Package Insert

Biotest logo

Intratect®

50 g/l; solution for infusion

Active substance
Human normal immunoglobulin (IVIg)

Composition
1 ml solution contains
– active substance(s):
  Human normal immunoglobulin 50 mg
  thereof immunoglobulin G ≥ 96 %
– excipient(s):
  glycine (300 µmol), water for injections.

The distribution of IgG subclasses is defined around 57 % IgG1, 37 % IgG2, 3 % IgG3 and 3 % IgG4.
The IgA content is ≤ 900 micrograms/ml.

Pharmaceutical form
Solution for infusion

Presentations
Vial with 20 ml, 50 ml, 100 ml and 200 ml.
Each vial of 20 ml contains: 1 g of human normal immunoglobulin
Each vial of 50 ml contains: 2.5 g of human normal immunoglobulin
Each vial of 100 ml contains: 5 g of human normal immunoglobulin
Each vial of 200 ml contains: 10 g of human normal immunoglobulin

Pharmacotherapeutic group
Human normal immunoglobulin for intravenous administration

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

Indications

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

- Primary immunodeficiency syndromes (PID) with impaired antibody production.
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l.

  *PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults. 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 Barre syndrome.
- Kawasaki disease (in conjunction with acetylsalicylic acid).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Contra-indications
Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients.
Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

Pregnancy, lactation and fertility:
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 expected.

Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns / infants are anticipated.

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

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 first injecting the product slowly (0.3 ml/kg/h corresponding to 0.005 ml/kg/min),
- 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 at the hospital 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 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.

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.

<u>Infusion 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 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently

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

<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.

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 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 stabilizer 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. Intratect® does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid 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
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.

Neutropenia/Leukopenia
A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. 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 characterized by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing
After the administration of immunoglobulin the transitory rise of 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 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 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.

Effects on ability to drive and to use machines:
Intratect 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.

Interactions with other drugs
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 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.

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

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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.

The dose may need to be individualized for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guideline

Replacement therapy in primary immunodeficiency syndromes:

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

The dose required to achieve a trough level of IgG of 6 g/l is of the order of 0.2 – 0.8 g/kg/month. The dosage interval when steady state has been reached varies from 3 - 4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Secondary immunodeficiencies:

The recommended dose is 0.2-0.4 *g/kg* every three to four weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free

Primary immune thrombocytopenia
There are two alternative treatment schedules:
• 0.8-1 *g/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 Barre syndrome
0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

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

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

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

Multifocal Motor Neuropathy (MMN)
Starting dose: 2 g/kg given over 2-5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

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

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of Injections
Replacement therapy		
Primary immunodeficiency syndromes	starting dose: 0.4-0.8 g/kg maintenance dose: 0.2-0.8 g/kg	every 3-4 weeks
Secondary immunodeficiencies	0.2-0.4 g/kg	Every 3-4 weeks
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 Barre syndrome	0.4 g/kg/d	for 5 days
Kawasaki disease	2 g/kg	In one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg	in divided doses over 2-5 days every 3 weeks over 1-2 days
Multifocal Motor Neuropathy (MMN)	Starting.dose: 2 g/kg Maintenance dose: 1 g/kg or 2 g/kg	over 2-5 consecutive days every 2-4 weeks or every 4-8 weeks over 2-5 days

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

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted.

Elderly
No dose adjustment unless clinically warranted.

Method of administration

Intravenous use.
Intratect should be infused intravenously at an initial rate of not more than 0.3ml/kg/h for 30 minutes. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated the rate of administration may gradually be increased to a maximum of 1.9 ml/kg/h.

The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used. The product 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 and patients with cardiac or renal impairment.

Undesirable effects
Summary of the safety profile
Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass:

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

Tabulated list of adverse reactions

Suspected Adverse Drug Reactions reported in completed clinical trials:

Three clinical studies have been performed with Intratect (50 g/l): two in patients with primary immunodeficiencies (PID) and one in patients with immune thrombocytopenic purpura (ITP). In the two PID studies overall 68 patients were treated with Intratect (50 g/l) and evaluated for safety. Treatment period was 6 and 12 months respectively. The ITP study was performed in 24 patients.
These 92 patients received a total of 830 infusions of Intratect (50 g/l), whereby a total of 51 adverse drug reactions (ADRs) were recorded.

