ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

THYMOGLOBULINE 5 mg/mL powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution:

Human anti-thymocyte rabbit immunoglobulin .....5 mg/ml

Corresponding to 25 mg/5 ml of human anti-thymocyte rabbit immunoglobulin per vial.

Excipient(s) with known effect:

Each 10 ml vial contains 0.171 mmol of sodium, which is 4 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Thymoglobuline is a creamy white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Immunosuppression in transplantation: prevention and treatment of transplant rejection.
- Prevention of acute and chronic graft-versus-host reaction in the case of haematopoietic stem cell transplantation.
- Treatment of acute steroid-resistant graft-versus-host reaction.
- Haematology: Treatment of aplastic anaemia.

4.2. Posology and method of administration

Posology

The posology depends on the indication, the administration regimen, and the combination with other immunosuppressive agents. The following recommendations may be used as a reference. Treatment can be discontinued without gradual tapering of the dose.

Immunosuppression in transplantation

- Prevention of acute graft rejection:
  1 to 1.5 mg/kg/day for 2 to 9 days after kidney, pancreatic, or renal transplantation and for 2 to 5 days after heart transplantation, i.e. a cumulative dose of 2 to 7.5 mg/kg in case of heart transplantation and 2 to 13.5 mg/kg for other organs.
- Treatment of acute graft rejection:
  1.5 mg/kg/day for 3 to 14 days, i.e. a cumulative dose of 4.5 to 21 mg/kg.

Prevention of acute and chronic graft-versus-host reaction

In the case of transplants (bone marrow or peripheral blood haematopoietic stem cells) from identical non-HLA related donors or HLA unrelated donors, it is recommended that adult patients administer Thymoglobuline as preliminary treatment at a dose of 2.5 mg/kg/day from day -4 to day -2 or -1, for a total dose of 7.5 to 10 mg/kg.

Treatment of acute steroid-resistant graft-versus-host reaction

The dosage should be defined according to each case. It is usually between 2 and 5 mg/kg/day for 5 days.

Treatment of aplastic anaemia

2.5 to 3.5 mg/kg/day for 5 consecutive days, i.e. a cumulative dose of 12.5 to 17.5 mg/kg.

The indication in bone marrow aplasia has not been established in controlled clinical trials conducted with this medicinal product.

Dose modifications

Thrombocytopenia and/or leukopenia (including lymphocytopenia and neutropenia) have been identified; these conditions are reversible after dose modifications. When thrombocytopenia and/or leukopenia are not part of the underlying condition or are not associated with the condition for which Thymoglobuline is administered, the following dose reductions are suggested:

- A dose reduction should be considered if the platelet count is between 50,000 and 75,000 cells/mm^3 or if the white blood cell count is between 2,000 and 3,000 cells/mm^3.
- Thymoglobuline treatment should be discontinued in the event of persistent and severe thrombocytopenia (<50,000 cells/mm^3) or the development of leukopenia (<2,000 cells/mm^3).

Paediatric population

The currently available data are described in sections 4.8 and 5.1, but no dosage recommendations can be provided. Available information indicates that paediatric patients do not require a different dosage from adult patients.

Method of administration

Human anti-thymocyte rabbit immunoglobulin is usually administered in the context of a therapeutic regimen combining multiple immunosuppressive agents.

Administer the necessary doses of intravenous corticosteroids and antihistamines prior to infusion of human anti-thymocyte rabbit immunoglobulin.

The reconstituted solution is clear or slightly opalescent.

Infuse slowly into a high-flow vein. Adjust the infusion rate so that the total duration of infusion is a minimum of 4 hours.

For reconstitution and dilution, see section 6.6.

4.3. Contraindications

- Hypersensitivity to rabbit proteins or to any of the excipients listed in section 6.1.
- Acute or chronic infections, which would contraindicate any additional immunosuppression.

4.4. Special warnings and precautions for use

Thymoglobuline should always be used under strict medical supervision in a hospital setting.

Close monitoring of the patient must continue during the infusion and for a period of time following the end of the infusion until the patient is stable.

