VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Intratect 50 g/l and Intratect 100 g/l are solutions for intravenous infusion (infusion into a vein) for restoration and support of the immune system functions.

Intratect preparations are used in all age groups. Patients who receive Intratect are often critically ill, attend an intensive care unit and have by their underlying diseases (clinical conditions after surgery, accidents, burn, etc.) an increased risk for even fatal outcome.

VI.2.2 Summary of treatment benefits

Intratect both strengths was studied in 122 patients for registration. An additional study in the indication chronic pain syndrome was performed in 39 patients.

Intratect contains antibodies that will substitute missing antibodies in patients with impaired immune system.

In clinical studies the following items were investigated: The therapeutic effect of the immunoglobulins, the safety and the tolerability of the product, affects on laboratory parameter, the blood level of the given immunoglobulins in relevant patient population of children, adolescent and adult age.

Immediately after infusion immunoglobulins (IVIgs) are available in the body fluid and will neutralize pathogens. The components of Intratect both strengths could modulate factors of the immune system. This is very helpful in chronically ill patients.

Mostly, IVIg is used in combination with other treatments to act together against infections. Harmful interactions with other treatments are not known.

VI.2.3 Unknowns relating to treatment benefits

No items known

VI.2.4 Summary of safety concerns

Table 30: Summary of Safety concerns – important identified risks

Risk	What is known	Preventability
Hypersensitivity reactions including anaphylactic shock to immunoglobulin or product ingredients (1)	Although most hypersensitivity reactions are mild. Intratect 50g/l and Intratect 100g/l must not be used if a patient is allergic (hypersensitive) to immunoglobulin preparations or to any of the other ingredients of Intratect 50g/l and Intratect 100g/l. Very rarely, severe reactions such as shock may occur.	Yes, by monitoring for early symptoms during infusion: Mild (non IgE-mediated/ anaphylactoid) reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Suspicion of allergic or anaphylactic type reactions requires an immediate stop of the infusion and appropriate treatment to be started.
	Anaphylactic shock is a serious, potentially life-threatening ADR with rapid onset after (start of) infusion. If appropriate preventative medication is available, the prognosis is generally good (Marx et al. 2010). Anaphylactic shock can be considered a severe ADR with rapid onset caused by release of mediators from certain types of blood cells and triggered by immunologic mechanisms.	Patients should be screened for IgA deficiency before starting IVIg treatment, as IVIgs in general are not indicated in those patients.

Risk	What is known	Preventability
Aseptic meningitis (2)	Aseptic meningitis is a rare and serious ADR that clinically presents with symptoms such as headache, nausea, vomiting, fever and nuchal rigidity. Pleocytosis and elevated protein levels in the CSF are observed in the majority of patients. Recovery time is approximately 5 days. (Knezevic-Maramica et al. 2003, Hamrock DJ 2006). Aseptic meningitis is usually a moderate ADR. Symptoms caused by inflammation of the meninges typically begin within 6 to 48 hours after the infusion was administered.	Reducing the infusion rate and pre-medicating with acetaminophen or antihistamines may lessen the risk in migraineurs. Pre-treatment with steroids has not been proven to be effective (Caress JB et al. 2010).
Haemolytic anaemia (3)	Reversible haemolytic reactions have been observed under IVIg treatment, especially in patients with blood groups A, B and AB. Haemolytic anaemia requiring transfusion is a rare and serious ADR. Haemolytic anaemia and haemolytic reactions are usually mild to moderate ADRs. Symptoms of haemolytic reactions develop within days.	It is difficult to predict the occurrence of haemolytic reactions associated with IVIg infusion. Cross-matching before infusion has been recommended. Another suggested strategy is to develop guidelines for preventing haemolysis, based on an algorithm including both, antibody titre and IVIg dose (Daw et al. 2008).

