Thymoglobulin® should only be used by physicians experienced in immunosuppressive therapy for the management of renal transplant patients.  

**DESCRIPTION**

Thymoglobulin® (Anti-Thymocyte Globulin (Rabbit)) is a purified, pasteurized, gamma immune globulin, obtained by immunization of rabbits with human thymocytes. This immunosuppressive product contains cytotoxic antibodies directed against antigens expressed on human T-lymphocytes.

Thymoglobulin is a sterile, freeze-dried product for intravenous administration after reconstitution with Sterile Water for Injection, USP (SWFI).

Each 10 mL vial contains 25 mg anti-thymocyte globulin (rabbit) as well as 50 mg glycine, 50 mg mannitol, and 10 mg sodium chloride.

After reconstitution with 5 mL SWFI, each vial of reconstituted product contains approximately 5 mg/mL of Thymoglobulin, of which >90% is gamma globulin immune globulin (IgG). The reconstituted solution has a pH of 6.5 - 7.2. Human red blood cells are used in the manufacturing process to deplete cross-reactive antibodies to non-T-cell antigens. The manufacturing process is validated to remove or inactivate potential exogenous viruses. All human red blood cells are from US registered or FDA licensed blood banks. A viral inactivation step (pasteurization, i.e., heat treatment of active ingredient at 60°C/10 hr) is performed for each lot. Each Thymoglobulin lot is released following potency testing (lymphocytotoxicity and E-rosette inhibition assays), and cross-reactive antibody testing (hemagglutination, platelet agglutination, anti-human serum protein antibody, antihemoglobin basement membrane antibody, and fibroblast toxicity assays on every fifth lot).

**PHARMACOLOGY**

**Mechanism of Action**

The mechanism of action by which polyclonal antilymphocyte preparations suppress immune responses is not fully understood. Possible mechanisms by which Thymoglobulin may induce immunosuppression in vivo include: T-cell clearance from the circulation and modulation of T-cell activation, homing, and cytotoxic activities. Thymoglobulin includes antibodies against T-cell markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chains, and 82 micro-globulin. In vitro, Thymoglobulin (concentrations >0.1 mg/mL) mediates T-cell suppressive effects via inhibition of proliferative responses to several mitogens. In patients, T-cell depletion is usually observed within a day from initiating Thymoglobulin therapy. Thymoglobulin has not been shown to be effective for treating antibody (humoral) mediated rejections.

**Pharmacokinetics and Immunogenicity**

After an intravenous dose of 1.25 to 1.5 mg/kg/day (over 4 hours for 7-11 days) 4-8 mcg/mL with a half-life of 2-3 days after the first dose, and 87 mcg/mL (23-170 mcg/mL) after an intravenous dose of 1.25 to 1.5 mg/kg/day (over 4 hours for 7-11 days) 4-8 mcg/mL after the last dose. During the Thymoglobulin® Phase 3 randomized trial, of the 108 of 163 patients evaluated, anti-rabbit antibodies developed in 68% of the Thymoglobulin-treated patients, and anti-horse antibodies developed in 78% of the Atgam®-treated patients. No controlled studies have been conducted to study the effect of anti-rabbit antibodies on repeat use of Thymoglobulin. However, monitoring the lymphocyte count to ensure that T-cell depletion is achieved upon retreatment with Thymoglobulin is recommended. Based on data collected from a limited number of patients (Clinical study Phase 3, n=12), T-cell counts are presented in the chart below. These data were collected using flow cytometry (FACSscan, Becton-Dickinson).

Mean T-Cell Counts Following Initiation of Thymoglobulin Therapy

- **CD2**: 200
- **CD3**: 150

**PRECAUTIONS**

**General**

Appropriate dosing for Thymoglobulin 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.

Thymoglobulin should be used under strict medical supervision in a hospital setting and patients should be carefully monitored during the infusion. The first dose should be infused over a minimum of 6 hours into a high-flow vein. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of infusion associated reactions (IARs). Additionally, reducing the infusion rate may minimize the incidence of infusion associated reactions (IARs).

