Summary of Product Characteristics (SmPC)

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% immunoglobulin with immunoglobulin M (IgM) 6 mg, immunoglobulin A (IgA) 6 mg and immunoglobulin G (IgG) 38 mg.

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

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, colourless to pale yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of bacterial infections with concomitant use of antibiotics.

Immunoglobulin replacement therapy for immunosuppressed patients and those with severe secondary antibody deficiency syndrome (immunocompromised patients and those with a suppressed immune system).

4.2 Posology and method of administration

Posology
Dosing depends on the patient's immune status and the severity of the condition. The following dosing recommendations can be used for guidance:

Neonates and infants
5 ml (0.25 g)/kg body weight (bw) daily on 3 consecutive days. Further infusions may be required depending on the clinical course.

Children and adults
a) Treatment of severe bacterial infections:
5 ml (0.25 g)/kg body weight daily on 3 consecutive days. Further infusions may be required depending on the clinical course.

b) Immunoglobulin replacement therapy for immunosuppressed patients and those with severe secondary antibody deficiency syndrome:
3 - 5 ml (0.15 - 0.25 g)/kg body weight. Repetition at weekly intervals if necessary.

Pentaglobin should be administered by intravenous infusion at the following rates of infusion:

in neonates and infants:	1.7 ml/kg bw/hour by infusion pump
in children and adults:	0.4 ml/kg bw/hour,
alternatively: for the first 100 ml	0.4 ml/kg bw/hour,
then continuously	0.2 ml/kg bw/hour
until reaching	15.0 ml/kg bw within 72 hours.

Examples:				
	Body weight	**Total dose on first day**	**Infusion rate**	**Infusion period**
Neonate	3 kg	15 ml	5 ml/h	3 h
Child	20 kg	100 ml	8 ml/h	12 ½ h
Adult	70 kg	350 ml	28 ml/h alternatively: 28 ml/h 14 ml/h	12 ½ h 3.5 h then continuously for 68 h

Method of administration
Intravenous use.
Pentaglobin should be brought to room or body temperature before use.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

4.4 Special warnings and precautions for use

Certain severe adverse 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 monitored and observed for any symptoms of adverse reactions throughout the infusion period.

Certain adverse reactions may occur more frequently
- in case of high rate of infusion
- in patients who receive human immunoglobulin for the first time or, in rare cases, when the 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 hypersensitive to human immunoglobulin by initially administering the product slowly (0.4 ml/kg body weight/hour).
- are carefully monitored and observed for any symptoms of adverse reactions throughout the infusion period. In particular, patients naive to human immunoglobulin, patients switched from an alternative immunoglobulin product or patients where there has been a long interval since the previous infusion must be monitored throughout the first infusion and for the first hour after the first infusion, in order to detect potential adverse reactions. All other patients should be observed for at least 20 minutes after administration.

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

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

In all patients, immunoglobulin administration requires
- adequate hydration prior to the initiation of the infusion of immunoglobulin,
- 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.

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

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

Thromboembolism
There is clinical evidence of an association between intravenous immunoglobulin (IVIg) administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (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 the following individuals: obese patients and patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus, a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients and 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 intravenous immunoglobulin (IVIg) therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years.

In case of renal impairment, discontinuation of the immunoglobulin product 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 immunoglobulin products that do not contain these excipients may be considered. Pentaglobin does not contain sucrose or maltose, but it contains glucose (see also section 'Pentaglobin contains 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)
Cases of aseptic meningitis syndrome (AMS) have been reported to occur in association with intravenous immunoglobulin (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 the start of 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
Intravenous immunoglobulins (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 cell (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 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 and 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 or 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 virus removal / inactivation 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 hepatitis A virus or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

The documentation obligation under the German Transfusion Act [Transfusionsgesetz] is pointed out. It is strongly recommended that every time that Pentaglobin 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.

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 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 (a main component of sodium chloride). One daily dose of approximately 350 ml for adults contains 27.3 mmol (627.6 mg) sodium. This is equivalent to approximately 31% of the maximum daily dietary sodium intake of 2 g recommended by the WHO for adults.

4.5 Interaction with other medicinal products and other forms of interaction

Pentaglobin should not be co-administered with calcium gluconate in infants because simultaneous administration is suspected to have the potential for adverse reactions.

Live attenuated vaccines
Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated 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 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
It is expected that the same interaction 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 evaluated in controlled clinical trials and, therefore, it should only be given to pregnant women and breast-feeding mothers after careful risk/benefit assessment. Intravenous IgG has been shown to cross the placenta, increasingly during the third trimester. IgM, which is also contained in this medicinal product, does not cross the placenta. Long-standing 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
IgG is excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry. IgM is not excreted into milk.

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

The ability to drive and operate machines may be impaired by some of the adverse reactions associated with the administration of Pentaglobin. 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
With human normal immunoglobulins the following adverse reactions have been observed:

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

Rarely, human normal immunoglobulin 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.

The following complications occur very rarely: thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses.

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

Tabulated summary 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	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	Hypersensitivity, anaphylactic shock
Nervous system disorders	Headache, dizziness
Renal and urinary disorders	Increase in serum creatinine level and/or acute renal failure
General disorders and administration site conditions	Chills, fever

Paediatric population
Frequency, type and severity of adverse reactions in the paediatric population are expected to be 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (contact details are specified in the national SmPCs).

4.9 Overdose

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

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 increased 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

Human 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.

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.

Immunoglobulin 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 has not produced any evidence of tumourigenic or mutagenic effects. Experimental studies in animals are not considered necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate (Ph. Eur.), 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). Store in the original package 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 may only be mixed with normal saline.

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

The product should be inspected visually prior to administration: The solution must be clear or faintly to moderately opalescent. Solutions that are cloudy or have deposits must not be used.

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

09/2018