

Thymoglobuline[®] 5 mg/ml

Powder for concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Rabbit anti-human thymocyte immunoglobulin 25 mg per vial. 1 mL reconstituted solution contains 5 mg rabbit, anti-human thymocyte immunoglobulin.

For a full list of excipients, see section List of Excipients.

PHARMACEUTICAL FORM

Powder for solution for infusion.

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 anemia.

Posology and Method of Administration

Posology

The posology depends on the indication, the administration regimen and the 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.

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 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.

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/mm³ or if the number of white blood cell count is between 2,000 and 3,000 cells/mm³;
- stopping Thymoglobuline treatment must be considered if persistent and severe thrombocytopenia (< 50,000 cells/mm³) or development of leucopenia (< 2,000 cells/mm³).

Method of Administration

Thymoglobuline is usually administered in the context of a therapeutic regimen combining multiple immunosuppressive agents.

It is recommended to administer pre-medication with intravenous corticosteroids and antihistamines prior to infusion of rabbit anti-human thymocyte globulin. Anti-pyretic agents (e.g., paracetamol) may also increase the tolerability of the initial infusion.

Rabbit anti-human thymocyte globulin is infused after dilution in isotonic 0.9% sodium chloride or 5% glucose solution. Inspect solution for particulate matter after reconstitution. To avoid

inadvertent administration of particulate matter from reconstitution, it is recommended that Thymoglobuline is administered through a 0.22 µm in-line filter.

Infuse slowly into a high-flow vein. Adjust the infusion rate so that the total duration of infusion is not less than 6 hours. See sections Special Warnings and Precautions for Use and Undesirable Effects: Adverse Events for advice about the management of any adverse events associated with infusion.

Contraindications

Thymoglobuline is contraindicated in patients with:

- Hypersensitivity to rabbit proteins or to any product excipients (see section List of Excipients).
- Active acute or chronic infections, which would contraindicate any additional immunosuppression.

Special Warnings and Precautions for Use

Thymoglobuline should be used under strict medical supervision in a hospital setting. Thymoglobuline must only be administered according to the instructions of a physician with experience of immunosuppressive therapy in the transplant setting. Patients should be carefully monitored during the infusion. Particular attention must be paid to monitoring the patient for any symptoms of anaphylactic shock. 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.

Prior to administration of Thymoglobuline it is advisable to determine whether the patient is allergic to rabbit proteins. Medical personnel and equipment, etc., must be readily at hand during the first days of therapy to provide emergency treatment if necessary.

Warnings

Immune-mediated Reactions

In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobuline and consist of anaphylaxis or a severe cytokine release syndrome (CRS).

Very rarely, fatal anaphylaxis has been reported (see section Undesirable Effects: Adverse Events). If an anaphylactic reaction occurs, the infusion should be terminated immediately and appropriate emergency treatment should be initiated. Equipment for emergency therapy for anaphylactic shock must be readily available.

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 sections Precautions and Adverse Events).

Infection

Thymoglobuline is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral, and protozoal), reactivation of infection (particularly 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 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. Physicians should therefore exercise care to ensure that the dose prescribed is appropriate for the ATG product being administered.

Thymoglobuline should be used under strict medical supervision in a hospital setting. Patients should be carefully monitored during the infusion and for a period of time following the end of the infusion until the patient is stable. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of 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 leucopenia (in particular lymphocytopenia and neutropenia) have been identified and are reversible following dose adjustments. When thrombocytopenia and/or leucopenia are not part of the underlying disease or associated with the condition for which Thymoglobuline is being administered, the following dose reductions are suggested:

- A reduction in dosage must be considered if the platelet count is between 50,000 and 75,000 cells/mm³ or if the white cell count is between 2,000 and 3,000 cells/mm³.
- Stopping Thymoglobuline treatment should be considered if persistent and severe thrombocytopenia (< 50,000 cells/mm³) occurs or leukopenia (< 2,000 cells/mm³) develops.

White blood cell and platelet counts should be monitored during and after Thymoglobuline therapy. Patients with severe neutropenic aplastic anaemia require very careful monitoring, appropriate prophylaxis and treatment of fevers and infections as well as adequate platelet transfusion support.

