Thymoglobulin®
Anti-thymocyte Globulin (Rabbit)

Sterile Lyophilized Preparation
For Intravenous Use Only

R_x only

WARNING
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 (WFI).

Each package contains two 7 mL vials:

Vial 1: Freeze-Dried Thymoglobulin Formulation	
Active ingredient: Anti-thymocyte Globulin (Rabbit)	25 mg
Inactive ingredients: Glycine (50 mg), mannitol (50 mg), sodium chloride (10 mg)	
Vial 2: Diluent	
Sterile Water for Injection, USP	5 mL

The reconstituted preparation contains approximately 5 mg/mL of Thymoglobulin, of which >90% is rabbit gamma immune globulin (IgG). The reconstituted solution has a pH of 7.0 ± 0.4. 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, antiglomerular basement membrane antibody, and fibroblast toxicity assays on every fifth lot).

PHARMACOLOGY

Mechanism of Action

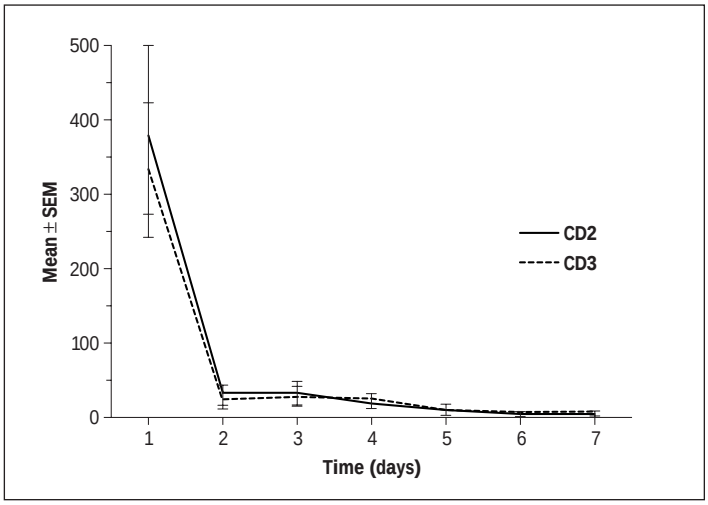
The mechanism of action by which polyclonal anti-lymphocyte preparations suppress immune responses is not fully understood. Possible mechanisms by which Thymoglobulin may induce immunosuppression *in vivo* include: T-cell clearance from the circulation and modulation of T-cell activation, homing, and 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 β2 microglobulin.[1,2,3,4,5] *In vitro*, Thymoglobulin (concentrations >0.1 mg/mL) mediates T-cell suppressive effects via inhibition of proliferative responses to several mitogens.[2,3,4] In patients, T-cell depletion is usually observed within a day from initiating Thymoglobulin therapy.[7,9,10] 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 hours post-infusion, Thymoglobulin levels were on average 21.5 µg/mL (10–40 µg/mL) with a half-life of 2–3 days after the first dose, and 87 µg/mL (23–170 µg/mL) after the last dose.[9] During the Thymoglobulin* Phase III 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 (p=n.s.). 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.[8]

Based on data collected from a limited number of patients (Clinical study Phase III, n=12), T-cell counts are presented in the chart below. These data were collected using flow cytometry (FACSCAN, Becton-Dickinson).

Mean T-Cell Counts Following Initiation of Thymoglobulin Therapy



Clinical Trials

US Phase III Study

A controlled, double-blind, multicenter, randomized clinical trial comparing Thymoglobulin and Atgam was conducted at 28 US transplant centers in renal transplant patients (n=163) with biopsy-proven Banff Grade II (moderate), Grade III (severe), or steroid-resistant Grade I (mild) acute graft rejection. This clinical trial rejected the null hypothesis that Thymoglobulin was more than 20% less effective in reversing acute rejection than Atgam. The overall weighted estimate of the treatment difference (Thymoglobulin–Atgam success rate) was 11.1% with a lower 95% confidence bound of 0.07%. Therefore, Thymoglobulin was at least as effective as Atgam in reversing acute rejection episodes.[8]

