Thymoglobuline® 5mg/ml

Powder for concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION
After reconstitution with 5ml Water for Injection (WFI), the solution contains 5mg rabbit anti-human thymocyte immunoglobulin/ ml (concentrate).

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

PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
Thymoglobuline® is a creamy-white lyophilized powder.

CLINICAL PARTICULARS
Therapeutic indications
- Immunosuppression in transplantation: prophylaxis and treatment of graft rejection.
- Prophylaxis of acute and chronic graft versus host disease, after haematopoietic stem cell transplantation related non-HLA-identical donors or from unrelated HLA-identical donors
- Treatment of steroid-resistant, acute graft versus host disease (GvHD).
- Haematology: treatment of aplastic anemia.

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

Immunosuppression in transplantation:
Prophylaxis of acute graft rejection:
1 to 1.5 mg/kg/day for 2 to 9 days after transplantation of a kidney, pancreas or liver and for 2 to 5 days after heart transplantation, corresponding to a cumulative dose of 2 to 7.5 mg/kg in heart transplantation and 2 to 13.5 mg/kg for other organs. The dosage must be determined on an individual basis.

Treatment of acute graft rejection:
1.5 mg/kg/day for 3 to 14 days, corresponding to a cumulative dose of 4.5 to 21 mg/kg.The dosage must be determined on an individual basis.

Prophylaxis of acute and chronic graft versus host disease:
In transplantation of grafts (bone marrow or haematopoietic stem cells from peripheral blood) from related non-HLA-identical donors or from unrelated HLA-identical donors, it is recommended in adult patients that Thymoglobuline be administered, as a preliminary therapy, at a dose of 2.5 mg/kg/day from day -4 to day -2 or -1, corresponding to a cumulative dose of 7.5 to 10 mg/kg. The dosage must be determined on an individual basis.

Treatment of steroid-resistant, acute graft versus host disease:
The dosage must be determined on an individual basis. It is usually between 2 and 5 mg/kg/day for 5 days.

Treatment of Aplastic anemia:
2.5 to 3.5 mg/kg/day for 5 consecutive days or a cumulative dose of 12.5 to 17.5 mg/kg. The indication for aplastic anemia has not been established by controlled clinical trials carried out with this medicinal product. The dosage must be determined on an individual basis.

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

- a reduction in dosage must be envisaged if the platelet count is between 50,000 and 75,000 cells/mm^3 or if the number of white blood cell count is between 2,000 and 3,000 cells/mm^3;
- stopping Thymoglobuline® treatment must be considered if persistent and severe thrombocytopenia (< 50,000 cells/mm^3) or development of leucopenia (< 2,000 cells/mm^3)

Method of administration
Rabbit anti-human thymocyte immunoglobulin is usually administered in the context of a therapeutic regimen combining several immunosuppressive agents.

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

The reconstituted solution is clear or slightly opalescent.

Infuse into a large vein. Adjust the infusion rate so that the total duration of infusion is at least 4 hours.

Contraindications
- Active, acute or chronic infections, which would contraindicate any additional immunosuppression.
- Hypersensitivity to rabbit proteins or any of the excipients.

Special warnings and special precautions for use
Thymoglobuline® must be used under strict medical supervision in a hospital setting and patients must be carefully monitored during the infusion.

Warnings
Immune-mediated reactions
In rare cases, serious immune-mediated reactions have been reported with the use of Thymoglobuline®; these reactions consist of anaphylaxis or a severe cytokine release syndrome (CRS). Very rare cases of fatal anaphylaxis have been reported. In the event of the onset of an anaphylactic reaction, the infusion must be suspended immediately and an appropriate emergency treatment must be introduced. Any further administration of Thymoglobuline® to a patient with a history of anaphylaxis to

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Thymoglobuline® must only be carried out after the benefits and the risks have been carefully weighed up.

The serious and acute infusion-associated reactions (IARs) correspond to a CRS attributed to the cytokine release by the activated monocytes and lymphocytes.
In rare cases, these reactions are associated with serious cardiorespiratory events and/or death.

