Product Monograph

Including Patient Medication Information

[Pr]THYMOGLOBULIN®

Anti-thymocyte Globulin [Rabbit]

Powder for Solution for Intravenous Infusion from Single Use Vials

25 mg/vial

Standard: Professed

ATC Code: L04AA04

sanofi-aventis Canada Inc.

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Date of Authorization:
2026-01-22

Control Number: 301218

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Certain sections or subsections that are not applicable at the time of authorization of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

THYMOGLOBULIN (Anti-thymocyte globulin [rabbit]) is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression and for induction in adult renal transplant recipients.

1.1. Pediatrics

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 studies undertaken in Europe and data collected in the United States.

1.2. Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2. Contraindications

THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) is contraindicated in patients with:

- Hypersensitivity to rabbit proteins or to any product excipients
- Active acute or chronic infections, which would contraindicate any additional immunosuppression

3. Serious Warnings and Precautions Box

- THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients.
- In rare instances, serious immune-mediated reactions have been reported with the use of THYMOGLOBULIN and consist of anaphylaxis or severe cytokine release syndrome (CRS). (see 7 Warnings and Precautions, Immune)

4. Dosage and Administration

4.1. Dosing Considerations

Medical surveillance is required during THYMOGLOBULIN infusion.

Appropriate dosing for THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) 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.

4.2. Recommended Dose and Dosage Adjustment

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. For prophylaxis in adult renal transplant recipients the recommended dose is 1.5 mg/kg/day intravenously for at least seven days beginning intraoperatively, through 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. For vial reconstitution, dilution in infusion solution and infusion procedure, see 4.3 Reconstitution and 4.4 Administration. Investigations indicate that THYMOGLOBULIN is well tolerated and less likely to produce side effects when administered at the recommended rate. Additionally, reducing the infusion rate may minimize IAR (see 7 Warnings and Precautions, General

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 counts falls below 2,000 cells/mm^3 or platelets below 50,000 cells/mm^3.

4.3. Reconstitution

- **Parenteral Products**

Vial Size	Volume to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
10 mL	5 mL SWFI	5 mL	5 mg/mL (25 mg/5 mL)

Reconstitution:

After calculating the number of vials needed, using aseptic technique, reconstitute each vial of THYMOGLOBULIN with 5 mL Sterile Water for Injections (SWFI), immediately before use. As THYMOGLOBULIN contains no preservatives, reconstituted product should be used as soon as possible. Infusion solutions of THYMOGLOBULIN must be used as soon as possible.

1. Allow THYMOGLOBULIN vials to reach room temperature before reconstituting the lyophilized product.
2. Aseptically remove caps to expose rubber stoppers.
3. Clean stoppers with germicidal or alcohol swab.
4. Aseptically reconstitute each vial of THYMOGLOBULIN lyophilized powder with the 5 mL of SWFI
5. Rotate vial gently until powder is completely dissolved. Each reconstituted vial contains 25 mg or 5 mg/mL of THYMOGLOBULIN.

6. 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.
3. Do not mix THYMOGLOBULIN with other solutions (see 4.4 Administration for additional compatibility considerations).

4.4. Administration

The recommended route of administration is intravenous infusion using a high-flow vein; however, it may be administered through a peripheral vein. When THYMOGLOBULIN 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 THYMOGLOBULIN, heparin, and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended.

THYMOGLOBULIN should be administered through an in-line 0.22 µm filter.

Administration of antiviral prophylactic therapy is recommended. Premedication with corticosteroids, acetaminophen, and/or antihistamine one hour prior to the infusion is recommended and may reduce the incidence and intensity of side effects during the infusion (see 7 Warnings and 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.

Infusion

1. Follow the manufacturer's instructions for the infusion administration set. Infuse using a central line through a 0.22 µm 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.

Special Considerations for THYMOGLOBULIN Infusion

As with any infusion, reactions at the infusion site can occur and may include pain, swelling, and erythema.

The recommended route of administration for THYMOGLOBULIN is intravenous infusion using a high flow vein; however, it may be administered through a peripheral vein. When THYMOGLOBULIN 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 THYMOGLOBULIN, heparin, and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended.