Thymoglobulin is contraindicated in patients with history of allergy or anaphylaxis to rabbit or horse proteins, or to any product excipients, or who have active acute or chronic infections which contraindicate any additional immunosuppression.

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**WARNINGS**

Thymoglobulin should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients. Medical surveillance is required during Thymoglobulin infusion.

Serious immune-mediated reactions have been reported with the use of Thymoglobulin and consist of anaphylaxis or severe cytokine release syndrome (CRS).

**Infusion**

Thymoglobulin is routinely used in combination with other immunosuppressive regimens. Infusions associated with particular cytokine profiles (CMV) and sepsis have been reported after Thymoglobulin administration in combination with multiple immunosuppressive agents. Severe acute infections can be fatal.

**ADVERSE REACTIONS**

- **Hematologic Effects**: Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments (See DOSAGE AND ADMINISTRATION).

**Drug Interactions**

- **No drug interaction studies have been performed.**

- **Because Thymoglobulin is administered to patients receiving a standard immunosuppressive regimen, this may predispose patients to overimmunosuppression. Many transplant centers decrease maintenance immunosuppression therapy during the period of antibody therapy.**

**Drug/Laboratory Test Interactions**

Thymoglobulin has not been shown to interfere with any routine clinical laboratory tests which do not use immunoglobulins. Thymoglobulin may interfere with rabbit antibody-based immunohistochemical and cross-matched positive reactive antibody cytotoxicity assays.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic and mutagenic potential of Thymoglobulin and its potential to impair fertility have not been studied.

**Pregnancy**

**Pregnancy Category C**

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

**Nursing Mothers**

Thymoglobulin has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because the drug, immune globulins, contained in Thymoglobulin, as well as human milk, breast-feeding should be discontinued during Thymoglobulin therapy.

**Pediatric Use**

The safety and effectiveness of Thymoglobulin in pediatric patients has not been established in controlled clinical studies. However, the dosage, efficacy, and adverse event profile are not thought to be different from adults based on limited European studies and US compassionate use.
Post-marketing Experience

The following adverse reactions have been identified during post approval use of Thymoglobulin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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 of Thymoglobulin or during a subsequent course of Thymoglobulin treatment. Clinical manifestations of Infusion-associated reactions IARs have included some of the following signs and symptoms: fever, chills/rigor, dyspnea, nausea, vomiting, diarrhoea, urticaria, hypotension, malaise or headache. IARs with Thymoglobulin are generally manageable with a reduction in infusion rates and/or with medications (See PRECAUTIONS). Serious and fatal anaphylactic reactions have been reported (See WARNINGS). The fatalities occurred in patients who did not receive epinephrine during the event.

IARs consistent with cytokine release syndrome (CRS) have been reported. Severe and potentially life-threatening CRS have also been reported.

Post-marketing reports of severe CRS have included cardiopulmonary dysfunction (including hypotension, acute respiratory distress syndrome, pulmonary edema, myocardial infarction, tachycardia, and/or death). During post-marketing surveillance, reactions such as fever, rash, arthralgia, and/or myalgia, indicating possible serum sickness, have been reported. Serum sickness tends to occur 5 to 15 days after onset of Thymoglobulin therapy.

Symptoms are manageable with corticosteroid treatment.

Adverse Events Due to Immunosuppression

Infections, rejection, infusion, and sepsis have been reported after Thymoglobulin administration in combination with multiple immunosuppressive agents (See WARNINGS and PRECAUTIONS). Malignancies including, but not limited to post-transplant lymphoproliferative disorder (PTLD) and other lymphomas as well as solid tumours have been reported (See PRECAUTIONS). These adverse events were reported with use of a combination of multiple immunosuppressive agents.

OVERDOSAGE

Thymoglobulin overdose may result in leukopenia (including lymphopenia and neutropenia) or thrombocytopenia, which can be managed with dose reduction (See DOSAGE AND ADMINISTRATION).