Risk	What is known	Preventability
Acute renal failure (4)	Acute renal failure (ARF) is a rare and serious ADR that is reversible in case of early diagnosis and with appropriate treatment (dialysis). IVIgs containing sucrose as stabilizer, causing a type of sucrose nephropathy confirmed by renal biopsy, were primarily found to trigger the development of ARF. This became evident after the FDA evaluated a case series of ARF in the late 1990s. Intratect 50g/l and Intratect 100 g/l do not contain sucrose as a stabiliser. Patients considered at increased risk for developing ARF from IVIg treatment are those with baseline renal insufficiency, diabetes mellitus, inadequate hydration, age >65 years, paraproteinaemia and receiving other nephrotoxic drugs (Pierce et al. 2003, Knezevic-Maramica et al. 2003, Hamrock DJ 2006).	Appropriate hydration of the patient should always precede the IVIg infusion. In addition, the recommended dose of IVIg should not be exceeded and recommended infusion rate should be strictly followed (Hamrock DJ 2006). According to an FDA Medical Bulletin in 2003, patients at increased risk for renal failure should have administration of IVIg products at the minimum concentration and rate of infusion practicable (Pierce et a. 2003).
Thromboembolic events (5)	Very rarely, thromboembolic events including myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis were reported. These serious ADRs are reversible in case of early diagnosis and with appropriate treatment but may have a fatal outcome in isolated cases. These ADRs are moderate to severe and may develop within hours or some days. Stroke mostly developed within 24 h of completing an infusion (Hamrock DJ 2006).	Appropriate hydration of the patient should always precede the IVIg infusion. In addition, the recommended dose of IVIg should not be exceeded and recommended infusion rate should be strictly followed (Hamrock DJ 2006).

Table 31: Summary of Safety concerns – important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Transmission of infective agents (1)	When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma is administered, the possibility of transmitting an infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. There are no reports of virus infections with Intratect manufactured to European Pharmacopoeia specifications by established processes.
Interference with live attenuated virus vaccine (2)	Intratect contains antibodies of the IgG class. The transfer of the antibodies is a kind of passive immunisation.
Interference with serological testing (3)	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. These interferences can be considered non-serious and resolve spontaneously.
High infusion rate (4)	Higher infusion rates of IVIgs may increase the rate of known hypersensitivity reactions (*see Identified Risk (1) section 1.5.2.1*) in susceptible patients. These unspecific hypersensitivity reactions are mostly non-serious and resolve spontaneously upon reducing the infusion rate or interruption of the infusion. Unspecific hypersensitivity reactions resulting from high infusion rate are usually mild to moderate.

Table 32: Summary of Safety concerns – missing information

Risk	What is known
Limited exposure for BT 090 to paediatric population in	Only small number of cases for Intratect 100 g/l obtained. Safety profile of the drug in children and adolescents

Risk	What is known
study 981	considered similar to that in adults.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Intratect 50g/l and for Intratect 100g/l can be found in the Paul-Ehrlich-Institute's EPAR page.

For the following safety concerns only routine risk minimisation measures are applied:

Important identified risk (1): Hypersensitivity reactions including anaphylactic shock to immunoglobulin or product ingredients

Important identified risk (2): Aseptic meningitis

Important identified risk (3): Haemolytic anaemia

Important identified risk (4): Acute renal failure

Important identified risk (5): Thromboembolic events

Important potential risk (1): Transmission of infective agents

Important potential risk (2): Interference of IVIG with live attenuated virus vaccines

Important potential risk (3): Interference with serological testing, laboratory test interference

Important potential risk (4): High infusion rate, incorrect drug administration rate

This medicine has no additional risk minimisation measures.

