Professional Information for THYMOGLOBULINE®

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

THYMOGLOBULINE® 25 mg powder for solution for infusion.

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.

Contains sugar alcohol: mannitol 50 mg.

Each 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 solution for infusion.

Lyophilisate: creamy white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Immunosuppression in transplantation:
  - Prophylaxis and treatment of solid organ graft rejection.
  - Prophylaxis of acute and chronic graft-versus-host disease (GvHD) in haematopoietic stem cell transplantation (HSCT).

- Treatment of severe aplastic anaemia when an immune mechanism is suspected, when an HLA identical sibling is not available, or the patient is older than 45 years.
- Treatment of graft-versus-host disease (GvHD).
- THYMOGLOBULINE may be used as a substitute for equine anti-lymphocyte immunoglobulin in the event of intolerance or contraindication to the latter.

4.2 Posology and method of administration

Posology

The posology depends on the indication, the administration regimen and combination with other immunosuppressive medicines. 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.

Severe 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.

Prophylaxis of acute and chronic graft-versus-host disease:

In transplantation of grafts (bone marrow or haematopoietic stem cells from peripheral blood) from mismatched related or matched unrelated 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 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.

Method of administration:

Route of administration: Intravenous infusion (after reconstitution and further dilution).
Rabbit anti-human thymocyte immunoglobulin is usually administered in the context of a therapeutic regimen combining several immunosuppressive medicines.
Administer the daily doses of intravenous corticosteroids and antihistamines required prior to infusion of rabbit anti-human thymocyte immunoglobulin. Anti-pyretic medicines (such as paracetamol) may also increase the tolerability of the initial infusion.

Before use each vial of THYMOGLOBULINE is reconstituted with 5 mL of sterile water for injection to form a limpid or slightly opalescent, colourless or pale yellow solution (see section 6.6 Reconstitution and dilution).
The reconstituted solution is further diluted in an isotonic solution of 0,9 % sodium chloride or of 5 % dextrose before infusion (see section 6.6).
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 large vein. Adjust the infusion rate so that the total duration of infusion is at least 4 hours.
ANY VIAL OPENED MUST BE USED IMMEDIATELY.

4.3 Contraindications

Known hypersensitivity to rabbit proteins or one of the components of THYMOGLOBULINE (see section 6.1).

Active acute or chronic infections which would contraindicate any additional immunosuppression.

4.4 Special warnings and precautions for use

Immune-mediated reactions

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

Fatal anaphylaxis has been reported (see section 4.8). Administration must immediately be discontinued and permanently withdrawn if an anaphylactic reaction occurs. Appropriate emergency treatment should be initiated promptly. Equipment for emergency therapy for anaphylactic shock must be readily available. Any anaphylactoid reaction during administration is a contraindication for further treatment.

Severe, acute infusion-associated reactions (IARs) are consistent with CRS 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 *General* below and section 4.8).

Infection

THYMOGLOBULINE is routinely used in combination with other immunosuppressive medicines. 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 medicines. In rare cases, these infections have been fatal. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

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. Healthcare practitioners 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 and patients should be carefully monitored during the infusions, and for a period of time following the end of the infusion until the patient is stable.

Infusion-associated reactions (IARs) may occur following the administration of THYMOGLOBULINE and may occur as soon as the first or second infusion during a single course of THYMOGLOBULINE treatment. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of IARs. Additionally, reducing the infusion rate may minimise many of these IARs or the infusion can be discontinued until the symptoms have resolved. 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 (including lymphopenia 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/mm^3 or if the white blood cell count is between 2 000 and 3 000 cells/mm^3.
- Discontinuation of THYMOGLOBULINE treatment should be considered if persistent and severe thrombocytopenia (< 50 000 cells/mm^3) occurs or leucopenia (< 2 000 cells/mm^3) develops.

White blood cell and platelet counts should be monitored during and after THYMOGLOBULINE therapy.

Malignancy

Use of immunosuppressive medicines, including THYMOGLOBULINE, may increase the incidence of malignancies, including lymphoproliferative disorders or lymphoma (which may be virally mediated). These events have sometimes been associated with fatal outcomes (see section 4.8).
It is important to note that concomitant or previous immunosuppressive treatments may contribute to the over-immunosuppression observed.

