

13.2. Elements for a Public Summary

I10 is used for:

- The treatment of patients who do not have sufficient antibodies (replacement therapy). There are five groups of patients:
 - Patients with inborn lack of antibody production (primary immunodeficiency syndromes).
 - Patients with a cancer of the blood (chronic lymphocytic leukaemia) that leads to a lack of antibody production and frequent infections when preventative antibiotics have failed.
 - Patients with cancer of the bone marrow (multiple myeloma) and lack of antibody production with frequent infections who have failed to respond to a vaccine against certain bacteria (pneumococci).
 - Patients with AIDS from birth and frequent bacterial infections.
 - Patients with low antibody production following transplantation of bone marrow cells from another person.
- The treatment of patients with certain inflammatory disorders (immunomodulation). There are three groups of patients:
 - Patients who do not have enough blood platelets (primary immune thrombocytopenia, ITP), and who are at high risk of bleeding or will have surgery in the near future.
 - Patients with a disease that is associated with multiple inflammations of the nerves in the whole body (Guillain Barré syndrome).
 - Patients with a disease which results in multiple inflammations of several organs of the body (Kawasaki disease).

13.2.1. Overview of disease epidemiology

13.2.1. 1. Patients who do not have sufficient antibodies:

Patients with inborn lack of antibody production (primary immunodeficiency syndromes).

Primary immunodeficiency disorders weaken the immune system, allowing repeated infections and other health problems to occur more easily. Many people with primary immunodeficiency are born missing some of the body's immune defenses, which leaves them more susceptible to germs that can cause infections. There are numerous types of primary immunodeficiency disorders. They can be broadly classified into six groups based on the part of the immune system affected:

- B cell (antibody) deficiencies
- T cell deficiencies
- Combination B and T cell deficiencies
- Defective phagocytes
- Complement deficiencies
- Unknown (idiopathic)

Complications caused by a primary immunodeficiency disorder vary and depend on the particular disorder. They can include:

- Recurrent infections
- Autoimmune disorders
- Damage to heart, lungs, nervous system or digestive tract
- Slowed growth
- Increased risk of cancer

- Death from serious infection

Treatments for primary immunodeficiency involve preventing and treating infections, boosting the immune system, and treating the underlying cause of the immune problem.

1. Patients with a cancer of the blood (chronic lymphocytic leukaemia)

Chronic lymphocytic leukaemia is a type of cancer of the blood and bone marrow. The term "chronic" comes from the fact that it progresses more slowly than other types of leukaemia. The term "lymphocytic" comes from the cells affected by the disease, a group of white blood cells called lymphocytes, which help the body fight infection. Beyond being ineffective, these abnormal lymphocytes continue to live and multiply, when normal lymphocytes would die. The abnormal lymphocytes accumulate in the blood and certain organs, where they cause complications. They may crowd healthy cells out of the bone marrow and interfere with normal blood cell production. Chronic lymphocytic leukaemia may cause complications such as: frequent infections, a switch to a more aggressive form of cancer, increased risk of other cancers, immune system problems. It most commonly affects older adults.

Chronic lymphocytic leukaemia treatments can help control the disease.

2. Patients with cancer of the bone marrow (multiple myeloma) and lack of antibody production with frequent infections who have failed to respond to a vaccine against certain bacteria (Pneumococci).

Multiple myeloma is a cancer of the plasma cells, a type of white blood cell present in your bone marrow. Plasma cells normally make proteins called antibodies to help fighting infections. Uncontrolled plasma cell growth can damage bones and surrounding tissue. It can also interfere with the immune system's ability to fight infections by inhibiting the body's production of normal antibodies. The majority of people who develop multiple myeloma are older than 50, with most diagnosed in their mid-60s. Few cases occur in people younger than 40. Myeloma cells inhibit the production of antibodies needed for normal immunity. Having multiple myeloma may make people more likely to develop infections, such as pneumonia, sinusitis, bladder or kidney infections, skin infections, and shingles.

Antibiotics and /or infusions of immunoglobulins may be necessary to help treat infections or to help reduce the risk of infection.

3. Patients with AIDS from birth and frequent bacterial infections.

AIDS (acquired immunodeficiency syndrome) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging the immune system, HIV interferes with the body's ability to fight the organisms that cause disease. HIV is a sexually transmitted infection. It can also be spread by contact with infected blood or from mother to child during pregnancy, childbirth or breast-feeding. HIV infection weakens the immune system, making people highly susceptible to numerous infections and certain types of cancers.