Safety concern in lay terms (medical term)

The patient needs to consult his doctor

if the patient has not received this medicine before or if there has been a long interval (e.g. several weeks) since the patient last received it. The patient will need to be closely monitored during the infusion and for an hour after the infusion has stopped.

if the patient has been given Intratect recently, the patient will need to be observed during the infusion and for at least 20 minutes after your infusion.

if the patient has had a reaction to other antibodies (in rare cases the patient may be at risk of allergic reactions), has or has had a kidney disorder or has received medicines that may harm the patient kidneys (if kidney function worsens, the doctor may need to stop treatment with Intratect)

The doctor will take special care if the patient is overweight, elderly, diabetic, or suffers from high blood pressure, low blood volume (hypovolaemia). Also, the doctor will take special care if the patient blood is thicker than normal (high blood viscosity), if the patient have been bed-

ridden or immobile for some time (immobilisation) or if the patient have problems with blood vessels (vascular diseases) or other risks for thrombotic events (blood clots).

The patient will be carefully observed during the infusion period with Intratect to make sure that the patient does not suffer a reaction. The patient's doctor will make sure that the rate at which Intratect is infused is suitable.

The patient will tell the doctor immediately, if the patient notice any of the following signs of a reaction, i.e. sudden wheeziness, difficulty in breathing, fast pulse, swelling of the eyelids, face, lips, throat or tongue, rash or itching (especially affecting the patient's whole body) during the infusion of Intratect. The rate of infusion can be slowed or the infusion can be stopped altogether.

Important identified risks are:

(1) Non-allergic and allergic hypersensitivity reactions with its potentially related symptoms such as headache, chills, dizziness, pyrexia, vomiting, nausea, transient cutaneous reactions, arthralgia, back pain and low blood pressure AND Anaphylactic shock - a serious allergic reaction that is rapid in onset and may cause death.

(2) Meningitis aseptic - an illness characterized by serous inflammation of the linings of the brain

(3) Haemolytic anaemia – an abnormal breakdown of red blood cells either in the blood vessels or elsewhere in the human body.

(4) Acute renal failure – acute kidney failure

(5) Diseases with severe decrease of blood platelets including myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis

Important potential risks are:

(1) Transmission of infective agents like viruses

(2) Interaction with anti-virus vaccines due to passive transfer of antibodies

(3) Interference with serological testing – leading to false test results and overlook of infectious disease.

(4) High infusion rate (incorrect drug administration rate, drug administration rate too fast)

Risk minimisation measure(s)
Objective and rationale
The risk minimisation measures are routine drug safety activities, including provision of patient information.
- Listen to your doctors instruction - Read patient information - In case of any suspicion, contact your doctor

VI.2.6 Planned post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 33: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 01	19-SEP-2008		First version of RMP
Version 02	29-OCT-2010	No new safety concerns	
Version 03	09-MAR-2012	No new safety concerns	Adapted to current RMP template
Version 04	23-OCT-2012	No new safety concerns	Adapted to current RMP template
Version 05	22-DEC-2015	No new safety concerns	Adapted to current EU RMP template

VI.2.8 Overall benefit-risk assessment

There was no registration of additional indications for Intratect 50 g/l treatment since the start of marketing authorization in 2004. Intratect 50 g/l and 100 g/l are licensed for replacement therapy in primary immunodeficiencies, hypogammaglobulinemia in patients with CLL and multiple myeloma and after HSCT as well as for immunotherapy in primary immune thrombocytopenia, Guillain-Barré syndrome and Kawasaki disease.

Approximately 783,561 Defined Single Standard Doses (infusions) for Intratect 50 g/l and 37,023 Defined Single Standard Doses for Intratect 100 g/l show the good tolerability and effectiveness in antibody deficiencies and autoimmune diseases. IVIg can be used as monotherapy (primary and secondary antibody deficiencies, Guillain-Barré syndrome, ITP) or in combination with other drugs (Kawasaki disease, therapy-refractory autoimmune diseases). Harmful interactions with other therapies are not known.

Overall, it can be stated, the benefit-risk profile of Intratect 50 g/l and 100 g/l in the approved and represented indications of immune replacement therapy and in autoimmune disorders remains favourable.