Special considerations for THYMOGLOBULINE 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 solution for injection may minimise 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 4.2 and section 6.2 (Incompatibilities)).

Immunisations

Immunisation with attenuated live vaccines is not recommended for patients who have recently received THYMOGLOBULINE because the safety of immunisation with attenuated live vaccines following THYMOGLOBULINE therapy has not been studied (see section 4.5).

Risk of transmission of infectious medicines

Human blood components (formaldehyde-treated red blood cells and thymus cells) are used in the manufacturing process for THYMOGLOBULINE. Standard measures to prevent infections resulting from the use of medicines prepared from human blood components include specific markers of infection and the inclusion of effective manufacturing steps for inactivation/removal of viruses. Despite these measures, when medicines prepared from human blood components are administered, the possibility of transmitting infective agents cannot be totally excluded. This risk also applies to unknown or emerging viruses and other pathogens.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicines and other forms of interaction

- While THYMOGLOBULINE is injected, it is advisable not to give blood or blood derivatives simultaneously and to avoid simultaneous infusions of any other solution, particularly lipids.
- Ciclosporin, tacrolimus, mycophenolate mofetil: risk of excessive immunosuppression with subsequent lymphoproliferation.
- Live attenuated vaccines: risk of systemic infection due to the vaccine which may potentially be fatal (see section 4.4). 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.
- Rabbit anti-human thymocyte immunoglobulin may interfere with ELISA tests using rabbit antibodies for a period of two months.
- 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.

4.6 Fertility, pregnancy and lactation

The safety of rabbit anti-human thymocyte immunoglobulins during pregnancy and lactation has not been established.

In consequence, rabbit anti-human thymocyte immunoglobulin must not be prescribed during pregnancy unless absolutely required. Breastfeeding 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 (CRS) (see section 4.8), it is recommended that patients should not drive or operate machinery.

4.8 Undesirable effects

Infections and infestations

Frequent: Infection (including reactivation of infection), sepsis, (see section 4.4), cytomegalovirus infection, urinary tract infection.

Less frequent: Herpes simplex infection, oral moniliasis.

Neoplasms benign and malignant (including cysts and polyps)

Frequent: Malignancy, lymphomas (which may be virally mediated), malignant neoplasms (solid tumours) (see section 4.4).

Less frequent: Lymphoproliferative disorder (see section 4.4).

Blood and the lymphatic system disorders

Frequent: Lymphopenia, leucopenia, thrombocytopenia, neutropenia (see section 4.4)

Less frequent: Coagulopathy.

Frequency unknown: Febrile neutropenia, disseminated intravascular coagulopathy.

Immune system disorders

Less frequent: Anaphylactic reaction (see section 4.4), allergic reactions, cytokine release syndrome*, serum sickness*.

** Side effects are described below*

Cardiac disorders

Frequent: Tachycardia.

Vascular disorders

Frequent: Hypotension.

Frequency unknown: Peripheral thrombophlebitis.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Gastrointestinal disorders

Frequent: Vomiting, nausea, diarrhoea.

Hepatobiliary disorders

Frequent: Increased transaminases*.

Less frequent: Hepatocellular injury, hepatotoxicity, hepatic failure*.

**Side effects are described below*

Skin and subcutaneous tissue disorders

Frequent: Pruritus, rash.

Musculoskeletal and connective tissue disorders

Frequent: Arthralgia, myalgia.

General disorders and administration site conditions

Frequent: Fever, chills, pain at the infusion site.

Less frequent: Infusion-associated reactions (IARs)*.

**Side effects are described below*

Description of selected adverse reactions

Infusion-associated reactions (IARs) and immune system disorders

IARs may occur following the administration of THYMOGLOBULINE and may occur as soon as the first or second infusion during a single course of THYMOGLOBULINE treatment. 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, decreased oxygen saturation and/or headache (see section 4.4).

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 haematological disease and/or stem cell transplant as confounding factors.

