

# **Thymoglobuline** Powder for concentrate for solution for infusion

## **1. NAME OF THE MEDICINAL PRODUCT**

Thymoglobuline

## **2. 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.

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 concentrate for solution for infusion.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Immunosuppression in transplantation: prevention and treatment of graft rejection.

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 17.5mg/kg.

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

Method of administration

Thymoglobuline is usually administered within the context of a therapeutic regimen combining several 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 section 4.4 and section 4.8 for advice about the management of any adverse events associated with infusion.

### **4.3 Contraindications**

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

### **4.4 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 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. 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 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 CMV) and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal.

#### *Hepatic diseases*

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

### 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. 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 leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments. When thrombocytopenia and/or leukopenia 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/mm<sup>3</sup> or if the white cell count is between 2,000 and 3,000 cells/mm<sup>3</sup>;
- Stopping Thymoglobuline treatment should be considered if persistent and severe thrombocytopenia (< 50,000 cells/mm<sup>3</sup>) occurs or leukopenia (< 2,000 cells/mm<sup>3</sup>) 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 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*

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 viruses such as HAV and parvovirus B19.

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

### *Special Considerations for Thymoglobuline Infusion*

As with any infusion, reactions at the injection 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 6.2).

### *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.

Thymoglobulin 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 of the administered product should be clearly recorded.

It is recommended to record the batch number as well.

### **4.5 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 include 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 6.2.

### **4.6 Fertility, pregnancy and lactation**

#### Fertility

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

#### Pregnancy

Animal reproduction studies have not been conducted with Thymoglobuline. It is not known whether Thymoglobuline can cause foetal harm. Thymoglobuline should be given to a

pregnant woman only if clearly needed. Thymoglobuline has not been studied in labour or delivery.

Breastfeeding

Thymoglobuline has not been studied in nursing women. It is not known whether this medicinal product 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 cytokine release syndrome, it is recommended that patients should not drive or operate machinery.

**4.8 Undesirable effects**

*Tabulated list of adverse reactions*

The adverse reactions observed in clinical studies and reported in post-marketing experience are detailed below.

Adverse reactions frequency is defined using the following convention: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Adverse events from French Multi-centre Post-marketing Surveillance Study are also included in the table below.

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 prophylaxis of acute rejection for renal transplant.

<b><u>Adverse reactions considered to be related to Thymoglobuline reported in clinical trials and post-marketing</u></b>	
<b>Blood and lymphatic system disorders</b>	Very common: <i>anaemia, lymphopenia, neutropenia, thrombocytopenia</i> Common: <i>febrile neutropenia</i>
<b>Gastrointestinal disorders</b>	Common: <i>diarrhoea, dysphagia, nausea, vomiting</i>
<b>General disorders and administrative site conditions</b>	Very common: <i>fever</i> Common: <i>shivering</i> Uncommon: <i>infusion related reactions (infusion associated reactions (IARs))*</i>

<b>Hepatobiliary disorders</b>	Common: <i>transaminases increased*</i> Uncommon: <i>hepatocellular injury, hepatotoxicity, hepatic failure*</i> Unknown: <i>Hyperbilirubinaemia</i>
<b>Immune system disorders</b>	Uncommon: <i>serum sickness*, cytokine release syndrome (CRS)*, anaphylactic reaction</i>
<b>Infections and infestations</b>	Very common: <i>infection (including reactivation of infection)</i> Common: <i>sepsis</i>
<b>Musculoskeletal and connective tissue disorders</b>	Common: <i>myalgia</i>
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	Common: <i>malignancy, lymphomas (which may be virally mediated), neoplasms malignant (solid tumours)</i> Uncommon: <i>lymphoproliferative disorder</i>
<b>Respiratory, thoracic and mediastinal disorders</b>	Common: <i>dyspnoea</i>
<b>Skin and subcutaneous tissue disorder</b>	Common: <i>pruritus, rash</i>
<b>Vascular disorder</b>	Common: <i>hypotension</i>

\*= see below

### **Description of selected adverse reactions**

#### **Infusion-Associated Reactions and Immune System Disorders**

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, urticaria, and/or headache. IARs with Thymoglobuline are usually mild and transient and are managed with reduced infusion rates and/or medications.

Serious and in very rare instances, fatal anaphylactic reactions have been reported (see section 4.4). 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 Cytokine Release Syndrome have been associated with cardiorespiratory dysfunction (including hypotension, ARDS, pulmonary oedema, myocardial infarction, tachycardia, and/or death).

#### **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 hematologic disease and/or stem cell transplant as confounding factors.

#### 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 treatment.

#### 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 4.4). These adverse events were always associated with a combination of multiple immunosuppressive agents.

For safety relating to transmissible agents, see section 4.4.

#### Paediatric Population

Currently available data are limited. Available information indicates that the safety 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il/>

## **4.9 Overdose**

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: 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.

This 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*, Thymoglobuline 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 cell surface epitopes (e.g. CD 3, 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, Thymoglobuline 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 down modulation of adhesion molecules results in interference with multiple pathways by which rejection occurs.

#### 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 safety and efficacy profiles in paediatric patients are not fundamentally different to that seen in adults.

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

## **5.2 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 40µg/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 Thymoglobuline (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.

### **5.3 Preclinical safety data**

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

glycine  
mannitol  
sodium chloride

Other components:

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

### **6.2 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 must not be mixed with other medicinal products in the same infusion.

### **6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials  
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 2-8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

#### **6.4 Special precautions for storage**

Store refrigerated (at 2°C - 8°C).

Do not freeze.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3

#### **6.5 Nature and contents of container**

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

#### **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 of protein per ml.

The solution is clear or slightly opalescent. 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 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 medicinal 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. MANUFACTURER**

Genzyme Europe B.V., Amsterdam, The Netherlands

### **8. REGISTRATION NUMBER**

123-24-25723-00

## **9. LICENSE HOLDER**

Sanofi-aventis Israel ltd., P.O.B 8090, Netanya.

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