4.5. Missed Dose

If a dose is missed, the dosing schedule should be adjusted based on the patient's clinical status and the judgment of the prescribing healthcare professional.

5. Overdose

Inadvertent overdosage of THYMOGLOBULIN may induce leukopenia (including lymphopenia and neutropenia) and thrombocytopenia, which can be managed with dose reduction. (See 4 Dosage and Administration).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) is available as sterile, lyophilized powder to be reconstituted with Sterile Water for Injections, EP.

Each package contains one 10 mL vial.

The reconstituted preparation contains approximately 5 mg/mL of THYMOGLOBULIN of which >95% 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 hours) is performed for each lot.

Ingredient/Component	Quantity per vial
Freeze Dried Powder :	
Anti-thymocyte Globulin (rabbit)	*25 mg*
Glycine	*50 mg*
Sodium Chloride	*10 mg*
D-Mannitol	*50 mg*

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 Injections, EP.

7. Warnings and 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 infusions. Infusion-associated reactions (IARs) including oxygen desaturation may occur during or following the administration of THYMOGLOBULIN and may occur as soon as the first or second infusion during a single course of THYMOGLOBULIN treatment.

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 acute IARs. 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 CRS. In rare instances, severe CRS can be fatal. (See 7 Warnings and Precautions, Immune)

Carcinogenesis and Genotoxicity

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

Dependence, Tolerance and/or Abuse Liability

THYMOGLOBULIN has not been studied for its potential to cause dependence, tolerance and/or abuse; however, there may be a theoretical risk of the occurrence of one or more of these risks. Healthcare professionals should consider the patient's history of drug use and monitor appropriately.

Driving and Operating Machinery

Given the possible adverse events that can occur during the period of THYMOGLOBULIN infusion, in particular CRS, it is recommended that patients should not drive or operate machinery during the course of THYMOGLOBULIN therapy.

Hematologic

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 THYMOGLOBULIN 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;
- Stopping THYMOGLOBULIN treatment should be considered if persistent and severe thrombocytopenia (< 50,000 cells/mm^3) occurs or leukopenia (< 2,000 cells/mm^3) develops.

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

Thrombotic Microangiopathy (TMA)

Thrombotic microangiopathy (TMA) may occur in patients treated with ATG for solid organ transplantation or hematopoietic stem cell transplantation (HSCT), particularly when concomitantly administered with calcineurin inhibitors.

Immune

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

Very rarely, fatal anaphylaxis has been reported (8.5 Post-Market Adverse Reactions). If an anaphylactic reaction occurs, 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.

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 8.5 Post-market Adverse Drug Reactions).

THYMOGLOBULIN contains a mixture primarily of antibodies to T cell antigens, but it is largely unknown which specificities mediate the alteration in immunoregulation. THYMOGLOBULIN may potentially

contain or promote undesired or harmful antibody specificities, but which may be difficult to predict, identify or to exclude.

Live vaccines should not be administered to patients about to receive, receiving, or after treatment with THYMOGLOBULIN. Concomitant administration of THYMOGLOBULIN with live virus vaccines carries a potential of uncontrolled viral replication in the immunosuppressed patient. There is insufficient information to fully define the extent of the risk, or the period of time during which the risk exists. If administered, live viruses may interfere with THYMOGLOBULIN treatment.

Skin testing is not advised prior to THYMOGLOBULIN administration.

Infection

THYMOGLOBULIN 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 THYMOGLOBULIN administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

Malignancy

Use of immunosuppressive agents, including THYMOGLOBULIN, may increase the incidence of malignancies, including lymphoma or post-transplant lymphoproliferative disease (PTLD) (See Post-market Adverse Drug Reactions). Appropriate antiviral, antibacterial, antiprotozoal, and/or antifungal prophylaxis is recommended.

Monitoring and Laboratory Tests

In some clinical studies, changes in lymphocyte subsets, including reversal of the CD4/CD8 ratio, have been observed for periods of up to 1 year after treatment with THYMOGLOBULIN (the longest duration of observation in these trials). Appropriate monitoring of lymphocyte subsets is recommended.

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 4 Dosage and Administration). THYMOGLOBULIN contains a mixture primarily of antibodies to T cell antigens, but it is largely unknown which specificities mediate the alteration in immunoregulation.