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

Precautions
General
The dose adjustment of Thymoglobuline® differs from that of other anti-thymocyte immunoglobulins insofar as protein composition and concentrations vary depending on the source of anti-thymocyte immunoglobulin used. Therefore, the doctors must ensure that the dose prescribed is suitable for the anti-thymocyte immunoglobulin administered.

Strict compliance with the recommended dosage and infusion periods may reduce the incidence and the severity of IARs. In addition, reducing the infusion rate allows a large number of these IARs to be minimized. Premedication with antipyretic agents, corticosteroids and/or antihistamines may reduce the incidence and severity of these adverse reactions.

Rapid infusion rates have been associated with case reports consistent with CRS.
In rare cases, a serious CRS can be fatal.

Haematological effects
Thrombocytopenia and/or leucopenia (in particular lymphocytopenia and neutropenia) have been identified; these conditions are reversible after dose adjustments. When thrombocytopenia and/or leucopenia are not part of the underlying condition or are not associated with the condition for which Thymoglobuline® is being administered, dose reductions are suggested.

Monitoring of white blood cells and platelet counts must be carried out during and after treatment with Thymoglobuline®.

In aplastic anemia, the immunosuppressive treatment contributes to the risk of infection (bacterial, fungal, protozoal and viral) associated with the aplastic anemia itself. The increased risk of lymphoproliferative disorders is to be taken into account.

Infection
Infections, reactivation of infection and sepsis have been reported after administration of Thymoglobuline® in association with multiple immunosuppressive agents. Careful monitoring of the patient and appropriate anti-infection prevention are recommended.

Malignancy
The use of immunosuppressive agents, including Thymoglobuline®, may increase the incidence of malignancies, in particular lymphoma or post-transplantation lymphoproliferative disease (PTLD).

Risk of Transmission of Infectious Agents
The manufacturing process of these rabbit immunoglobulins utilizes products from human origin. The standard measures to prevent risk of transmission of infective agents for products from human blood include a careful selection of raw material and effective manufacturing steps for the inactivation/removal of viruses. However, the risk of transmission infective agents could not be totally excluded. This applies also to unknown or emerging viruses or other types of infective agents.

The measures taken 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 value against non-enveloped viruses such as Parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with some type of anaemia or with immunodeficiency.

With the context of product traceability, it is strongly recommended that every time that Thymoglobuline® is administered, the patient's name and the batch number of the product are recorded.

Special considerations for Thymoglobuline® infusion
As for all infusions, reactions at the infusion site are likely to occur and may include pains, swelling, and erythema.

Immunizations
The safety of immunization with attenuated live vaccines after a treatment with Thymoglobuline® has not been studied; therefore, immunization with attenuated vaccines is not recommended for patients who have recently received Thymoglobuline®.

Interactions with other medicinal products and other forms of interaction
Combinations to be taken into account:
- Cyclosporine, tacrolimus, mycophenolate mofetil: risk of over-immunosuppression with a risk of lymphoproliferation.
- Live attenuated vaccines: risk of systemic infection due to the vaccine which may potentially be fatal. This risk is increased in subjects who are already immunocompromised due to the underlying disease (aplastic anemia).

Rabbit anti-human thymocyte immunoglobulin may induce the formation of antibodies which react with other rabbit immunoglobulins.

Thymoglobuline® has not been shown to interfere with any routine clinical laboratory tests which use immunoglobulins. However, Thymoglobuline® could interfere with rabbit antibody based immunoassays and with cross-match or panel-reactive antibody cytotoxicity tests.

Pregnancy and lactation
No reproduction studies have been carried out with Thymoglobuline®. The potential risk for human beings is not known. Thymoglobuline® must not be used during pregnancy unless absolutely required.

It is unknown whether rabbit anti-human thymocyte immunoglobulin is excreted in human breast milk. Because other immunoglobulins are excreted in human milk, breast feeding must be discontinued during Thymoglobuline® therapy.