*Thymoglobulin is a registered trademark of Genzyme Corporation, Cambridge, MA, USA

**Atgam is a registered trademark of Pharmacia & Upjohn, Kalamazoo, MI, USA

In the study, patients were randomized to receive 7 to 14 days of Thymoglobulin (1.5 mg/kg/day) or Atgam (15 mg/kg/day). For the entire study, the two treatment groups were comparable with respect to donor and recipient characteristics. During the trial, the FDA approved new maintenance immunosuppressive agents (tacrolimus and mycophenolate). Off-protocol use of these agents occurred during the second half of the study in some patients without affecting the overall conclusions (Thymoglobulin 22/43, Atgam 20/37; p=0.826). The results however are presented for the first and second halves of the study (Table 1). In Table 1, successful treatment is presented as those patients whose serum creatinine levels (14 days from the diagnosis of rejection) returned to baseline and whose graft was functioning on day 30 after the end of therapy.

Table 1. Response to Study Treatment by Rejection Severity and Study Half

	Total		First Half		Second Half	
	Thymoglobulin	Atgam	Thymoglobulin	Atgam	Thymoglobulin	Atgam
Baseline Rejection Severity:	**Success/n (%)**		**Success/n (%)**		**Success/n (%)**	
Mild	9/10 (90.0%)	5/8 (62.5%)	5/5 (100%)	1/3 (33.3%)	4/5 (80.0%)	4/5 (80.0%)
Moderate	44/58 (75.5%)	41/58 (70.7%)	22/26 (84.6%)	22/32 (68.8%)	22/32 (68.8%)	19/26 (73.1%)
Severe	11/14 (71.6%)	8/14 (57.1%)	6/8 (75.0%)	3/8 (37.5%)	5/6 (83.3%)	5/6 (83.3%)
Overall	64/82 (78.0%)	54/80 (67.5%)	33/39 (84.6%)	26/43 (60.5%)	31/43 (72.1%)	28/37 (75.7%)
Weighted estimate of difference (Thymoglobulin–Atgam)	11.1%[a]		19.3%		–3.2%	
Lower one-sided 95% confidence bound	0.07%		4.6%		–19.7%	
p-value[b]	0.061[c]		0.008[d]		0.625[d]	

a. across rejection severity and study half
b. under null hypothesis of equivalence (Cochran-Mantel-Haenszel test)
c. one-sided stratified on rejection severity and study half
d. one-sided stratified on rejection severity

There were no significant differences between the two treatments with respect to (i) day 30 serum creatinine levels relative to baseline, (ii) improvement rate in post-treatment histology, (iii) one-year post-rejection Kaplan-Meier patient survival (Thymoglobulin 93%, n=82 and Atgam 96%, n=80), (iv) day 30 and (v) one-year post-rejection graft survival (Thymoglobulin 83%, n=82; Atgam 75%, n=80).

INDICATIONS AND USAGE

Thymoglobulin is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression.

CONTRAINDICATIONS

Thymoglobulin is contraindicated in patients with history of allergy or anaphylaxis to rabbit proteins, or who have an acute viral illness.

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. In rare instances, anaphylaxis has been reported with Thymoglobulin use. In such cases, the infusion should be terminated immediately. Medical personnel should be available to treat patients who experience anaphylaxis. Emergency treatment such as 0.3 mL to 0.5 mL aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated, should be provided. Thymoglobulin or other rabbit immunoglobulins should not be administered again for such patients. Thrombocytopenia or neutropenia may result from cross-reactive antibodies and is reversible following dose adjustments.

PRECAUTIONS

General

Thymoglobulin infusion may produce fever and chills. To minimize these, the first dose should be infused over a minimum of 6 hours into a high-flow vein. Also, premedication with corticosteroids, acetaminophen, and/or an antihistamine and/or slowing the infusion rate may reduce reaction incidence and intensity (see **DOSAGE AND ADMINISTRATION**).