Warnings

Hepatic diseases

Thymoglobuline has to be administered with special caution in patients with hepatic diseases as pre-existing clotting disorders may worsen. Careful monitoring of thrombocytes and clotting parameters is recommended.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobuline and consist of anaphylaxis or severe cytokine release syndrome (CRS). Very rarely, fatal anaphylaxis has been reported (see section 4.8). If an anaphylactic reaction occurs, the infusion should be terminated immediately and appropriate emergency treatment should be initiated. Any further administration of Thymoglobuline to a patient who has a history of anaphylaxis to Thymoglobuline should only be undertaken after serious consideration.

Severe, acute infusion-associated reactions (IARs) are consistent with CRS which is attributed to the release of cytokines by activated monocytes and lymphocytes. In rare instances, these reported reactions are associated with serious cardiorespiratory events and/or death (see below “Precautions” and section 4.8).

Infection

Thymoglobuline is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral and protozoal), reactivation of infection (particularly cytomegalovirus [CMV]) and septicaemia have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal.

Precautions for use

General

Appropriate dosing for Thymoglobuline is different from dosing for other anti-thymocyte immunoglobulin products, as protein composition and concentrations vary depending on the source of anti-thymocyte immunoglobulin used. Physicians should therefore exercise care to ensure that the dose prescribed is appropriate for the anti-thymocyte immunoglobulin product being administered.

Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of infusion associated reactions (IARs). Additionally, reducing the infusion rate may minimize many of these adverse reactions. Premedication with antipyretics, corticosteroids, and/or antihistamines may decrease both the incidence and severity of these adverse reactions.

Rapid infusion rates have been associated with case reports consistent with cytokine release syndrome (CRS). In rare instances, severe CRS can be fatal.

Haematological effects

Thrombocytopenia and/or leukopenia (including lymphocytopenia and neutropenia) have been identified; these conditions are reversible after dose modifications. When thrombocytopenia and/or leukopenia are not part of the underlying condition or are not associated with the condition for which Thymoglobuline is administered, the following dose reductions are suggested (see section 4.2).

White blood cell and leukocyte count should be monitored during and after Thymoglobuline therapy.

Infection

Infections, reactivation of infection and septicaemia have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. Careful patient monitoring and appropriate anti-infective prevention are recommended.

Malignancy

Use of immunosuppressive agents, including Thymoglobulin, may increase the incidence of malignant tumours, lymphoma or lymphoproliferative disorders (which may be virally mediated). These events have sometimes been associated with fatal outcomes (see section 4.8).

Risk of transmission of infectious agents

The manufacturing process for these rabbit immunoglobulins involves products of human origin. Standard measures to prevent infections resulting from the use of medicinal products prepared using human components include selection of donors, screening of individual donations for specific markers of infection and the inclusion of effective manufacturing steps for inactivation/removal of viruses.

Despite this, the possibility of transmitting infective agents cannot be totally excluded. This risk also applies to unknown or emerging viruses and other types of infectious agents.

The measures taken for Thymoglobuline are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV.

The measures taken may be of limited efficacy with regard to non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection can be severe in foetuses and in people with certain types of anaemia or immunodeficiency.

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

Special considerations for Thymoglobuline infusions

As with any infusion, reactions at the injection site can occur and may include pain, swelling, and erythema.

Immunisations

The safety of immunisation with attenuated live vaccines following Thymoglobuline therapy has not been studied; therefore, immunisation with attenuated live vaccines is not recommended for patients who have recently received Thymoglobuline (see section 4.5).

Thymoglobuline contains sodium

This medicinal product contains 4 mg sodium per vial, equivalent to 0.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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.

4.5. Interaction with other medicinal products and other forms of interaction

Combinations to be taken into account

+ Cyclosporine, tacrolimus, mycophenolate mofetil

Risk of excessive immunosuppression with risk of lymphoproliferation.

+ Live attenuated vaccines

Risk of general infection due to the vaccine, which may be fatal. This risk is increased in already immunocompromised patients due to the underlying pathology (bone marrow aplasia).