Effects on the ability to drive and use machines
Given the undesirable adverse events likely to occur during the Thymoglobuline® infusion period, in particular a CRS, it is not advisable for patients to drive vehicles or use machines during the treatment with Thymoglobuline®.

Undesirable effects
Adverse events from French Multi-Center Post-marketing Surveillance Study From June 1997 to March 1998, 18 French transplantation centres participated in the French Multicenter Post-marketing Surveillance Study-00PTF0.

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

The safety data in the table represent all adverse events reported in the study regardless of relationship to Thymoglobuline®.

Blood and lymphatic system disorders
Very common*: Lymphopenia, neutropenia, thrombocytopenia

Respiratory, thoracic and mediastinal disorders
Common**: Dyspnoea

Gastrointestinal disorders
Common: Diarrhoea, dysphagia, nausea, vomiting

Skin and subcutaneous tissue disorder
Common: Pruritus, rash

Musculoskeletal and connective tissue disorders
Common: Myalgia

Infections and infestations
Very common: Infection

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common**: Malignancy

Vascular disorders
Common: Hypotension

General disorders and administration site conditions
Very common: Fever
Common: Shivering

Immune system disorders
Common: Serum sickness

** Very common (≥1/10)*
*** Common: (≥1/100 to <1/10)*

Infusion-Associated Reactions and Immune System Conditions
IARs are likely to occur after the administration of Thymoglobuline®, following the first or second infusion during a single cycle of treatment with Thymoglobuline®.
The clinical manifestations of IARs may include some of the following signs and symptoms: fever, chills/rigors, dyspnoea, nausea/vomiting, diarrhoea, hypotension or hypertension, malaise, rash, and/or headache. IARs with Thymoglobuline® are usually mild and transient and are managed with reduction in infusion rate and/or with medications. Serious, and in very rare cases, fatal anaphylactic reactions have been reported. The fatalities occurred in patients who had not received adrenaline during the event.

IARs consistent with CRS have been reported. 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 [ARDS], pulmonary oedema, myocardial infarction, tachycardia, and/or death).

During post-marketing surveillance, reactions such as fever, rash, arthralgia, and/or myalgia, indicating a possible serum sickness, have been reported.
Serum sickness tends to occur 5 to 15 days after onset of Thymoglobuline® therapy. The symptoms are usually clear up spontaneously or recede rapidly with corticosteroid therapy.

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

Adverse Events Due to Immunosuppression
Infections, reactivation of infection and sepsis have been reported after Thymoglobuline® administration in combination with multiple immunosuppressive agents. In rare instances, malignancies including, but not limited to PTLD and other lymphomas as well as solid tumours have been reported. These adverse events were always associated with a combination of multiple immunosuppressive agents.

Overdose
An accidental overdose may induce leucopenia (including lymphocytopenia and neutropenia) and thrombocytopenia. The effects are reversible after dose adjustments or discontinuation of the treatment. There are no antidotes.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: selective immunosuppressive agents
ATC code: L04AA04

Pharmacodynamic properties
Rabbit anti-human thymocyte immunoglobulin is a selective immunosuppressive agent (acting on T lymphocytes).

The mechanism of action of rabbit anti-human thymocyte immunoglobulin is as follows:
- Lymphocyte depletion probably constitutes the primary mechanism of the immunosuppression induced by rabbit anti-human thymocyte immunoglobulin.

Thymoglobuline® recognizes most of the molecules involved in the T-cell activation cascade during graft rejection such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, HLA-DR and HLA class I. T-cells are eliminated from the circulation by complement dependent lysis and, more likely by an Fc-dependent opsonization mechanism mediated by the monocyte and phagocyte cell system.

- Rabbit anti-human thymocyte immunoglobulin, in addition to its T-cell depletion effect, triggers other lymphocyte functions related to its immunosuppressive activity.