7.1. Special Populations

7.1.1. Pregnancy

Females of childbearing age should be informed of the lack of information on the risks associated with the administration of THYMOGLOBULIN during pregnancy and that adequate/appropriate contraception

is recommended, during, and for a period after treatment. Therefore, THYMOGLOBULIN should only be given to a pregnant woman if the benefits clearly outweigh the risks.

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.

7.1.2. Breastfeeding

THYMOGLOBULIN has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because other immunoglobulins are excreted in human milk, breastfeeding should be discontinued during THYMOGLOBULIN therapy.

7.1.3. Pediatrics

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 studies undertaken in Europe and data collected in the United States.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Medical surveillance is required during THYMOGLOBULIN infusion. See 2 Contraindications and 7 Warnings and Precautions, sections for serious adverse drug reactions.

THYMOGLOBULIN adverse events are generally manageable or reversible. The most frequent reported adverse events (more than 25% of patients) include: fever, chills, leukopenia, pain, headache, abdominal pain, diarrhea, hypertension, nausea, thrombocytopenia, peripheral edema, dyspnea, asthenia, hyperkalemia, tachycardia, and infection.

Serious immune-mediated reactions have been reported with the use of THYMOGLOBULIN and consist of anaphylaxis or severe cytokine release syndrome (CRS). Fatal anaphylaxis has been reported. Severe, acute infusion-associated reactions (IARs) are consistent with CRS and can cause serious cardiorespiratory events and/or death. IARs may occur as soon as the first or second infusion during a single course of THYMOGLOBULIN treatment. During post-marketing surveillance, fever, rash, arthralgia and/or myalgia have been reported to occur 5 to 15 days after onset of THYMOGLOBULIN therapy, indicating possible serum sickness. These symptoms are manageable with corticosteroid treatment. Infections, reactivation of infection, sepsis, malignancies including post-transplant lymphoproliferative disorder (PTLD) and other lymphomas as well as solid tumors have been reported after THYMOGLOBULIN administration in combination with multiple immunosuppressive agents.

Prolonged use or overdose of THYMOGLOBULIN in association with other immunosuppressive agents

may cause over-immunosuppression. During THYMOGLOBULIN therapy, monitoring the lymphocyte count may help assess the degree of T-cell depletion. WBC and platelet counts should also be monitored (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

Rare allergic reactions such as serum sickness (fever, pruritus, rash associated with arthralgia, myalgia) may occur seven to fifteen days after onset of treatment. Immediate serious allergic reactions are rare. The most frequent, as well as the most severe adverse reactions, occur following the first infusion. The mechanism of some of these adverse reactions is more likely related to a cytokine release. Premedication with corticosteroids and antihistamines decreases both incidence and severity of these adverse reactions. Reducing the infusion rate may lead to a reduction of some of these adverse reactions.

8.2. Clinical Trial Adverse Reactions

Adverse Reactions in US Phase III Study on Acute Renal Graft Rejection

THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) 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® in acute renal graft rejection, there were no significant differences in clinically significant adverse events between the two treatment groups (Table 2). Malignancies were reported in three patients who received THYMOGLOBULIN and in three 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. In the THYMOGLOBULIN group one additional patient was diagnosed with leukemia (LGL).

Table 2 Frequently Reported and Significant Adverse Events in Patients Receiving THYMOGLOBULIN or Atgam for Treatment of Acute Rejection*

Preferred Term	THYMOGLOBULIN n=82		Atgam n=81		p-value†
	No. of Patients (%)		No. of Patients (%)		
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

* Frequently reported adverse events are those reported by more than 25% of patients in a treatment group regardless of causality; 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 adverse event incidence between treatment groups.

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 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 3 Infections in Patients Receiving THYMOGLOBULIN or Atgam® for Treatment of Acute Rejection

BODY SYSTEM Preferred Term	THYMOGLOBULIN n=82			Atgam n=81			p-value†
	No. of Patients	(%)	Total Reports	No. of Patients	(%)	Total Reports	
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.

