Package leaflet: Information for the user

Pentaglobin®

Active substance:
Human normal immunoglobulin for intravenous administration

Composition
One ml solution contains:

- Active substance:

Human plasma protein	50 mg
of which immunoglobulin is at least	95%
Immunoglobulin M (IgM)	6 mg
Immunoglobulin A (IgA)	6 mg
Immunoglobulin G (IgG)	38 mg

- excipients:
  Glucose monohydrate (27.5 mg) corresponding to 25mg glucose, sodium chloride (78 µmol), water for injections ad 1 ml

The distribution of IgG subclasses is approx. 63% IgG1, 26% IgG2, 4% IgG3 and 7% IgG4

Pharmaceutical form and contents of container
Solution for intravenous infusion.
Pack size of 1 vial with 10 ml (0.5 g), 50 ml (2.5 g) or 100 ml (5.0 g) solution.

Pharmacotherapeutic group
Immunoglobulins, normal human, for intravascular administration

Name and address of authorisation holder and manufacturer
Biotest Pharma GmbH
Landsteinerstrasse 5
63303 Dreieich
Germany

Indications
Adjuvant therapy of severe bacterial infections additional to antibiotic therapy.
Product is only intended for use in high risk patients with proven bacterial sepsis and who are unlikely to have underlying IgA deficiency.
Immunoglobulin substitution in immunocompromized patients.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed above.
Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

Pregnancy and lactation
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. Pentaglobin also contains IgM which does not cross the placenta. 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.

IgG are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate. IgM is not excreted into the milk.

Special warnings and precautions for use
Certain severe drug reactions may be related to the rate of infusion. The recommended infusion rate given under "Dosage instructions and mode of administration" must be closely followed as the incidence of adverse events tends to increase with the rate of infusion. Patients must be closely monitored and carefully 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 with hypo- or agammaglobulinemia with or without IgA deficiency,
- 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 (0.4 ml/kg body weight/hour)
- are carefully monitored for any symptoms of adverse reactions throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative immunoglobulin 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 reactions. 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 the IVIg administration requires
- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine level
- avoidance of concomitant use of loop diuretics

<u>Hypersensitivity</u>
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.

<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 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 hypovolemic patients, patients with disease 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 preexisting renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years.

In case of renal impairment the discontinuation of the immunoglobulin administration 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.
Pentaglobin does not contain sucrose, but 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)
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 mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.
AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

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.

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, 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 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 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 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:
1 ml solution for infusion contains 25 mg glucose (approx. 0.0021 BE). A daily dose for adults of 350 ml contains 8.75 g glucose according to approx. 0.735 BE (bread exchange). 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 350ml for adults contains 27.3 mmol (627.6mg) sodium. This is equivalent to approximately 31% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

Interactions with other medicaments and other forms of interactions
Pentaglobin should not be administered to infants concomitantly with calcium gluconate as the suspicion exists that adverse reactions may occur after simultaneous administration.

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 virus vaccines such as measles, rubella, mumps and 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 one year. Therefore patients receiving measles vaccine should have their antibody status checked.

Note:
Pentaglobin is miscible with physiological saline solution. However, no other preparations must be added to the Pentaglobin solution, as a change in the electrolyte concentration or of the pH value may give rise to precipitation or denaturing of the proteins.

Dosage instructions and method of administration
The dosage is dependent on the patient's immune status and on the severity of the disease. The following dosage suggestions may be used as reference:

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

2. Children and adults:
a) Therapy 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 substitution in immunocompromized patients:
3 - 5 ml (0.15 - 0.25 g)/kg body weight. Repetition at weekly intervals if necessary.

Pentaglobin should be infused intravenously at the following rates:

in neonates and infants:	1.7 ml/kg/hour by infusion pump
in children and adults:	0.4 ml/kg/hour
alternatively:	the first 100 ml at 0.4 ml/kg/hour then 0.2 ml/kg/hour continuously until 15 ml/kg is reached within 72 hours

Examples	Body weight	Total dose day 1	Infusion rate	Infusion duration
Neonate	3 kg	15 ml	5 ml/h	3 h
Child	20 kg	100 ml	8 ml/h	12.5 h
Adult	70 kg	350 ml	28 ml/h	12.5 h
			Alternatively:	
			28 ml/h	3.5 h initially, then
			14 ml/h	for 68 h continuously

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

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

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 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.

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

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

Information on safety with regard to transmissible agents, see “Special warnings and precautions for use”.

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
Gastrointestinal disorders	Low blood pressure, hypotension	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

The patient is recommended to communicate any undesirable effect not mentioned above to his doctor or pharmacist.

Storage and special precautions for the handling
Do not use after expiry date indicated on the label and outer package.
Keep the vial in the outer carton in order to protect from light.
Store in a refrigerator (2°C - 8°C). Do not freeze.

Pentaglobin should be inspected visually prior to administration. Do not use solutions which are cloudy or which have deposits. The slightly opalescence is a property of Pentaglobin.

Once a container has been opened, the content should be used immediately. Any unused solution must be discarded because of bacterial contamination risk.

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