity
Nervous system disorders	Headache, dizziness
Cardiac disorders	Tachycardia
Vascular disorders	Flushing
Respiratory, thoratic and mediastinal disorders	Dyspnoea
Skin and subcutaneous tissue disorders	Pruritus
Renal and urinary disorders	Acute renal failure and/or increase in serum creatinine level
General disorders and administration site conditions	Chills, pyrexia

Paediatric population
Although the nature and frequency of adverse reactions in the age groups neonates and infants are generally comparable to the adverse reactions in other age groups (e.g. infusion reactions, anaphylactic reactions, hypersensitivity), their clinical presentation in terms of the reported signs and symptoms

vary and may additionally include e.g. changes in heart rate (tachycardia or bradycardia), tachypnea, oxygen saturation decreased, skin discolorations including pallor and/or cyanosis, and hypotonia.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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, human immunoglobulin for intravenous use, ATC code: J06BA02

Pentaglobin contains immunoglobulin G (IgG) and elevated concentrations of immunoglobulin A (IgA) and immunoglobulin M (IgM) with a broad spectrum of antibodies to a variety of infectious agents and their toxins.

Pentaglobin contains the antibody spectrum present in the normal population. As a result of its increased concentrations of IgA and in particular IgM, Pentaglobin has higher titres of agglutinating antibodies to bacterial antigens, compared to products that contain only IgG. Pentaglobin is prepared from pooled plasma from at least 1000 donors. Adequate doses of this medicinal product may restore abnormally low immunoglobulin levels to the normal range.

The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

5.2 Pharmacokinetic properties

Absorption
Human 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
The half-life of the immunoglobulins contained in Pentaglobin is similar to the half-lives of endogenous immunoglobulins. This half-life may vary from patient to patient, in particular in primary immunodeficiency syndromes.

Immunoglobulins and immunoglobulin complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

Immunoglobulins are normal components of the human body. Chronic toxicity and embryofoetal toxicity studies are impracticable due to the induction of, and interference with, antibodies. Effects of the product on the immune system of the neonate have not been studied.

Clinical experience provides no hint for tumorigenic or mutagenic effects. Experimental studies in animals are not considered necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate, sodium chloride, water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

After opening the container, the solution for infusion should be administered immediately. Discard unused solution for infusion due to the risk of bacterial contamination.

6.5 Nature and contents of container

Colourless (type II) glass vials, with bromobutyl rubber stopper and aluminium crimp cap.

Pack size of 1 vial with 10 ml (0.5 g), 50 ml (2.5 g) or 100 ml (5.0 g) solution.

6.6 Special precautions for disposal and other handling

Pentaglobin should only be mixed with normal saline.

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

The medicinal product should be inspected visually prior to administration: The solution must be clear or faintly to moderately opalescent. Do not use solutions which are cloudy or which have deposits.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF INFORMATION

09/2023