With Intratect 100 g/l one clinical study has been performed in patients with PID. 30 patients were treated with Intratect 100 g/l over 3 to 6 months and evaluated for safety. These 30 patients received a total of
165 infusions of Intratect 100 g/l, whereof a total of 19 infusions (11.5%) were associated with adverse drug reactions (ADRs).

The majority of these ADRs was mild to moderate and self-limiting. No serious ADRs were observed during the studies.

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).

Frequency of Adverse Drug Reactions (ADRs) in clinical studies with Intratect (50 g/l), indications PID and ITP *(Frequencies are calculated per infusions administered (n=830) and patients treated (n=92) respectively.)*

MedDRA System Organ Class (SOC)	**Adverse reaction (MedDRA preferred term (PT))**	**Frequency** *based on infusions administered (n=830)*	**Frequency** *based on patients treated (n=92)*
Blood and lymphatic system disorders	Haemolysis (mild)	Uncommon	Common
Nervous system disorders	Headache	Common	Very Common
	Dysgeusia	Uncommon	Common
Vascular disorders	Hypertension, thrombophlebitis superficial	Uncommon	Common
Gastrointestinal disorders	Nausea, vomiting, gastrointestinal pain	Uncommon	Common
Skin and subcutaneous tissue disorders	Papular rash	Uncommon	Common
General disorders and administration site conditions	Pyrexia	Common	Very common
	Chills, feeling hot	Uncommon	Common
Investigations	Body temperature increased, Coombs test (indirect and direct) positive	Uncommon	Common

Frequency of Adverse Drug Reactions (ADRs) in a clinical study with Intratect 100 g/l, indication PID
(Frequencies are calculated per infusions administered (n=165 and patients treated (n=30) respectively)

MedDRA System Organ Class (SOC)	**Adverse reaction (MedDRA preferred term (PT))**	**Frequency** *based on infusions administered (n=165)*	**Frequency** *based on patients treated (n=30)*
Immune system disorders	Infusion related reaction	Common	Common
	Hypersensitivity	Uncommon	Common
Nervous system disorders	Headache	Common	Common
	Sensory disturbance	Uncommon	Common
Cardiac Disorders	Palpitations	Common	Common
Vascular disorders	Hyperaemia, hypertension	Uncommon	Common
Gastrointestinal disorders	Diarrhoea, abdominal pain	Uncommon	Common
Skin and subcutaneous tissue disorders	Pain of skin, rash	Uncommon	Common
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, bone pain	Common	Common
	Myalgia	Uncommon	Common
General disorders and administration site conditions	Discomfort	Common	Very Common
	Fatigue, chills, hypothermia	Uncommon	Uncommon

Details of further spontaneously reported adverse reactions:
Frequency: not known (cannot be estimated from the available data)
Cardiac disorders: Angina pectoris
General disorders and administrations site conditions: Rigors
Immune system disorders: Anaphylactic shock, allergic reaction
Investigations: Blood pressure decreased
Musculoskeletal and connective tissue disorders: Back pain
Respiratory, thoracic and mediastinal disorders: Dyspnoea NOS
Vascular disorders: Shock
Blood and lymphatic system disorders: leukopenia
For safety with respect to transmissible agents, see “Precautions for use".
The patient is invited to communicate any undesirable effect not mentioned above to his doctor or pharmacist.

Pharmacological properties

Pharmacodynamic properties
Human normal immunoglobulin contains mainly immunoglobulin G (lgG) 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 IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

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. Intratect has a half-life of about 27 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.

Preclinical safety data
Immunoglobulins are normal constituents of the human body. Repeated dose toxicity testing and embryofoetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the new-born have not been studied.
Since clinical experience provides no hint for tumorigenic and mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary

Shelf-life and special precautions for storage
Keep the vial in the outer carton in order to protect from light. Do not store above 25 °C. Do not freeze. The product should not be used after the expiry date indicated on the label.
The solution should be administered immediately after opening the receptacle.
Any unused solution must be discarded because of bacterial contamination risk.

Date of information
July 2020