Package leaflet: Information for the user

Intratect 50 g/l, solution for infusion
Human normal immunoglobulin (IVIg)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Intratect is and what it is used for

Intratect is an extract of human blood which contains antibodies (the body's own defensive substances) to diseases, available in the form of a solution for infusion. The solution is ready for infusion into a vein (a "drip").

Intratect contains human normal immunoglobulin (antibodies) from blood donated by a broad spectrum of the population and is likely to contain antibodies to most common infectious diseases. Adequate doses of Intratect can restore normal values when blood levels of Immunoglobulin G (IgG) are low.

Intratect is used in adults, children, and adolescents (0–18 years) who do not have sufficient antibodies (replacement therapy) in cases of:
- Patients who are born with a lack of antibodies (primary immunodeficiency syndromes, PID)
- Acquired lack of antibodies (secondary immunodeficiency syndrome, SID) in patients who suffer from severe or recurrent infections and ineffective antimicrobial treatment with either proven specific antibody failure or low IgG level (< 4 g/l)

Intratect is also used in adults, children, and adolescents (0–18 years) to treat inflammatory disorders (immunomodulation) such as:
- Primary immune thrombocytopenia (ITP, where a patient has reduced blood platelets) when the patient will have surgery in the near future or is at risk of bleeding
- Guillain-Barré syndrome (a disease that damages nerves and may lead to generalised palsy)
- Kawasaki disease (a disease in children which causes inflammations of several organs of the body and where the arteries in the heart become enlarged) together with acetylsalicylic acid
- Chronic inflammatory demyelinating polyneuropathy (CIDP). This is a chronic disease that is characterised by inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and upper limbs.
- Multifocal motor neuropathy (MMN). This is a rare condition characterized by slow progressive asymmetrical weakness of limbs without sensory loss.

2. What you need to know before you use Intratect

Do not use Intratect
- if you are allergic to human immunoglobulin or any of the other ingredients of this medicine (listed in section 6).
- if you have an immunoglobulin A deficiency, especially if you have antibodies against immunoglobulin A in your blood, because this might lead to anaphylaxis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Intratect if you
- have not received this medicine before or if there has been a long interval (e.g. several weeks) since you last received it (you will need to be closely monitored during your infusion and for an hour after your infusion has stopped)
- have been given Intratect recently (you will need to be observed during the infusion and for at least 20 minutes after your infusion)
- have an active infection or underlying chronic inflammation
- have had a reaction to other antibodies (in rare cases you may be at risk of allergic reactions)
- have or have had a kidney disorder
- have received medicines that may harm your kidneys (if your kidney function worsens, you may need to stop treatment with Intratect)

Your doctor will take special care if you are overweight, elderly, diabetic, or if you suffer from high blood pressure, low blood volume (hypovolaemia), if your blood is thicker than normal (high blood viscosity), if you have been bed-ridden or immobile for some time (immobilisation) or if you have problems with your blood vessels (vascular diseases) or other risks for thrombotic events (blood clots).

Please note - reactions
You will be carefully observed during the infusion period with Intratect to make sure that you do not suffer a reaction (e.g. anaphylaxis). Your doctor will make sure that the rate at which Intratect is infused is suitable for you.

If you notice any of the following signs of a reaction, i.e. headache, flushing, chills, muscle pain, wheezing, rapid heartbeat, lower back pain, nausea, low blood pressure during the infusion of Intratect, tell your doctor immediately. The rate of infusion can be slowed or the infusion can be stopped altogether.

After the Intratect infusion you might have a low concentration of white blood cells (neutropenia) which resolves spontaneously within 7 to 14 days. If you are not sure about symptoms, please contact your doctor.

In very rare cases transfusion-related acute lung injury (TRALI) can occur after receiving immunoglobulins. This will lead to non-heart related accumulation of fluid in the air spaces of the lungs (non-cardiogenic pulmonary oedema). You will experience severe difficulty in breathing (respiratory distress), rapid breathing (tachypnoe), abnormally low level of oxygen in the blood (hypoxia), and increased body temperature (fever). Symptoms typically appear within 1 to 6 hours after receiving treatment. Tell your doctor immediately if you notice such reactions during the infusion of Intratect, he will stop the infusion immediately.

Information on transmission of infectious agents
Intratect is made from human plasma (the liquid part of blood). When medicines are made from human blood or plasma, it is important to prevent infections being passed on to patients. Blood donors are tested for viruses and infections. Manufacturers of these products also process the blood or plasma to inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are given, the possibility of passing on infection cannot be totally excluded.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus.

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

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you are given a dose of Intratect your doctor records the name and batch number of the product. The batch number provides information about the particular starting materials of your medicine. If necessary, a connection between you and the starting material used can thereby be made.

Other medicines and Intratect
Tell your doctor if you are using, have recently used or might use any other medicines.

Intratect can reduce the effectiveness of some vaccines such as:
- measles
- rubella
- mumps
- chicken pox

You may have to wait up to 3 months before you can have some vaccines and up to a year before you can have a measles vaccine.

Please avoid the concomitant use of loop diuretics together with Intratect.

Effects on blood tests
Intratect can affect blood tests. If you have a blood test after receiving Intratect, please inform the person taking your blood or your doctor that you have received Intratect.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Your doctor will decide if Intratect may be used during pregnancy and breast-feeding.

Driving and using machines
Intratect has a 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

3. How to use Intratect

Intratect is intended for intravenous administration (infusion into a vein). It is given to you by a doctor or nurse. The dose will depend on your condition and your body weight. Your doctor will know the right amount to give you.

At the beginning of your infusion you will receive Intratect at a slow rate. Your doctor may then gradually increase the infusion rate.
The infusion rate and its frequency are dependent on the reason you are being given Intratect.