Human anti-thymocyte rabbit immunoglobulin is likely to induce the formation of antibodies that react with other rabbit immunoglobulins.

Thymoglobuline does not appear to interfere with routine laboratory tests using immunoglobulins. However, Thymoglobuline may interfere with rabbit antibody-based immunoassays and cross-compatibility or panel-reactive antibody cytotoxicity assays.

4.6. Fertility, pregnancy and lactation

Fertility

Animal reproduction studies have not been conducted with Thymoglobulin. It is not known whether Thymoglobuline can affect reproductive capacity.

Pregnancy

Animal reproduction studies have not been conducted with Thymoglobuline (see section 5.3). It is not known whether Thymoglobuline can cause foetal harm. Thymoglobuline should not be given to a pregnant woman unless clearly needed. Thymoglobuline has not been studied in labour or delivery.

Breast-feeding

It is not known whether human anti-thymocyte rabbit immunoglobulin is excreted in human milk. Because other immunoglobulins are excreted in human milk, breast-feeding should be discontinued during Thymoglobuline therapy.

4.7. Effects on ability to drive and use machines

Given the possible adverse events which can occur during the period of Thymoglobuline infusion, in particular CRS, it is recommended that patients should not drive or operate machinery during Thymoglobuline therapy.

4.8. Undesirable effects

Adverse events observed during a French multicentre post-marketing surveillance study:

From June 1997 to March 1998, 18 French transplantation centres participated in the French Multicentre Post-marketing Surveillance Study-00PTF0.

A total of 240 patients participated in this prospective, single arm, observational cohort study. All patients received Thymoglobuline as a prevention of acute rejection for renal transplant.

The safety data reproduced in the table represent all adverse events reported during the study, regardless of their relationship to Thymoglobulin.

Adverse reactions considered to be related to Thymoglobuline reported in clinical trials and post-marketing.	
Blood and lymphatic system disorders	Very common: lymphocytopenia, neutropenia, thrombocytopenia, anaemia. Common: febrile neutropenia.
Gastrointestinal disorders	Common: diarrhoea, dysphagia, nausea, vomiting.
General disorders and administration site conditions	Very common: fever. Common: shivering. Uncommon: Infusion associated reactions (IARs)*.
Hepatobiliary disorders	Common: increased transaminases*. Uncommon: hepatocellular injury, hepatotoxicity, hepatic failure*. Not known: hyperbilirubinemia.
Immune system disorders	Common: serum sickness*, cytokine release syndrome (CRS)*, anaphylactic reaction.
Infections and infestations	Very common: infection (including reactivation of infection). Common: sepsis.
Musculoskeletal and connective tissue disorders	Common: myalgia.
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Common: malignant tumour, lymphoma (which may be virally mediated), malignant tumours (solid tumours). Uncommon: lymphoproliferative disorder.
Respiratory, thoracic and mediastinal disorders	Common: dyspnoea.
Skin and subcutaneous tissue disorders	Common: pruritus, rash.
Vascular disorders	Common: hypotension.

* = see below.

Description of selected undesirable effects

IARs may occur following the administration of Thymoglobuline and may occur as soon as the first or second infusion during a single Thymoglobuline therapy cycle. Clinical manifestations of IARs have included some of the following signs and symptoms: fever, chills/rigors, dyspnoea, nausea/vomiting, diarrhoea, hypotension or hypertension, malaise, rash, urticaria, and/or headache.

IARs with Thymoglobuline are usually mild and transient and are managed with reduced infusion rates and/or medications (see section 4.4). Serious and, in very rare instances, fatal anaphylactic reactions have been reported (see section 4.4). These fatal reactions occurred in patients who did not receive epinephrine during the event.

IARs consistent with CRS have been reported (see section 4.4). Severe and potentially life-threatening CRS is rarely reported. Post-marketing reports of severe CRS have been associated with cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome, pulmonary oedema, myocardial infarction, tachycardia, and/or death).