4. Patients with low antibody production following transplantation of bone marrow cells from another person.

A stem cell (blood or marrow) transplant is the infusion, or injection, of healthy stem cells into the body to replace damaged or diseased stem cells. A stem cell transplant may be necessary if the bone marrow stops working and doesn't produce enough healthy stem cells. A stem cell transplant also may be performed if high-dose chemotherapy or radiation therapy is given in the treatment of blood disorders such as leukaemia, lymphoma or multiple myeloma. A stem cell transplant can help the body make enough healthy white blood cells, red blood cells or platelets, and reduce the risk of life-threatening infections, anaemia and bleeding.

13.2.1. 2. Patients with certain inflammatory disorders:

5. Primary immune thrombocytopenia

Primary immune thrombocytopenia (ITP) is a disorder that can lead to easy or excessive bruising and bleeding. The bleeding results from unusually low levels of platelets, the cells that help the blood clot. ITP affects both children and adults. Children often develop ITP after a viral infection and usually recover fully without treatment. In adults, however, the disorder is often chronic. A normal platelet count is generally higher than 150,000 platelets per microliter of circulating blood. People with ITP often have platelet counts below 20,000. As the number of platelets decreases, the risk of bleeding increases. The greatest risk is when the platelet count falls below 10,000 platelets per microliter. At this point, internal bleeding may occur despite a lack of any injury.

The goal of treating ITP is to ensure a safe platelet count and prevent bleeding complications while minimizing treatment side effects.

6. Guillain Barré syndrome

Guillain Barré syndrome is a rare disorder in which body's immune system attacks the nerves. Weakness and tingling in the extremities are usually the first symptoms. These sensations can quickly spread, eventually paralyzing the whole body. The exact cause of Guillain-Barre syndrome is unknown but it is often preceded by an infectious illness. Guillain-Barre syndrome can affect all age groups. But man and older adult have slightly greater risk to develop Guillain-Barré syndrome.

Two types of treatments can speed recovery and reduce the severity of the illness:

- Plasma exchange (plasmapheresis). The liquid part of the blood (plasma) is removed and separated from the blood cells and the blood cells are then put back into the body. Plasmapheresis may work by ridding plasma of certain antibodies that contribute to the immune system's attack on the peripheral nerves.
- Immunoglobulin therapy: High doses of immunoglobulin can block the damaging antibodies that may contribute to Guillain-Barre syndrome.

7. Kawasaki disease

Kawasaki disease is a condition that causes inflammation in the walls of medium-sized arteries, including the coronary arteries, which supply blood to the heart muscle. Kawasaki disease may be observed after viral or bacterial infectious disease. Inflammation of the coronary arteries can lead to weakening and bulging of the artery wall (aneurysm). Three things are known to increase the risk of developing Kawasaki disease: age (children under 5 years old), sex (boys are slightly more likely than girls) and ethnicity (children of Asian descent, such as Japanese or Korean).

To reduce the risk of complications, the treatment of Kawasaki disease should be started as soon as possible after the appearance of signs and symptoms, preferably while the child still has a fever.

The goals of this treatment are to lower fever and inflammation and prevent heart damage. This treatment included infusion of immunoglobulin and administration of high doses of aspirin.

13.2.2. Summary of treatment benefits

Two studies have been performed in order to apply for a marketing authorization for I10, study I10E-0718 in patients with primary immunodeficiency (PID) and study I10E-0719 in patients with chronic primary immune thrombocytopenia (ITP),

1. Study I10E-0718 was a phase II-III, multinational, multicenter, interventional, prospective, non-randomized, open-label, uncontrolled, single-arm, efficacy, safety and pharmacokinetic study of I10 in patients with PID.

This study was carried out in patients with PID to evaluate the tolerance of I10 and to measure how effective the product is in preventing infections, and particularly serious bacterial infections (SBI).

A total of 62 patients were included in this study.

The main criterion used to evaluate the efficacy of I10 was the annual number of serious bacterial infections per patient. Only one case of serious bacterial infection occurred during the study, resulting in an annual rate of 0.017 per patient with an upper 98% CI (confidence interval) of 0.115, below the threshold of one SBI/patient/year. As a result, I10 was considered as effective.

