

# Thymoglobuline<sup>®</sup> 5 mg/ml

**Powder for concentrate for solution for infusion**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution:

Rabbit anti-human thymocyte immunoglobulin ..... 5 mg/ml.

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

## PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Thymoglobuline<sup>®</sup> is a creamy-white 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.
- Treatment of steroid-resistant, acute graft versus host disease (GvHD).
- Haematology: treatment of aplastic anaemia.

### Posology and method of administration

#### Posology

The posology depends on the indication, the administration regimen and the possible association of combination with other immunosuppressive agents. The following dosage recommendations may be used as a reference. The 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.
  - 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.

##### – 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.

##### – 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 anaemia

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 anaemia has not been established by controlled clinical trials carried out with this medicinal product.

#### Dose adjustments

Thrombocytopenia and/or leucopenia (particularly 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<sup>3</sup> or if the number of white blood cells is between 2,000 and 3,000 cells/mm<sup>3</sup>;
- Stopping Thymoglobuline treatment must be considered if persistent and severe thrombocytopenia (< 50,000 cells/mm<sup>3</sup>) occurs or leucopenia (< 2,000 cells/mm<sup>3</sup>) develops.

#### 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 slowly into a large vein. Adjust the infusion rate so that the total duration of infusion takes 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 infusions.

### 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 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 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]), febrile neutropenia, and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these reactions have been fatal.

### Precautions

#### General

Appropriate dosing for Thymoglobuline is different from dosing for other anti-thymocyte globulin (ATG) products, as protein composition and concentrations vary depending on the source of ATG used. Therefore, physicians must exercise care to ensure that the dose prescribed is suitable for the ATG product being administered.

Strict compliance with the recommended dosages 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 minimised. Premedication with antipyretic agents, corticosteroid and/or antihistamines may reduce the incidence and severity of these adverse reactions.

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

#### Haematological effects

Thrombocytopenia and/or leucopenia (in particular lymphopenia 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 the treatment with Thymoglobuline.

#### Infection

Infections, reactivation of infection, febrile neutropenia, 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 and post-transplantation lymphoproliferative disease (PTLD). Lymphoproliferative disorder with fatal outcome has been reported.

#### 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 infective agents for products from human origin include a careful selection of the 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 types of anaemia or with immunodeficiency.

Within 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 the infusion of Thymoglobuline

As with any infusion, reactions at the infusion site are likely to occur and may include pains, swelling and erythema.

#### Immunisations

Safety of immunisation with live attenuated vaccines after a treatment with Thymoglobuline has not been studied; therefore, immunisation with live attenuated vaccines is not recommended for patients who have recently received Thymoglobuline.

### Interaction with other medicinal products and other forms of interaction

Combinations to be taken into account

- Cyclosporin, 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 anaemia).

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 may 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 ability to drive vehicles and use machines

Given the undesirable 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 Multicenter Post-Marketing Surveillance Study

From June 1997 to March 1998, 18 French transplantation centers participated in the French Multicenter Post-marketing Surveillance Study-OOPTF01.

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 conditions*

Common:Diarrhoea, dysphagia, nausea, vomiting

#### *Skin and subcutaneous tissue disorders*

Common:Pruritus, rash, urticaria

#### *Musculoskeletal and connective tissue disorders*

Common:Myalgia

#### *Infections and infestations*

Very common:Infection

#### *Neoplasms, benign, malignant and non specified tumours (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 due to Thymoglobuline are usually mild and transient and are managed with reduction in infusion rate and/or with medications. Transient reversible changes in liver enzymes and markers of coagulation without any clinical sign have also been reported. Serious, and in very rare cases, fatal anaphylactic reactions have been reported. The fatalities occurred in patients who had not received adrenalin 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 cardio-respiratory 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 and 15 days after the onset Thymoglobuline therapy. Symptoms are usually self-limited or resolve 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, febrile neutropenia, and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal. In rare instances, malignancies, including but not limited to PTLD and other lymphomas as well as solid tumours have been reported. Lymphoproliferative disorder with fatal outcome has been reported. These adverse events were always associated with a combination of multiple immunosuppressive agents.

### Overdose

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

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressive agents, ATC code: L04AA04.

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

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

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

Thymoglobuline recognises the majority 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 1.

T-cells are eliminated from circulation by complement dependent lysis and further, by an Fc-dependent opsonisation mechanism mediated by the monocyto-phagocytic 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 posttranscriptional blockade of IFN-γ and CD25 synthesis but no decrease in IL-2 secretion.

*In vitro*, Thymoglobuline does not activate B-cells.

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

- no activation of B-cells with, as a result, non-differentiation of plasmocytes;
- anti-proliferative activity against B-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 B-lymphocytes and monocytes shows marked depletion (over 85 % for CD2, CD3, CD4, CD8, CD25, CD56 and CD57).

At the beginning of treatment, monocytes undergo less marked depletion. B-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 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 and 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.

### 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 2-8°C for 24 hours.

### Special precautions for storage

Store in a refrigerator (between 2°C and 8°C).

### Nature and contents of container

25 mg of powder in vial (type 1 glass) with a stopper (chlorobutyl) – box of 1.

### Special precautions for disposal and handling

Reconstitute the powder with 5 ml of water for injection to obtain a solution containing 5 mg of proteins 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 remain. If particulate matter persists, discard the vial. Immediate use of reconstituted product is recommended. Each vial is for single use. 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 0.2 µm in-line filter during the administration of Thymoglobuline. The daily dose is diluted in an infusion solution (9 mg/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 must be administered on the same day.

Any unused product or waste material must be disposed in accordance with local requirements.

## MARKETING AUTHORISATION HOLDER

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