During post-marketing surveillance, reactions such as fever, rash, urticaria, arthralgia, and/or myalgia, indicating possible serum sickness, have been reported. Serum sickness tends to occur 5 to 15 days after onset of Thymoglobuline therapy. Symptoms are usually self-limited or resolve rapidly with corticosteroid treatment.

Local adverse reactions such as infusion site pain and peripheral thrombophlebitis have also been reported.

Hepatobiliary disorders

Transient reversible elevations in transaminases without any clinical signs or symptoms have also been reported during Thymoglobuline administration.

Cases of hepatic failure have been reported secondary to allergic hepatitis and reactivation of hepatitis in patients with haematologic disease and/or stem cell transplant as confounding factors.

Adverse events due to immunosuppression

Infections, reactivation of infection, febrile neutropenia, and septicaemia have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents (see section 4.4). In rare cases, these infections have been fatal. Malignant tumours including, but not limited to lymphoproliferative disorders (LPD) and other lymphomas (which may be virally mediated) as well as solid tumours have been reported (see section 4.4). These adverse events were always associated with a combination of multiple immunosuppressive agents. These adverse events have sometimes been associated with fatal outcome.

For safety relating to transmissible agents, see section 4.4.

Paediatric population

Currently available data are limited. Available information indicates that the tolerability profile of Thymoglobuline in paediatric patients is not fundamentally different to that seen 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: French National Agency for the Safety of Medicines and Health Products (*Agence nationale de sécurité du médicament et des produits de santé*, ANSM) and the network of *Centres Régionaux de Pharmacovigilance* [Regional Pharmacovigilance Centres] - Website: https://signalement.social-sante.gouv.fr.

4.9. Overdose

Accidental overdose may induce leukopenia (including lymphocytopenia and neutropenia) and thrombocytopenia. These effects are reversible after dose modifications or therapy cessation (see section 4.2). There is no antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA04.

Human anti-thymocyte rabbit immunoglobulin is a selective immunosuppressive agent (mostly acting on T lymphocytes).

The mechanism of action of human anti-thymocyte rabbit immunoglobulin is as follows:

Lymphocyte depletion probably constitutes the primary mechanism of the immunosuppression induced by human anti-thymocyte rabbit immunoglobulin.

Thymoglobuline recognises most molecules involved in the T-cell activation cascade during transplant rejection such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, HLA-DR and HLA Class I.

T cells are removed from circulation by complement-dependent lysis and, moreover, by an Fc-dependent opsonization mechanism involving the monocyte-phagocytic cell system.

In addition to its T-cell depleting effect, human anti-thymocyte rabbit immunoglobulin triggers other lymphocyte functions in relation to its immunosuppressive activity.

In vitro, at a concentration of around 0.1 mg/ml, Thymoglobuline activates T cells and stimulates their proliferation (in the same way for both $CD4^+$ and $CD8^+$ subpopulations) with synthesis of IL-2 and IFN-gamma and CD25 expression. This mitogenic activity primarily involves the CD2 pathway. At higher concentrations, human anti-thymocyte rabbit immunoglobulin inhibits proliferative lymphocytic responses to other mitogens, with post-transcriptional blockade of the synthesis of IFN-gamma and CD25 but without a decrease in IL-2 secretion.

In vitro, Thymoglobuline does not activate B cells.

The low risk of developing B cell lymphoma observed in patients treated with Thymoglobuline may be explained by the following mechanisms:

- Lack of B cell activation, resulting in non-differentiation of plasma cells.
- Anti-proliferative activity against B cells and certain lymphoblastoid cell lines.

In the context of immunosuppression in transplantation, patients treated with human anti-thymocyte rabbit immunoglobulin present with profound lymphopenia (defined as a depletion greater than 50% of the initial value), starting on the first day after the start of treatment. This lymphopenia persists throughout treatment and beyond. On average, about 40% of people recover more than 50% of the initial lymphocyte count at 3 months.

Monitoring lymphocyte subpopulations (CD2, CD3, CD4, CD8, CD14, CD19, and CD25) confirms the wide range of Thymoglobuline specificities towards T cells. During the first two weeks of treatment, the absolute number of all subpopulations, except B cells and monocytes, shows very significant depletion (more than 85% for CD2, CD3, CD4, CD8, CD25, CD56, and CD57).