2. Study (I10E-0719) was a phase III, multinational, multicentre, open-label and single arm, efficacy and safety study of I10 in patients with chronic primary ITP.

This study was carried out in patients with chronic primary ITP to evaluate the tolerance of I10 and to measure how effective the product is in increasing the number of platelet in the blood and controlling the bleedings.

A total of 38 patients were included in this study.

The main criterion to evaluate the efficacy of I10 was the patients who achieved Response, i.e. platelet count $\geq 30 \times 10^9/L$ and at least 2-fold increase from baseline confirmed at least 7 days apart, absence of new bleeding and no intake of medications that could increase platelet count or induce bleeding cessation. This stringent definition of response was based on the recently updated EMA note for guidance on the clinical investigation of IVIg EMA/CHMP/BPWP/94033/2007 rev. 2 [131]. The Response rate was 63.2 % (95 %CI: 46.0; 78.2) on an intention-to-treat basis.

Taking into account the definition of response of the previous EMA note for guidance on the clinical investigation of IVIg commonly used in published studies EMA/CHMP/BPWP/94033/2007 rev. 2 [131], 82.6 % (95 % CI: 61.2; 95.0) of the 23 patients with a baseline platelet count $\leq 20 \times 10^9/L$ were responders, i.e. achieved a platelet count $\geq 50 \times 10^9/L$ at least once until Day 5.

13.2.3. Unknown relating to the treatment

benefits Children and adolescents

Among 100 patients who received I10 in the clinical development program (in I10E-0718 and I10E-0719 studies), 26 patients were less than 18 years. They were between 2 and 17 years old and were suffering from primary immunodeficiency. They were all treated in the study I10E-0718.

No specific safety issues were identified on children and adolescents who were treated with I10 in the study I10E-0718.

No children and adolescents patients were treated with I10 in the study I10E-0719.

Based on the information known on the others intravenous immunoglobulin, efficacy and safety data were not expected to be different from the adult patients.

During the clinical development conducted with I10, a waiver was granted for paediatric patients below 24 months in replacement therapy and for all age subsets of the paediatric population in immunomodulation. The decision was taken “on the grounds that clinical studies cannot be expected to be of significant therapeutic benefit”.

Elderly (over 65 years old)

This medicine may very rarely cause or worsen a kidney disease (acute kidney failure) or a disease of the heart and blood vessels (myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis). Patients who are already suffering from a disease or who have certain risk factors must take care when using this medicine.

Patients over 65 years old were not enrolled in any of studies conducted with I10 in order to minimise the occurrence of these diseases during the studies.

Efficacy and safety results were not expected to be different from the adults patients in elderly patients treated with I10 in the 2 indications.

Pregnant or breast feeding women

No reproduction studies have been performed with I10 in animals.

Experience in pregnant women is very limited. Pregnant or breast feeding women were not studied in any of the 2 studies conducted with I10. Pregnancy was an exclusion criterion in both studies, and women with childbearing potential were to have an effective contraception.

During the study I10E-0718, one patient became pregnant (because of an ineffective contraception). The patient received I10 during the first trimester of pregnancy. She discontinued the study and gave birth to a child in good health 7 months after the exposition to the product.

No pregnant patient received I10 in the study I10E-0719.

No babies received I10 via breast feeding during studies conducted with I10.

Efficacy results were not expected to be different in pregnant or breast feeding women.

Patients with hepatic impairment

In the clinical trials conducted with I10, patients with hepatic impairment were not enrolled in order to minimize confounding factors that could influence evaluation of safety parameters and efficacy parameters (platelets count and bleedings in ITP study).

Furthermore, there was no signal from preclinical studies indicating that the liver could be a target organ for I10 and there are no hepatic adverse reactions or risks anticipated with IVIg treatment.

No hepatic adverse reaction was reported in any of the 2 clinical trials completed with I10 and evaluation of clinical data did not conclude to any potential hepatic adverse reactions with I10.

Liver toxicity is not a risk reported to be associated with IVIg. Therefore, it is not anticipated that the target population (including patients with hepatic impairment) treated with I10 could have liver implications.