Prolonged use or overdosage of Thymoglobulin in association with other immunosuppressive agents may cause over-immunosuppression resulting in severe infections and may increase the incidence of lymphoma or post-transplant lymphoproliferative disease (PTLD) or other malignancies. Appropriate antiviral, antibacterial, antiprotozoal, and/or antifungal prophylaxis is recommended.

Laboratory Tests

During Thymoglobulin therapy, monitoring the lymphocyte count (i.e., total lymphocyte and/or T-cell subset) may help assess the degree of T-cell depletion (see **Pharmacokinetics and Immunogenicity**). For safety, WBC and platelet counts should also be monitored (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

- Because Thymoglobulin is administered to patients receiving a standard immunosuppressive regimen, this may predispose patients to over-immunosuppression. Many transplant centers decrease maintenance immunosuppression therapy during the period of antibody therapy.
- Thymoglobulin can stimulate the production of antibodies which cross-react with rabbit immune globulins. (See **Pharmacokinetics and Immunogenicity.**)

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 immunoassays and with cross-match or panel-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 reproduction 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 many drugs are excreted in human milk, caution should be exercised when Thymoglobulin is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Thymoglobulin in pediatric patients has not been established in controlled trials. However, the dose, efficacy, and adverse event profile are not thought to be different from adults based on limited European studies and US compassionate use.[6]

ADVERSE REACTIONS

Thymoglobulin adverse events are generally manageable or reversible. In the US Phase III controlled clinical trial (n = 163) comparing the efficacy and safety of Thymoglobulin and Atgam, there were no significant differences in clinically significant adverse events between the two treatment groups (Table 2). Malignancies were reported in 3 patients who received Thymoglobulin and in 3 patients who received Atgam during the one-year follow-up period. These included two PTLDs in the Thymoglobulin group and two PTLDs in the Atgam group. Infections occurring in both treatment groups during the 3-month follow-up are summarized in Table 3. No significant differences were seen between the Thymoglobulin and Atgam groups for all types of infections, and the incidence of cytomegalovirus (CMV) infection was equivalent in both groups. (Viral prophylaxis was by the center's discretion during antibody treatment, but all centers used gancyclovir infusion during treatment.)

Table 2. Frequently Reported and Significant Adverse Events*

	Thymoglobulin n=82		Atgam n=81		
Preferred Term	**No. of Patients**	**(%)**	**No. of Patients**	**(%)**	**p Value†**
Frequently Reported Events					
Fever	52	(63.4)	51	(63.0)	1.0
Chills	47	(57.3)	35	(43.2)	0.086
Leukopenia	47	(57.3)	24	(29.6)	<0.001
Pain	38	(46.3)	35	(43.2)	0.753
Headache	33	(40.2)	28	(34.6)	0.518
Abdominal pain	31	(37.8)	22	(27.2)	0.181
Diarrhea	30	(36.6)	26	(32.1)	0.622
Hypertension	30	(36.6)	23	(28.4)	0.316
Nausea	30	(36.6)	23	(28.4)	0.316
Thrombocytopenia	30	(36.6)	36	(44.4)	0.341
Peripheral edema	28	(34.1)	28	(34.6)	1.0
Dyspnea	23	(28.0)	16	(19.8)	0.271
Asthenia	22	(26.8)	26	(32.1)	0.495
Hyperkalemia	22	(26.8)	15	(18.5)	0.262
Tachycardia	22	(26.8)	19	(23.5)	0.719
Significant Events§					
Leukopenia	47	(57.3)	24	(29.6)	<0.001
Malaise	11	(13.4)	3	(3.7)	0.047
Dizziness	7	(8.5)	20	(24.7)	0.006

*Treatment Emergent Adverse Events (TEAE) are summarized. Frequently reported adverse events are those reported by more than 25% of patients in a treatment group; significant adverse events are those where the incidence rate differed between treatment groups by a significance level of ≤0.05.

†p value comparing treatment groups using Fisher's exact test.