Adverse Reactions in US Phase II Prophylaxis Trial

In the phase II study for the prophylaxis of acute organ rejection, leukopenia (white blood cells <3000/mm^3) occurred almost exclusively during the induction period and more commonly among the THYMOGLOBULIN-treated patients (56.3%) than among the Atgam®-treated patients (4.2%) (p <0.0001). Lymphopenia persisted for more than 180 days in the THYMOGLOBULIN patients but resolved by day 14 in Atgam® patients (p=0.012). Thrombocytopenia was equal between groups. An additional subset analysis of 17 THYMOGLOBULIN-treated patients and 13 Atgam®-treated patients, at 22 months, showed that the long-term CD4 counts were lower for THYMOGLOBULIN (237/mm^3 versus 466/ mm^3; p=0.007). The CD4/CD8 ratio showed a tendency to be lower in the THYMOGLOBULIN group (1.6 versus 2.4; p=0.103).

Despite this, there was no difference between groups in the incidence of infections. Among recipients of THYMOGLOBULIN, 56.3% developed infection at any time during the study, compared with 75% of Atgam® recipients. The mean number of infections was 1.2 ± 1.9 versus 1.8 ± 1.9 for THYMOGLOBULIN and Atgam®-treated patients, respectively (p = NS). The incidence of CMV disease at 6 months was lower among THYMOGLOBULIN-treated patients (5 of 48, 10.4%) than among those treated with Atgam® (8 of 24, 33.3%) (p=0.025). Over 1 year, CMV disease tended to be less common among THYMOGLOBULIN-treated patients than among Atgam®-treated patients: 6 of 48 (12.5%) versus 8 of 24 (33.3%) (p=0.056). Calculation of the relative risk of development of CMV disease for the THYMOGLOBULIN group compared with the Atgam® group yielded a RR of 0.28 (95% CI, 0.10 – 0.81). This represented a 72% reduction in the incidence of CMV over the course of 1 year in recipients of THYMOGLOBULIN. Pertinently, all CMV disease reported in this study developed after discontinuation of prophylactic oral ganciclovir.

Table 4. Selected Adverse Events of Special Interest in Transplant Patients receiving Immunosuppressive Therapy: Incidence during 1 year of Follow-up.

Variable	**THYMOGLOBULIN**	**Atgam**	***p*-value**	**Overall**
Delayed graft function, n (%)	1 (2.1)	0	1.0	1 (1.4)
CMV disease, n (%)	6 (12.6)	8 (33.3)	0.0560	14 (19.4)
Malignancy, n (%)	1 (2.1)	0	1.00	1 (1.4)
Leukopenia, n (%)	27 (56.3)	1 (4.2)	<0.0001	28 (38.9)
Thrombocytopenia, n (%)	5 (10.4)	2 (8.3)	1.0	7 (9.7)
Infection, n (%)	27 (56.3)	18 (75.0)	0.196	45 (62.5)

Infections per patient				
mean ± SD	1.2 ± 1.9	1.8 ± 1.9	0.149	1.4 ± 1.7
median (range)	1 (0-7)	1.0 (0-7)	0.162*	1 (0-7)
Serious adverse events per patient				
mean ± SD	1.2 ± 2.3	1.8 ± 1.5	0.258	1.3 ± 2.0
median (range)	0 (0-11)	1.0 (0-5)	0.013*	1 (0-11)

*Wilcoxon rank sums test

8.3. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

- Decreased oxygen saturation (as part of IAR)

8.5. Post-Market Adverse Reactions

Infections and infestations

- Infection (including reactivation of infection)
- Sepsis

(See 7 Warnings and Precautions, Infection)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

- Lymphoproliferative disorder
- Lymphomas (which may be virally mediated)
- Neoplasms malignant (Solid tumors) (See 7 Warnings and Precautions, Malignancy)

Blood and lymphatic system disorders

- Febrile neutropenia
- Disseminated intravascular coagulopathy
- Coagulopathy
- Anemia

Immune System disorders

- Cytokine release syndrome (CRS) Post-marketing reports of severe CRS have been associated with cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome [ARDS], pulmonary edema, myocardial infarction, tachycardia, and/or death). (See 7 Warnings and Precautions, Immune)
- Anaphylactic reaction (See 7 Warnings and Precautions, Immune)

- Serum Sickness (including reactions such as fever, rash, urticaria, arthralgia, and/or myalgia). Serum sickness tends to occur 5 to 15 days after onset of THYMOGLOBULIN therapy. Symptoms are usually self-limited or resolve rapidly with corticosteroid treatment.