In vitro, at concentrations of around 0.1 mg/ml, Thymoglobuline® activates T-cells and stimulates their proliferation (in the same manner for the CD4+ and CD8+ subsets) with the synthesis of IL-2 and IFN-γ and the expression of CD25. This mitogenic activity primarily involves the CD2 pathway. At higher concentrations, rabbit anti-human thymocyte immunoglobulin inhibits the proliferative responses of lymphocytes to other mitogens with post-transcriptional blockade of IFN-γ and CD25 synthesis but no decrease in IL-2 secretion.

- *In vitro*, Thymoglobuline® does not activate β-cells.

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

- No activation of β-cells with, as a result, non-differentiation of plasmocytes.
- Antiproliferative activity against β-cells and certain lymphoblastoid cell lines.

In the course of immunosuppression in the context of organ transplantation, patients treated with rabbit anti-human thymocyte immunoglobulin experience profound lymphopenia (defined as more than 50 % depletion compared to the baseline value) as early as 1 day post-treatment initiation. The lymphopenia persists throughout treatment and after the course. On average, about 40 % of patients recover more than 50 % of the initial lymphocyte count at 3 months.

Monitoring of lymphocyte subsets (CD2, CD3, CD4, CD8, CD14, CD19 and CD25) has confirmed the broad range of T-cell specificities of Thymoglobuline®. Over the first 2 weeks of treatment, the absolute count for all subsets except β-lymphocytes and monocytes shows marked depletion (over 85% for CD2, CD3, CD4, CD8, CD25, CD56 and CD57).

At the start of treatment, monocytes undergo less marked depletion.
β-lymphocytes are almost unaffected. Most of the subsets have recovered more than 50 % of their initial value before the end of the second month. CD4-cell depletion is very long-lasting and persists at 6 months with, as a result, an inversion of the CD4/CD8 ratio.

Pharmacokinetic properties
Following the first infusion of 1.25 mg/kg of Thymoglobuline® (in cases of kidney-transplant), serum rabbit IgG levels of between 10 and 40 µg/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 to reach 20 to 170 µg/ml at the end of an 11-day course of treatment. A gradual decline is subsequently observed following discontinuation of treatment with rabbit anti-human thymocyte immunoglobulin. However, rabbit IgG remains detectable in 80 % of patients at 2 months.

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

Preclinical safety data
Non-clinical data reveal from toxicity studies with single and repeated administrations did not reveal the specific toxicity of Thymoglobuline®.

No mutagenicity, reproduction or genotoxicity studies have been conducted with Thymoglobuline®.

PHARMACEUTICAL PARTICULARS
List of excipients
- Glycine
- Sodium chloride
- Mannitol

Incompatibilities
According to a single compatibility study, the association of Thymoglobuline®, heparin, and hydrocortisone in a dextrose infusion solution caused precipitates and is not recommended.
In the absence of other compatibility studies, this medicinal product must not be mixed with other medicinal products with the exception of those mentioned in the special precautions for disposal and handling.

Shelf life
3 years.
After reconstitution and dilution, immediate use is recommended from a microbiological point of view. However, chemical and physical stability during use has been demonstrated at 2 to 8°C for 24 hours.

Special precautions for storage
Store in a refrigerator between +2°C and +8°C (36°F to 46°F). Do not freeze.

Nature and contents of outer packaging
Powder in a vial (type I glass) with a stopper (chlorobutyl) in one box.

Instructions for use and handling
Reconstitute the powder using 5 ml of sterile water for injection to obtain a solution containing 5mg protein per ml.

The reconstitution must be carried out in accordance with good practice regulations, particularly in terms of asepsis.

The solution is clear or slightly opalescent. Reconstituted 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 remains. If particulate matter persists, discard the vial. Immediate use of reconstituted product is recommended. Each vial is for single use only.

Depending on the daily dose, the 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 to use a 0.22 µm in-line filter during the administration of Thymoglobuline®. The daily dose is diluted in an infusion solution (9mg/ml sodium chloride(0.9%) solution for injection or 5% dextrose) 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 product or waste material must be disposed of in accordance with local requirements.

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