DOSE AND ADMINISTRATION

The recommended dosage of Thymoglobulin for treatment of acute renal graft rejection is 1.5 mg/kg of body weight administered daily for 7 to 14 days. The recommended route of administration is intravenous infusion using a high-flow vein. Thymoglobulin should be infused over a minimum of 6 hours for the first infusion and over at least 4 hours on subsequent days of therapy.

Thymoglobulin should be administered through an in-line 0.22 micrometer filter. Thymoglobulin is supplied as a 10 mL vial containing lyophilized (solid) Thymoglobulin.

Post-Marketing Experience

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Thymoglobulin should be administered through an in-line 0.22 micrometer filter. Thymoglobulin is supplied as a 10 mL vial containing lyophilized (solid) Thymoglobulin (25 mg).

Please see Preparation for Administration for vial reconstitution and dilution in infusion solution recommendations. Investigations indicate that Thymoglobulin is less likely to produce side effects when administered at the recommended infusion rate. Administration of antiviral prophylactic therapy is recommended. Premedication with corticosteroids, acetaminophen, and/or an antihistamine 1 hour prior to the infusion is recommended and may reduce the incidence and intensity of side effects during the infusion (See PRECAUTIONS: General and Adverse Reactions: Post-Marketing Experience). Medical personnel should monitor patients for adverse events during and after infusion. Monitoring T-cell counts (absolute and/or percentage) to assess the level of T-cell depletion is recommended. Total white blood cell and platelet counts should be monitored.

Overdosage of Thymoglobulin may result in leukopenia (including lymphopenia and neutropenia) or thrombocytopenia. The Thymoglobulin dose should be reduced by one-half if the WBC count is between 2,000 and 3,000 cells/mm^3 or if the platelet count is between 50,000 and 75,000 cells/mm^3. Stopping Thymoglobulin treatment should be considered if the WBC count falls below 2,000 cells/mm^3 or platelet counts below 50,000 cells/mm^3.

Preparation for Administration

Reconstitution

After calculating the number of vials needed, using aseptic technique, reconstitute each vial of Thymoglobulin with 5 mL of Sterile Water for Injection, USP (SWFI). Reconstituted Thymoglobulin is physically and chemically stable for up to 24 hours at room temperature; however, room temperature storage is not recommended. As Thymoglobulin contains no preservatives, reconstituted product should be used immediately.

1. 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.

Dilution

1. Transfer the contents of the calculated number of Thymoglobulin vials into the bag of infusion solution (saline or dextrose). Recommended volume: per one vial of Thymoglobulin use 50 mL of infusion solution (total volume usually between 50 to 500 mL).

2. Mix the solution by inverting the bag gently only once or twice.

Infusion

1. Follow the manufacturer’s instructions for the infusion administration set. Infuse through a 0.22 micrometer filter into a high-flow vein.

2. Set the flow rate to deliver the minimum of 6 hours for the first dose and over at least 4 hours for subsequent doses.

HOW SUPPLIED

Thymoglobulin is available as sterile, lyophilized powder to be reconstituted with sterile Water for Injection, USP (SWFI). Each package contains a 10 mL vial of freeze-dried Thymoglobulin (25 mg) NDC# 58489-0080-1.

Storage

• Store in refrigerator at 2°C to 8°C (36°F to 46°F).

• Protect from light.

• Do not freeze.

• Do not use after the expiration date indicated on the label.

• Reconstituted Thymoglobulin is physically and chemically stable for up to 24 hours at room temperature; however, room temperature storage is not recommended. As Thymoglobulin contains no preservatives, reconstituted product should be used immediately.

• Infusion solutions of Thymoglobulin must be used immediately.

• Any unused drug remaining after infusion must be discarded.

REFERENCES


Manufactured for:

By: Genzyme Corporation
Genzyme Polyclonals, S.A.S.
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