Hepatobiliary disorders

- Transaminases increased

Transient reversible elevations in transaminases without any clinical signs or symptoms have also been reported during THYMOGLOBULIN administration.

- 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).
- Hyperbilirubinemia

General disorders and administration site conditions

- Infusion related reactions (Infusion associated Reactions (IARs))

Clinical manifestations of IARs have included some of the following signs and symptoms: fever, chills/rigors, dyspnea, nausea/vomiting, diarrhea, hypotension or hypertension, malaise, rash, urticaria, and/or headache. (See 7 Warnings and Precautions, General).

- Infusion-site reactions (ISRs)

Pain, swelling, and erythema have been reported.

9. Drug Interactions

9.2. Drug Interactions Overview

Because THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) 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 10.3 Pharmacokinetics).

Pharmaceutical Incompatibilities

Based on a single compatibility study, the combination of THYMOGLOBULIN, 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, THYMOGLOBULIN should not be mixed with other medicinal products in the same infusion.

9.3. Drug-Behaviour Interactions

The interaction of THYMOGLOBULIN with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5. Drug-Food Interactions

Interactions with food and drink are unlikely.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. 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 PRA cytotoxicity assays, in particular.

10. Clinical Pharmacology

10.1. Mechanism of Action

The *in vitro* mechanism of action by which polyclonal anti-lymphocyte preparations suppress immune responses is not fully understood. THYMOGLOBULIN (Anti-thymocyte Globulin [Rabbit]) includes antibodies against T cell markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD 44, CD45, HLA-DR, HLA Class I heavy chains, and ß2 microglobulin. *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.

The *in vivo* mechanism of action of THYMOGLOBULIN is also not fully understood. The possible mechanisms by which THYMOGLOBULIN may induce immunosuppression *in vivo* include the following:

i. T cell clearance from the circulation
ii. Modulation of T cell activation, homing and cytotoxic activities

Following clinical administration of THYMOGLOBULIN, T cell depletion is promptly observed. This may result from the complement-dependent lysis in the intravascular space or the opsonization and subsequent phagocytosis by macrophages. When THYMOGLOBULIN is given with other immunosuppressive therapies, such as corticosteroids, azathioprine, cyclosporine, etc., there is a

decrease in the patient's own antibody formation. Monitoring THYMOGLOBULIN therapy reveals that T cell depletion in peripheral blood persists for several days to several weeks following cessation of THYMOGLOBULIN therapy.

THYMOGLOBULIN is a potent immunosuppressive agent that demonstrates a rapid and profound pharmacodynamic effect resulting in lower white blood cell, T cell and T cell subset counts. The magnitude and duration of lymphopenia is consistent; reductions of 83% to 92% from pre-treatment values were seen after a single dose of THYMOGLOBULIN and were sustained throughout the daily dosing period in four clinical pharmacology studies. Recovery from treatment-induced lymphocyte depletion was gradual, beginning two months after initiation of therapy, with most recovery by three months, but was not seen in all cases even at six months. T cell subsets determined by flow cytometry also demonstrate similar dramatic decreases.

10.2. Pharmacodynamics

The pharmacodynamic effects of THYMOGLOBULIN were assessed in the measurements of total lymphocytes and of lymphocyte subpopulations. Total lymphocyte values were used to assess the degree, time to induction, and duration of lymphopenia. Also assessed was the degree of lymphopenia in absolute values and percentages of lymphocyte subsets with phenotypes CD2 (T cells, sheep erythrocyte receptor), CD3 (T lymphocytes), CD4 (T cells, helper-inducer subset), CD8 (T cells, cytotoxic/suppressor subset), CD14 (monocytes), CD19 (B lymphocytes), CD25 (activated T and B lymphocytes and activated macrophages), CD56 (NK cells), and CD57 (NK cells).

The pharmacodynamic effect of THYMOGLOBULIN was demonstrated by a marked decrease in lymphocyte counts as well as nearly all subsets.

10.3. Pharmacokinetics

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 (Anti-thymocyte Globulin [Rabbit]) 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.