§statistically significant differences in the AEs

Table 3. Infections

	Thymoglobulin n=82			Atgam n=81			
BODY SYSTEM Preferred Term	**No. of Patients**	**(%)**	**Total Reports**	**No. of Patients**	**(%)**	**Total Reports**	**p Value†**
BODY AS A WHOLE	30	(36.6)	36	22	(27.2)	29	0.240
Infection	25	(30.5)	26	19	(23.5)	21	0.378
Other	14	(17.1)	15	11	(13.6)	12	0.665
CMV	11	(13.4)	11	9	(11.1)	9	0.812
Sepsis	10	(12.2)	10	7	(9.6)	7	0.610
Moniliasis	0	(0.0)	0	1	(1.2)	1	0.497
DIGESTIVE	5	(6.1)	5	3	(3.7)	3	0.720
Gastrointestinal moniliasis	4	(4.9)	4	1	(1.2)	1	0.367
Oral moniliasis	3	(3.7)	0	2	(2.5)	1	0.497
Gastritis	1	(1.2)	1	0	(0.0)	0	1.000
RESPIRATORY	0	(0.0)	0	1	(1.2)	1	0.497
Pneumonia	0	(0.0)	0	1	(1.2)	1	0.497
SKIN	4	(4.9)	4	0	(0.0)	0	0.120
Herpes simplex	4	(4.9)	4	0	(0.0)	0	0.120
UROGENITAL	15	(18.3)	15	22	(29.2)	22	0.195
Urinary tract infection	15	(18.3)	15	21	(25.9)	21	0.262
Vaginitis	0	(0.0)	0	1	(1.2)	1	0.497
NOT SPECIFIED	0	(0.0)	0	2	(2.5)	2	0.245

†p value comparing treatment groups using Fisher's exact test.

OVERDOSAGE

Thymoglobulin overdosage may result in leukopenia or thrombocytopenia, which can be managed with dose reduction (see **DOSAGE AND ADMINISTRATION**).

DOSAGE 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 µm filter.

Thymoglobulin is supplied as two vials: one vial contains lyophilized (solid) Thymoglobulin (25 mg) and the second vial contains 5 mL sterile Water for Injection, USP (WFI) labeled as "Diluent." For vial reconstitution, dilution in infusion solution and infusion procedure, see **Preparation for Administration**. Investigations indicate that Thymoglobulin is well tolerated and less likely to produce side effects when administered at the recommended 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**). Medical personnel should monitor patients for adverse events during and after infusion. Monitoring T-cell counts (absolute and/or subsets) 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 and/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 platelets below 50,000 cells/mm^3.

Preparation for Administration

Reconstitution

After calculating the number of vials needed, using aseptic technique, reconstitute Thymoglobulin with the supplied Diluent, sterile Water for Injection, USP (WFI), immediately before use. Thymoglobulin should be used within 4 hours after reconstitution if kept at room temperature.

1. Allow Thymoglobulin and diluent (sterile WFI) vials to reach room temperature before reconstituting the lyophilized product.
2. Aseptically remove caps and tabs of the aluminum seals to expose rubber stoppers.
3. Clean stoppers with germicidal or alcohol swab.
4. Aseptically remove 5 mL of diluent (sterile WFI) using a sterile, single-use syringe and inject it slowly into the vial containing Thymoglobulin lyophilized powder.
5. Reconstitute each vial of Thymoglobulin lyophilized powder with 5 mL of sterile diluent.
6. Rotate vial gently until powder is completely dissolved. Each reconstituted vial contains 25 mg or 5 mg/mL of Thymoglobulin.
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.

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-micron filter into a high-flow vein.
2. Set the flow rate to deliver the dose over a 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 diluent. Each package contains two 7 mL vials:

Vial 1:
Freeze-Dried Thymoglobulin Formulation (25 mg)
NDC# 58468-0080-1

Vial 2:
Diluent (sterile Water for Injection, USP) (>5 mL)
NDC# 58468-0110-1

Storage

- Store in refrigerator between +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 vials of Thymoglobulin should be used within 4 hours.
- Infusion solutions of Thymoglobulin must be used immediately.
- Any unused drug remaining after infusion must be discarded.

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