13.2.4. Summary of safety concerns

13.2.4. 1. Important identified risks

Risk	What is known	Preventability
Anaphylactic /anaphylactoid reactions	<p>If you have an immunoglobulin A deficiency, you may have antibodies against immunoglobulin A in your blood. Since this medicine contains trace amounts of immunoglobulin A, you might get an allergic reaction.</p> <p>If an allergy develops, you will recognize the initial signs by dizziness, swelling of the face/legs, shortness of breath, spots on the skin and/or itching. In this situation you must call your doctor or nurse immediately.</p> <p>Two cases of anaphylactic/anaphylactoid reaction have been reported during the studies conducted with I10.</p>	<p>You should not use I10:</p> <ul style="list-style-type: none"> - If you are allergic to immunoglobulins or to any other ingredients of this medicine. - If you have an immunoglobulin A deficiency. <p>In order to avoid a risk of a reaction the doctor will check the infusion rate and adjust it so it is suitable for you. During the infusion, your doctor will put in place medical monitoring in order to detect any signs of allergy or any other reactions.</p> <p>If a reaction occurs, the doctor may decide to reduce the rate of infusion or to stop it. He/she may also start treatment for the allergy if he/she considers this to be necessary.</p>
Aseptic meningitis	<p>Aseptic meningitis is an inflammation of the protective membranes that cover the brain and spinal cord without any infectious agent found. Symptoms of meningitis may include headache, fever, stiff neck, nausea, vomiting, rash, and sensitivity to light. The syndrome usually begins within several hours to 2 days following intravenous immunoglobulin (IVIg) treatment. Discontinuation of IVIg treatment resulted in remission of aseptic meningitis within several days without sequelae. Aseptic meningitis may occur more frequently in association with high-dose (2 g/kg).</p> <p>One case of aseptic meningitis has been reported during the studies conducted with I10.</p>	<p>No real preventability measures exist except applying general cautions for use concerning hydration and progressive increase of flow rate.</p>

13.2.4. 2.Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Thromboembolic events	<p>Formation of blood clots may occur in the blood circulation. Formation of blood clots in the blood circulation has been observed with other intravenous immunoglobulins. It may:</p> <ul style="list-style-type: none"> – block the supply of blood and oxygen to the heart and cause heart attack. The warning signs are sudden chest pain or shortness of breath. – block the supply of blood and oxygen to the brain and cause stroke. The warning signs are sudden onset of muscle weakness, loss of sensation and/or balance, decreased alertness or difficulty in speaking. – block the supply of blood and oxygen to the lungs and cause a serious condition called pulmonary embolism. The warning signs are chest pain, difficulty in breathing or coughing up blood. – cause clot in a vein (venous thrombosis). The warning signs are redness, feel warmth, pain, tenderness, or have a swelling of one or both legs. <p>Occurrence of thromboembolic events is considered as a potential risk for I10 because it is a known class effect of intravenous immunoglobulins but no case has been reported during the pivotal studies conducted with I10.</p>
Acute renal failure	<p>Intravenous immunoglobulins may very rarely cause or worsen a kidney disease (acute kidney failure). Patients who are already suffering from a kidney disease or who have certain risk factors:</p> <ul style="list-style-type: none"> – intake of medicines which may be dangerous for kidneys, – high level of sugar (diabetes), – insufficient volume of blood in the body (hypovolemia), – weight too high (obesity), – age over 65 years old, <p>must take care when using this medicine.</p> <p>If you have any of the above predisposing factors, the doctor will adjust the dose and infusion rate at which I10 is administered.</p> <p>Occurrence of acute renal failure is considered as a potential risk for I10 because it is a known class effect of intravenous immunoglobulins but no case has been reported during the pivotal studies conducted with I10.</p>
Haemolysis / haemolytic anaemia	<p>Decreased number of red blood cells (haemolytic reactions) especially in patients with blood groups A, B, and AB had been observed with other intravenous immunoglobulins.</p> <p>Occurrence of haemolysis/haemolytic anaemia is considered as a potential risk for I10 because it is a known class effect of intravenous immunoglobulins but no such case has been reported during the pivotal studies conducted with I10.</p>
Risk	What is known (Including reason why it is considered a potential risk)
Transfusion related acute lung injury	<p>There have been reports of noncardiogenic pulmonary edema (Transfusion Related Acute Lung Injury, TRALI) in patients administered IVIg.</p> <p>Occurrence of transfusion-related lung injury is considered as a potential risk for I10 but no such case has been reported during the pivotal studies conducted with I10. .</p>