At the beginning of treatment, monocytes undergo a lower depletion. B cells are virtually unaffected. Most subpopulations recover more than 50% of their baseline value by the end of the second month. CD4 lymphocyte depletion persists for a very long time and is still observed at 6 months, resulting in reversal of the CD4/CD8 ratio.

Paediatric population

Multiple reports regarding the use of Thymoglobuline in children have been published. These reports reflect the broad clinical experience with this product in paediatric patients and suggest that the tolerability and efficacy profiles in paediatric patients are not fundamentally different from that seen in adults.

However, there is no clear consensus with regards to the dosing in paediatric patients. As in adults, dosing in paediatrics depends on the indication, the administration regimen, and the combination with other immunosuppressive agents. These elements should be considered by physicians before deciding on the appropriate dose in paediatric patients.

5.2. Pharmacokinetic properties

Following the first infusion of 1.25 mg/kg of Thymoglobuline (in renal transplant recipients), total serum rabbit IgG levels of between 10 and 40 micrograms/ml are obtained. The serum levels decline steadily until the following infusion with an estimated elimination half-life of 2–3 days.

The trough rabbit IgG levels increase progressively reaching 20 to 170 micrograms/ml at the end of an 11-day course of treatment. A gradual decline is subsequently observed following the discontinuation of treatment with human anti-thymocyte rabbit immunoglobulin. However, total rabbit IgG remains detectable in 80% of patients at 2 months.

Significant immunisation against rabbit IgG is observed in about 40% of patients. In most cases, immunisation develops within the first 15 days of treatment initiation. Patients presenting with immunisation show a faster decline in minimal concentrations of rabbit IgG.

5.3. Preclinical safety data

Non-clinical data reveal no special Thymoglobuline toxicity based on single and repeated dose toxicity studies.

No mutagenicity, reproduction, or genotoxicity studies have been performed with Thymoglobulin.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycine, sodium chloride, and mannitol.

6.2. Incompatibilities

Based on a single compatibility study, the combination of Thymoglobulin, heparin, and hydrocortisone in a glucose infusion solution has been noted to precipitate and is not recommended. In the absence of additional compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

3 years.

Immediate use after reconstitution and dilution is recommended in order to prevent microbial contamination.

However, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

6.4. Special precautions for storage

Store in a refrigerator (2°C–8°C). Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

25 mg of powder in a vial (type I glass) equipped with a stopper (chlorobutyl). Box of 1.

6.6. Special precautions for disposal and other handling

Reconstitute the powder with 5 ml of sterile water for injections to obtain a solution containing 5 mg protein per ml.

Reconstitution must be carried out in accordance with the rules of good practice, particularly with respect to asepsis.

The solution is clear or slightly opalescent. The reconstituted medicinal product should be inspected visually for particulate matter and discoloration. Should some particulate matter remain, continue to gently rotate the vial until no particulate matter is visible. If particulate matter persists, discard the vial. Immediate use of the reconstituted product is recommended. Each vial is for single use only. Depending on the daily dose, reconstitution of several vials of Thymoglobuline powder might be needed. Determine the number of vials to be used and round up to the nearest vial.

To avoid inadvertent administration of particulate matter from reconstitution, it is recommended that Thymoglobuline is administered through a 0.2 micrometre in-line filter. The daily dose is diluted in an infusion solution (9 mg/ml (0.9%) sodium chloride or 5% glucose solution) so as to obtain a total infusion volume of 50 to 500 ml (usually 50 ml/vial).

The product should be administered on the same day.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SANOFI B.V.
PAASHEUVELWEG 25
1105 BP AMSTERDAM
THE NETHERLANDS

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 570 281 8 3: Powder in a vial (type I glass) with a stopper (chlorobutyl). Box of 1.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be filled in later by the MA Holder]

10. DATE OF REVISION OF THE TEXT

[to be filled in later by the MA Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.

Reserved for hospital use.