Infection

Infections, reactivation of infection (particularly CMV), and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. Careful patient monitoring of the patients and appropriate anti-infective prophylaxis are recommended.

Malignancy

Use of immunosuppressive agents, including Thymoglobuline, may increase the incidence of malignancies, lymphoma or lymphoproliferative disorders (which may be virally mediated). These events have sometimes been associated with fatal outcomes (see section Undesirable Effects: Adverse Events).

Risk of Transmission of Infectious Agents

Human blood components (formaldehyde treated red blood cells), as well as thymus cells are used in the manufacturing process for Thymoglobuline. 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, when medicinal products prepared using human components are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken for Thymoglobuline are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV and parvovirus B19.

It is strongly recommended that every time that Thymoglobuline is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Special Considerations for Thymoglobuline Infusion

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

The recommended route of administration for Thymoglobuline is intravenous infusion using a high-flow vein; however, it may be administered through a peripheral vein. When Thymoglobuline is administered through a peripheral vein, concomitant use of heparin and

hydrocortisone in an infusion solution of 0.9% sodium chloride may minimize the potential for superficial thrombophlebitis and deep vein thrombosis.

The combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended (see section Incompatibilities).

Immunisations

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

Interaction with Other Medicinal Products and Other Forms of Interaction

No drug interaction studies have been performed.

Interactions with food and drink are unlikely.

Thymoglobuline has not been shown to interfere with any routine clinical laboratory tests which use immunoglobulins. However, Thymoglobuline can induce production of human anti-rabbit antibodies which may interfere with rabbit antibody-based immunoassays and with cross-match or panel-reactive antibody cytotoxicity assays. Thymoglobuline may interfere with ELISA tests.

See also section Incompatibilities.

Fertility, Pregnancy and Lactation

Animal reproduction studies have not been conducted with Thymoglobuline. It is not known whether Thymoglobuline can cause foetal harm or can affect reproductive capacity. Thymoglobuline should be given to a pregnant woman only if clearly needed.

Thymoglobuline has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because other immunoglobulins are excreted in human milk, breast feeding should be discontinued during Thymoglobuline therapy.

Thymoglobuline has not been studied in labour or delivery.

Effects on the Ability to Drive and Use Machines

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

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
Gastrointestinal Disorders
Common*: Diarrhoea, dysphagia, nausea, vomiting
General Disorders and Administration Site Conditions
Very common: Fever
Common: Shivering
Immune System Disorders
Common: Serum sickness
Infections and Infestations
Very common: Infection
Musculoskeletal and Connective Tissue Disorders
Common: Myalgia
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)
Common**: Malignancy
Respiratory, Thoracic and Mediastinal Disorders
<i>Respiratory, thoracic and mediastinal disorders</i>
Common**: Dyspnoea
Skin and Subcutaneous Tissue Disorder
Common: Pruritus, rash
Vascular Disorders
Common: Hypotension

* *Common: ($\geq 1/100$ to $< 1/10$)*

** *Very common ($\geq 1/10$)*

Undesirable effects which have been discussed in other sections of this document are listed per clinical disorder below. Because these events are from post marketing surveillance, their true frequencies are not known.

Infusion-Associated Reactions and Immune System Conditions

Infusion-associated reactions (**IAR**) may occur following the administration of Thymoglobuline, and may occur as soon as the first or second dose. 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, urticarial, and/or headache. IARs with

Thymoglobuline are usually mild and transient and are managed with reduction in infusion rate and/or with medications. Transient reversible elevations in transaminases without any clinical signs or symptoms have also been reported during Thymoglobuline administration. Serious and in very rare cases, fatal anaphylactic reactions have been reported (see section Special Warnings and Precautions for Use: Warnings). The fatal reactions occurred in patients who did not receive adrenaline during the event.

IARs consistent with **Cytokine Release Syndrome (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).

Serum Sickness

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 therapy.

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. Malignancies including, but not limited to Lymphoproliferative disorders (LPD) and other lymphomas (which may be virally mediated) as well as solid tumours have been reported. These events have sometimes been associated with fatal outcome (see section Special Warnings and Precautions for Use: Precautions). These adverse events were always associated with a combination of multiple immunosuppressive agents.