<p>Impairment in effectiveness of the lived attenuated viruses vaccines</p>	<p>The use of intravenous immunoglobulins may reduce the effectiveness of vaccines against measles, rubella, mumps and/or varicella for 3 months. It is recommended that a period of 3 months elapse between the last administration of immunoglobulins and administration of these vaccines. It may be necessary to wait for 1 year after the last administration of immunoglobulins for the measles vaccine.</p> <p>Occurrence of impairment in effectiveness of the lived attenuated viruses vaccines is considered as a potential risk for I10 because it is a known class effect of intravenous immunoglobulins but no such case has been reported during the pivotal studies conducted with I10.</p>
<p>Transmission of infective agents such as viruses, emerging viruses, other not identified infective agents or pathogens</p>	<p>This medicine is made from human blood plasma (this is the liquid part of the blood).</p> <p>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:</p> <ul style="list-style-type: none"> – careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, – the testing of each donation and pools of plasma for signs of virus/infections, – the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses. <p>Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses and other types of infections.</p> <p>The measures taken are considered effective for viruses such as human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, hepatitis A virus and parvovirus B19.</p> <p>Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections, possibly because antibodies against these infections, which are contained in the product, are protective.</p> <p>Occurrence of transmission of infective agents such as viruses, emerging viruses, other not identified infective agents or pathogens is considered as a potential risk for I10 because it is theoretical risk for human intravenous immunoglobulins but no such case has been reported during the pivotal studies conducted with I10 and measures described above should prevent infections being passed on to patients.</p>
<p>Interference with serological testing</p>	<p>Some antibodies contained in I10 may invalidate the results of certain blood tests. If your doctor or the person who is taking your blood sample does not know that you have received I10, please tell him/her before having this blood test.</p>

13.2.4. 3. Important missing information

Risk	What is known
<p>Infants/toddlers from 0-2 years of age</p>	<p>Use in children and adolescents: The same indications, dose and frequency of infusion as for adults apply for children and adolescents (aged 0 to 18).</p>

Elderly patients above 65	<p>This medicine may very rarely cause or worsen a kidney disease (acute kidney failure) or a disease of the heart and blood vessels (myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis). Patients who are already suffering from a disease or who have certain risk factors (including advanced age) must take care when using this medicine.</p> <p>Overdose is very unlikely to occur because this medicine is usually administered under medical supervision. If, in spite of this, you receive more I10 than you should, your blood may become too thick (hyperviscous). This may happen particularly if you are a patient at risk, for example if you are elderly or if you have problems with your heart or kidneys.</p>
Patients with renal impairment	<p>This medicine may very rarely cause or worsen a kidney disease (acute kidney failure). [...]. Patients who are already suffering from a kidney disease or who have certain risk factors must take care when using this medicine.</p> <p>Overdose is very unlikely to occur because this medicine is usually administered under medical supervision. If, in spite of this, you receive more I10 than you should, your blood may become too thick (hyperviscous). This may happen particularly if you are a patient at risk, for example if you are elderly or if you have problems with your heart or kidneys.</p>
Patients with hepatic impairment	<p>There was no signal from preclinical studies indicating that the liver could be a target organ for I10 and there are no hepatic adverse reactions or risks anticipated with IVIg treatment.</p> <p>Liver toxicity is not a risk reported to be associated with IVIg. Therefore, it is not anticipated that treatment with I10 in the target population could have liver implications.</p>
Pregnant and breast feeding women	<p>If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.</p> <ul style="list-style-type: none"> • No reproduction studies have been performed with I10 in animals and experience in pregnant women is limited. • The antibodies contained in I10 are excreted in human plasma and may contribute to protecting your baby from certain infections.

13.2.5. Summary of risk minimisation measures by safety concern

Summary of product characteristics of I10 provides healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them.

I10 has no additional risk minimisation measures.

13.2.6. Planned post-authorisation development plan

13.2.6. 1. List of studies in post authorisation development plan

Not applicable.

13.2.6. 2. Studies which are a condition of the marketing authorisation

Not applicable.

13.2.7. Summary of changes to the Risk Management Plan over time

Not applicable.