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

Use in children and adolescents
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.

For replacement therapy in patients with a weak immune system (primary or secondary immunodeficiency) the infusion is given every 3 to 4 weeks.

To treat inflammatory disorders (immunomodulation) the infusion may be given as followed:
- Primary immune thrombocytopenia: for the treatment of an acute episode an infusion is given on day 1, this dose may be repeated once in 3 days. Alternatively a lower dosage may be given daily for 2 to 5 days.
- Guillain Barré syndrome: the infusion is given for 5 days.
- Kawasaki disease: the infusion should be administered as a single dose together with acetylsalicylic acid.
- Chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy: the treatment effect should be evaluated after each cycle of administration.

If you receive more Intratect than you should
An overdose can lead to fluid overload and increased thickness of the blood, especially in children, elderly patients or patients with impaired heart or kidney function. Make sure that you drink adequate fluids so you are not dehydrated and tell your doctor about any medical problems. If you think you have been given too much Intratect, tell your doctor, who will decide if the infusion should be stopped and an alternative treatment given.

If you miss an infusion
Intratect will be given to you in hospital by a doctor or nurse so you are unlikely to miss an infusion. However, tell your doctor if you think you have missed an infusion.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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

If you notice any of the following effects, tell your doctor immediately:
- rash,
- itching,
- wheezing,
- difficulty in breathing,
- swelling of the eyelids, face, lips, throat or tongue,
- extremely low blood pressure with symptoms like dizziness, confusion, fainting, fast pulse

This can be an allergic or a serious allergic reaction (anaphylactic shock) or a hypersensitivity reaction.

The following side effects have been reported during clinical trials with Intratect 50 g/l:
Common (may occur with up to 1 in 10 infusions):
- headache
- fever

Uncommon (may occur with up to 1 in 100 infusions):

- mildly increased breakdown of red blood cells in the blood vessels (haemolysis)
- disturbed sense of taste
- high blood pressure
- inflammation of a superficial vein
- feeling sick (nausea)
- vomiting
- abdominal pain
- rash with raised spots
- chills
- feeling hot
- increased body temperature
- positive blood test for antibodies against red blood cells

The following side effects have been reported spontaneously with Intratect:
Not known (frequency cannot be estimated from the available data)
- severe chest pain or chest pressure (angina pectoris)
- shivering or trembling (rigors)
- (anaphylactic) shock, allergic reaction
- difficulty in breathing (dyspnoea)
- low blood pressure
- back pain
- decrease in number of white blood cells (leukopenia)

Human immunoglobulin preparations in general may cause the following side effects (in decreasing frequency):
- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, joint pain, low blood pressure and moderate low back pain
- decrease in the number of red blood cells due to a breakdown of these cells in the blood vessels ((reversible) haemolytic reactions) and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as heart attack (myocardial infarction), stroke, blood clots in blood vessels in the lung (pulmonary embolism), blood clots in a vein (deep vein thromboses)
- cases of temporary acute inflammation of the protective membranes covering the brain and spinal cord (reversible aseptic meningitis)
- cases of blood test results which indicate that the renal function is impaired and/or sudden kidney failure
- cases of Transfusion Related Acute Lung Injury (TRALI) see also section “Warnings and precautions”

If a side effect occurs, the infusion rate will be decreased or stopped.

Reporting of side effects
If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Intratect

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and carton after EXP.
After first opening, immediate use is recommended.

Do not store above 25°C. Do not freeze. Keep the vial in the outer carton in order to protect from light.
Do not use this medicine if the solution is cloudy or contains deposits.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Intratect contains

- The active substance of Intratect is human immunoglobulin for intravenous administration. Intratect contains 50 g/l human normal immunoglobulin of which at least 96% is immunoglobulin G (IgG). The IgG subclass distribution is approx. 57% IgG1, 37% IgG2, 3% IgG3 and 3% IgG4. The maximum immunoglobulin A (IgA) content is 900 micrograms/ml.

- The other ingredients are: glycine and water for injections.

What Intratect looks like and contents of the pack
Intratect is a solution for infusion. The solution is clear or faintly opalescent (milky colours like an opal) and colourless to pale yellow.

20 ml, 50 ml, 100 ml or 200 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a cap (aluminium).

Pack with 1 vial with 20 ml, 50 ml, 100 ml or 200 ml solution.
Pack with 3 vials with 200 ml solution.

Not all pack sizes may be marketed.

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The following information is intended for healthcare professionals only:

Special Precautions

Infusion-related reaction

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.

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

It is strongly recommended that every time Intratect is administered to a patient, the name and batch number of the product is recorded.

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

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 studies (CSF) 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 (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.

Dosage

The dose and dose regimen are dependent on the indication.
The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guidance:

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. 3–6 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 3–4 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.

Replacement therapy in 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.

Immunomodulation in:

Primary immune thrombocytopenia:
There are two alternative treatment schedules:
- 0.8–1 g/kg given on day 1, this dose may be repeated once within 3 days
- 0.4 g/kg given daily for 2–5 days.

The treatment can be repeated if relapse occurs.

Guillain Barré 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 divided 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 physician's 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 divided 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 physician's 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 infusions**
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 (as defined in section indication)	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 Barré 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 in divided doses over 1–2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg or 2 g/kg	in divided doses over 2–5 consecutive days every 2–4 weeks or every 4–8 weeks in divided doses 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 must be adjusted to the clinical outcome of the above mentioned conditions.

Method of administration
Intravenous use
Intratect should be infused intravenously at an initial rate of not more than 0.3 ml/kg/h for 30 minutes. See “Warnings and precautions”. 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.

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