

INTRATECT 50 g/l

1. NAME OF THE MEDICINAL PRODUCT

Intratect 50 g/l, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:

Human normal immunoglobulin 50 mg (purity of at least 96% IgG)

Each vial of 20 ml contains: 1 g

Each vial of 50 ml contains: 2.5 g

Each vial of 100 ml contains: 5 g

Each vial of 200 ml contains: 10 g

Distribution of the IgG subclasses (approx. values):

IgG1 57%

IgG2 37%

IgG3 3%

IgG4 3%

The maximum IgA content is 900 micrograms/ml.

Produced from the plasma of human donors.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear to slightly opalescent and colourless to pale yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Primary immunodeficiency 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.

4.2 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 syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 8-16 ml (0.4-0.8 g)/kg given once, followed by at least 4 ml (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 4-16 ml (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 4-8 ml (0.2-0.4 g)/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation

The recommended dose is 4-8 ml (0.2-0.4 g)/kg every three to four weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 16-20 ml (0.8-1 g)/kg given on day one, this dose may be repeated once within 3 days.
- 8 ml (0.4 g)/kg given daily for two to five days.

The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

8 ml (0.4 g)/kg/day over 5 days.

Kawasaki disease

32-40 ml (1.6-2.0 g)/kg should be administered in divided doses over two to five days or 40 ml (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 infusions
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 level 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 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.

Intratect should be infused intravenously at an initial rate of not more than 1.4 ml/kg/h for 30 minutes.

If well tolerated (see section 4.4), the rate of administration may gradually be increased to a maximum of 1.9 ml/kg/h for the remainder of the infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).
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 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 (1.4 ml/kg/h corresponding to 0.023 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 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, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years.

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. Intratect 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 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. (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, 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.

It is strongly recommended that every time that Intratect 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.

Paediatric population

The special warnings and precautions for use mentioned for the adults should also be considered for the paediatric population.

4.5 Interactions 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.

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 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.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Intratect. 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

Frequencies outlined below have been generally calculated based on number of patients treated if not otherwise specified, e.g. by number of infusions.

Unspecific hypersensitivity 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

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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: Dyspnoe NOS

Vascular disorders: Shock

Blood and lymphatic system disorders: leukopenia

Description of selected adverse reactions

The reported adverse reactions for Intratect are in the expected profile for human normal immunoglobulins.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>). Additionally, you should also report to Kamada LTD.

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.

Paediatric population

In the paediatric population at risk, e.g. with cardiac or renal impairment, overdose may lead to fluid overload and hyperviscosity as with any other intravenous immunoglobulins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

Paediatric population

The pharmacodynamic properties in the paediatric population are expected to be the same as in adults.

5.2 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.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body. Repeated dose toxicity testing and embryo-foetal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening, an immediate use is recommended.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

20 ml or 50 ml or 100 ml or 200 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a cap (aluminium) – pack size of one vial.
Not all pack sizes may be marketed.

6.6 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 not be used.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Biotest Pharma GmbH, Landsteinerstrasse 5, 63303 Dreieich, Germany

8. LICENSE HOLDER

Kamada Ltd., Beit Kama, Israel

LICENSE NUMBER
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