For safety relating to transmissible agents, see section Special Warnings and Precautions for Use: Precautions.

Overdose

Inadvertent overdose may induce leucopenia (including lymphopenia and neutropenia) and thrombocytopenia.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: selective immunosuppressive agents, ATC code: L04AA04

Rabbit anti-human thymocyte globulin is a selective immunosuppressive agent (mostly acting on T lymphocytes). Lymphocyte depletion probably constitutes the primary mechanism of the immunosuppression induced by rabbit anti-human thymocyte globulin. This depletion is both peripheral and central; peripheral lymphocyte depletion can be detected as early as 24 hours after the first infusion. Lymphocyte counts start to rise as soon as Thymoglobuline is discontinued.

The lymphocyte depletion has been shown to occur *in vitro* by a number of different mechanisms (e.g., apoptosis, complement dependent lysis and antibody dependent cytotoxicity); the exact mechanisms which take place *in vivo* remain undetermined.

In addition to the T cell depletion, Thymoglobuline also has effects on dendritic cells (causing apoptosis), and on B cells. *In vitro*, Thymoglobiline does not activate B-cells. Antiproliferative activity against B-cells and certain lymphoblastoid cell lines has also been demonstrated *in vitro*. This effect may be partially protective against the development of PTLD.

Thymoglobuline also has activity against a number of cells surface epitopes (e.g., CD3, CD7, CD8, CD19, CD20, CD32, CD28), binding to them and causing downmodulation. The epitopes targeted include those involved in the immune response, in apoptosis, and in signal transduction, and include both B and T cell epitopes. In particular, Thymoglobiline has activity against both leucocyte and endothelial cell adhesion molecules (e.g., CD11a, CD18, CD11b, CD44, CD54, LPAM 1) which in animal studies has been shown to reduce tethering of leucocytes to the endothelium. Effector cells are thus unable to migrate through the endothelium to the graft. This effect may also, in theory, reduce ischaemia-reperfusion injury by allowing better flow through the microcirculation.

The combination of T cell depletion and downmodulation of adhesion molecules results in interference with multiple pathways by which rejection occurs.

Pharmacokinetic Properties

Following the first infusion of 1.25 mg/kg of Thymoglobuline (in kidney transplant recipients), total 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. There has been shown to be a relationship between dose given and total Thymoglobuline levels. The trough rabbit IgG levels increase progressively reaching 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 globulin. However, total rabbit IgG remains detectable in 81 % of patients at 2 months. Active Thymoglobiline (that is IgG which is available to bind to human lymphocytes and which causes the desired immunological effects) has a less noticeable relationship with dose given, and disappears from the circulation faster, with only 12% of patients having detectable active Thymoglobuline levels at day 90.

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 total but not active rabbit IgG levels.

Preclinical Safety Data

No mutagenicity, reproduction or genotoxicity studies have been conducted due to the nature and intended use of the product.

PHARMACEUTICAL PARTICULARS

List of Excipients

- Glycine
- Sodium chloride
- Mannitol

Other components:

Thymoglobuline may also contain residues of polysorbate, from the manufacturing process.

Incompatibilities

Based on a single compatibility study (Trissel LA., 2003; *Am J Health Syst Pharm*) the combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended.

In the absence of additional pharmaceutical incompatibility data, Thymoglobuline should not be mixed with other medicinal products in the same infusion.

Shelf Life

3 years.

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

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

Special Precautions for Storage

Store and transport refrigerated at 2°C and 8°C.

Do not freeze.

During transport a temperature excursion up to 25°C for 3 days will not alter the product characteristics.

For storage conditions of the reconstituted and diluted medicinal product, see section Shelf Life.

Nature and Contents of Container

Powder in a vial (type I glass) closed with a stopper (chlorobutyl). Each pack contains one 10 ml vial.

Special Precautions for Disposal and Other Handling

Reconstitute the powder using 5 ml of sterile water for injections to obtain a solution containing 5 mg protein per ml. 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 is visible. 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, 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 0.22 µm in-line filter.

The daily dose is diluted in an infusion solution (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 product or waste material must be disposed of in accordance with local requirements.

Manufactured by:

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DATE OF REVISION OF THE TEXT

Based on the EU SmPC 28 April 2012