1. Thymoglobuline® 5mg/ml

Powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 5ml vial contains 25mg of rabbit anti-human thymocyte immunoglobulin.

After reconstitution with 5ml WFI:
Rabbit anti-human thymocyte immunoglobulin (concentrate)……….. ……..5mg/ml
Corresponding to 25 mg/5 ml of rabbit anti-human thymocyte immunoglobulin per vial.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Thymoglobuline is a creamy-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute graft versus host disease (GvHD).
Hematology treatment of aplastic anemia.

4.2 Posology and method of administration

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

- Treatment of acute graft versus host disease
The dosage must be defined depending on 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, corresponding to a cumulative dose of 12.5 to 17.5 mg/kg.

The indication for aplastic anaemia has not been established by controlled trials carried out with this medicinal product.

Dose adjustments

Thrombocytopenia and/or leukopenia (particularly lymphocytopenia and neutropenia) have been identified; these conditions are reversible after dose adjustments. When thrombocytopenia and/or leukopenia 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 cells 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 leukopenia (< 2,000 cells/mm³) develops.

Method of administration

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

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

The reconstituted solution is clear or slightly opalescent.

Infuse slowly into a large vein

Adapt the infusion rate so that the total duration of the infusion is 4 hours at least.

For reconstitution and dilution, see Section 6.6

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Thymoglobuline must be used under strict medical supervision in a hospital and the 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 rarely, fatal anaphylaxis has been reported (see section 4.8). If an anaphylactic reaction occurs, the infusion must be terminated immediately and appropriate emergency treatment must be initiated. 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 weighed up.

Severe, acute infusion-associated reactions (IARs) are consistent with CRS attributed to cytokine release by the activated monocytes and lymphocytes. In rare instances these reported reactions are associated with serious cardio-respiratory events and/or death (See "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 sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal.

Precautions
General

Adaptation of 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 appropriate for the ATG product being administered.

Thymoglobulin should be used under strict medical supervision in a hospital setting, and patients should be carefully monitored during the infusions. Infusion-Associated Reactions (IARs) may occur following the administration of Thymoglobulin and may occur as soon as the first or second infusion during a single course of Thymoglobulin treatment.

Strict 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 IARs. Premedication with antipyretic 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 CRS. In rare instances, severe CRS can be fatal.

Haematological effects

Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified; these conditions are reversible after dose adjustment. When thrombocytopenia and/or leukopenia are not part of the underlying disease or associated with the condition for which Thymoglobuline is being administered, dose reductions are suggested (see section 4.2).
White blood cell and platelet counts must be monitored during and after Thymoglobuline therapy.

**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-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 4.8).

**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 of human origin include a careful selection of the raw material and the effective manufacturing steps for the inactivation / removal of viruses. However, the risk of transmission infective agents cannot 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. The 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 Thymoglobuline is administered, the patient’s name and the batch number of the product are recorded.

**Special considerations for Thymoglobuline infusion**

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

**Immunisations**

Safety of immunization with live attenuated vaccines after a treatment with Thymoglobuline has not been studied; therefore, immunization with live attenuated vaccines is not recommended for patients who have recently received Thymoglobuline (see section 4.5).

**4.5 Interaction with other medicinal products and other forms of interactions**

- 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 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 assays.

4.6 Pregnancy and lactation

No reproduction studies have been carried out with Thymoglobuline (see section 5.3). 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, breastfeeding must be discontinued during the treatment with Thymoglobuline.

4.7 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.

4.8 Undesirable effects

Adverse events from French Multi-Centre Post-marketing Surveillance Study

From June 1997 to March 1998, 18 French transplantation centres participated in the French Multicenter Post-marketing Surveillance Study-00PTF01.

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*: Lymphocytopenia, neutropenia, thrombocytopenia

**Respiratory, thoracic and mediastinal disorders**

Common**: Dyspnea

**Gastrointestinal disorders**

Common: Diarrhoea, dysphagia, nausea, vomiting

**Skin and subcutaneous tissue disorders**
Common: Pruritus, skin rashes

Musculoskeletal and systemic disorders
Common: Myalgia

Infections and infestations
Very common: Infection

Neoplasms, benign, malignant and non specified tumours (including cysts and polyps)
Common: Malignant tumors

Vascular disorders
Common: Hypotension

General disorders and abnormalities at the administration site
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 Disorders

IARs may occur following the administration of Thymoglobulin, and may occur as soon as the first or second infusion during a single course of treatment with Thymoglobulin. 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, urticaria, and/or headache. IARs with Thymoglobulin are usually mild and transient and are managed with reduction in infusion rates and/or with medications (see section 4.4). Transient reversible elevations in transaminases without any clinical signs or symptoms have also been reported during Thymoglobulin administration. In addition, hepatocellular injury, hepatotoxicity, hepatic failure (cases have been reported secondary to allergic hepatitis and reactivation of hepatitis in patients with hematologic disease and/or stem cell transplant as confounding factors).

Serious, and in very rare instances fatal anaphylactic reactions have been reported (see section 4.4). The fatalities occurred in patients who did not receive adrenaline 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 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, 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 pain at the infusion site and peripheral thrombophlebitis have also been reported. In addition: disseminated intravascular coagulopathy and coagulopathy 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 (see section 4.4). In rare instances cases these infections have been fatal. Malignancies, including but not limited to lymphoproliferative disorders 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 4.4 “Precautions”). These adverse events were always associated with a combination of multiple immunosuppressive agents.

For safety with respect to transmissible agents see section 4.4.

4.5 Overdose
An accidental overdose may induce leukopenia (including lymphopenia and neutropenia) and thrombocytopenia. These effects are reversible after dose adjustments or discontinuation of the treatment (see section 4.2). There are no antidotes.

5. PHARMACOLOGICAL PROPERTIES
5.1 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:

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

Thymoglobuline recognises the 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 1.

T-cells are eliminated from circulation by complement dependent lysis and more likely, by an Fc-dependent opsonisation mechanism mediated by the monocyte and phagocyte system.

-Rabbit anti-human thymocyte immunoglobulin, in addition to its T-cell depletion effect, triggers other lymphocyte functions in relation 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 CD4+ and CD8+ subsets) with 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 of IL-2 secretion.

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

The low risk of developing 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 base line 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 two weeks of treatment, the absolute count for all subsets except of B-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. 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.

5.2 Pharmacokinetic properties

Following the first infusion of 1.25 mg/kg of Thymoglobuline (in kidney transplant recipients) serum rabbit IgG levels 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 through 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 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 through rabbit IgG levels.

5.3 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 carried out with Thymoglobuline.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Glycine, sodium chloride and mannitol.

6.2 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 exception of those mentioned in section 6.6.

6.3 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.

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C). Do not freeze. For storage conditions for reconstituted product, see section 6.3

6.5 Nature and contents of container
25 mg of powder in vial (type 1 glass) with a stopper (chlorobutyl) – box of 1 vial.

6.6 Special precautions for disposal and other 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 remain. Should some 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, 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%glucose) 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 in accordance with local requirements.

7. MANUFACTURER: Genzyme Europe B.V., Naarden, The Netherlands
8. REGISTRATION NUMBER: 123-24-25723-00
9. LICENSE HOLDER:
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