Cytokine release syndrome (CRS)

Severe CRS have been associated with cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome, pulmonary oedema, myocardial infarction, tachycardia and/or death) (See section 4.4).

Serum sickness

Serum sickness (including reactions such as fever, skin rash, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of THYMOGLOBULINE is important. It allows continued monitoring of the benefit/risk balance of THYMOGLOBULINE. Health care professionals are asked to report any suspected adverse reactions to: The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Accidental overdosage can lead to leucopenia (including lymphopenia and neutropenia) and thrombocytopenia.

Prolonged use longer than 3 weeks of rabbit anti-human thymocyte immunoglobulin may induce severe infections and increase the risk of lymphoma.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

THYMOGLOBULINE belongs to the medicine class A 30.2 Biologicals – Antibodies.

Pharmacotherapeutic group: Immunosuppressive agents, ATC Code: L04AA04.

Rabbit anti-human thymocyte immunoglobulin is a selective immunosuppressive medicine (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 recognises 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 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 related to its immunosuppressive activity.

  In vitro, at concentrations of approximately 0,1 mg/mL, THYMOGLOBULINE activates T-cells and stimulates their proliferation (in the same manner for the $CD4^+$ and $CD8^+$ subsets) with synthesis of IL-2 and IFN-γ and 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 INF-γ and CD25 synthesis but no decrease in IL-2 secretion.
- *In vitro*, THYMOGLOBULINE does not activate 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-lymphocytes with, as a result, non-differentiation of plasmocytes.

– antiproliferative activity against B-lymphocytes 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.
- Retrospective clinical studies have provided evidence strongly in favour of reducing the risk of acute GvHD disease. However, no beneficial effects on patient survival have been demonstrated.

5.2 Pharmacokinetic properties

Following the first infusion of 1,25 mg/kg of THYMOGLOBULINE (in kidney-transplant recipients), 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 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 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 trough rabbit IgG levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Sodium chloride

Mannitol.

6.2 Incompatibilities

Based on a single compatibility study 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 medicines in the same infusion.

6.3 Shelf life

36 months.

Chemical and physical stability during use has been demonstrated for reconstituted THYMOGLOBULINE at 25 °C for 24 hours. However, THYMOGLOBULINE contains no preservatives and storage is not recommended. The reconstituted product should be used immediately.

6.4 Special precautions for storage

Store between 2 °C and 8 °C.

Do not freeze. Protect from light.

ANY VIAL OPENED MUST BE USED IMMEDIATELY.

Reconstituted product: see section 6.3.

6.5 Nature and contents of container

Powder in a vial (10 mL, type 1 glass) equipped with a stopper (chlorobutyl). Each vial is packed in a carton box.

6.6 Special precautions for disposal and other handling

Reconstitution and dilution:

1. After calculating the number of vials needed, using aseptic technique, reconstitute each vial of THYMOGLOBULINE with 5 mL of sterile water for injection (SWFI). As THYMOGLOBULINE contains no preservatives, reconstituted product should be used immediately (see section 6.4).
2. Allow THYMOGLOBULINE vials to reach room temperature before reconstituting the lyophilised product.
3. Aseptically remove caps to expose rubber stoppers.
4. Clean stoppers with a germicidal or alcohol swab.
5. Aseptically reconstitute each vial of THYMOGLOBULINE lyophilised powder with 5 mL of SWFI.
6. Invert the vials gently until powder is completely dissolved. Each reconstituted vial contains 25 mg/5 mL or 5 mg/mL of THYMOGLOBULINE. The reconstituted solution is a limpid or slightly opalescent, colourless or pale yellow solution.
7. Inspect solution for particulate matter after reconstitution. Should some particulate matter remain, continue to gently rotate the vial until no particulate matter is visible. If particulate matter persists, discard this vial.
8. The reconstituted solution is then diluted in an infusion solution of an isotonic solution of 0,9 % sodium chloride or 5 % dextrose solution (see Method of administration in section 4.2).

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

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8 REGISTRATION NUMBER

W/30.2/75

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 February 1989

10 DATE OF REVISION OF THE TEXT

15 April 2022