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

During the THYMOGLOBULIN Phase III randomized trial, of the 108 of 163 patients evaluated, no difference was seen in sensitization level to horse IgG after Atgam® (lymphocyte immune globulin anti-thymocyte [equine] sterile solution) treatment (78.5%) or to rabbit IgG after THYMOGLOBULIN treatment (69%)(p=0.4).

In a Phase II randomized trial for the prophylaxis of rejection, the assays used indicated that 6 of 48 (12%) of those receiving THYMOGLOBULIN versus 1 of 25 (4%) of those receiving Atgam® had detectable antibody to rabbit or horse immunoglobulin, respectively, prior to initiation of the study (p=0.412). The incidence of new onset sensitization was lower with THYMOGLOBULIN than with Atgam® when presensitized patients were excluded from the analysis (43% versus 78%; p=0.22). Including presensitized patients, fewer THYMOGLOBULIN patients than Atgam® patients had evidence of sensitization (51% versus 81%; p=0.031). In neither group did the presence of preformed antibody correlate with serious adverse events or effectiveness of therapy. 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 re-treatment with THYMOGLOBULIN is recommended.

11. Storage, Stability, and Disposal

- Store in refrigerator between +2°C and +8°C (36°F to 46°F). A higher temperature of ≤37°C during transport for a total excursion time of ≤10 days will do the product no harm.
- Protect from light.
- Do not freeze.
- Do not use after the expiration date indicated on the label.
- Any unused drug remaining after infusion must be discarded.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance(s): Anti-thymocyte Globulin (Rabbit)

Chemical name: L04AA04 (anti-thymocyte immunoglobulin).

Molecular formula and molecular mass: >95% monomer + dimer

Structural formula: Rabbit Gamma immune globulin >95%

Physicochemical properties: THYMOGLOBULIN (anti-thymocyte globulin [rabbit]) is a purified, pasteurized, gamma immune globulin obtained by immunization of rabbits with human thymocytes.

Gamma immune globulin or Immunoglobulins are heavy plasma proteins, often with added sugar chains on N-terminal. The variable regions of the heavy and light chains may express sites for N-linked glycosylation. For normal polyclonal IgG ~ 10 – 20% of molecules bear N-linked oligosaccharides in the variable region.

The basic unit of each antibody is a monomer. The monomer is a "Y"-shape molecule that consists of four polypeptide chains: two identical heavy chains and two identical light chains connected by disulfide bonds. Together this gives six to eight constant domains and four variable domains. Each half of the forked end of the "Y" is called a Fab fragment. It is composed of one constant and one variable domain of each the heavy and the light chain, which together shape the antigen binding site at the amino terminal end of the monomer. The two variable domains bind their specific antigens.

Pharmaceutical standard: Professed

Product Characteristics:

THYMOGLOBULIN® (Anti-thymocyte globulin [rabbit]) is a purified, pasteurized, gamma immune globulin obtained by immunization of rabbits with human thymocytes. Gamma immune globulin or Immunoglobulins are heavy plasma proteins, often with added sugar chains on N-terminal.

Detailed Pharmacology

In Vitro Pharmacology

There is evidence that THYMOGLOBULIN recognizes most of the molecules involved in the T cell activation cascade during graft rejection, such as CD2, CD3, CD4, CD8, CD11a, CD18, HLA-DR, and HLA class I. Antibodies against β2-microglobulin and CD45 can also be detected.

ATGs can, in addition to their T cell depleting effect, trigger other lymphocyte functional responses that are probably important to their immunosuppressive activity. At concentrations of 0.1 mg/mL, THYMOGLOBULIN activates T-lymphocytes (both CD4 and CD8 subsets) with synthesis of IL-2, IFN-γ, expression CD25, and subsequent proliferation. This mitogenic activity involves primarily CD2 pathway. This activation of T-lymphocytes is associated with increased expression of Fas-ligand and a corresponding increase of cells undergoing apoptosis. At higher concentrations, THYMOGLOBULIN

inhibits cell proliferative responses to other mitogens, with post-transcriptional blockade of IFN-γ and CD25 synthesis but no decrease of IL-2 secretion. Such a mechanism of action differs from those reported with corticosteroids and cyclic peptides like cyclosporine A, FK506 or Rapamycin.

THYMOGLOBULIN, *in vitro,* does not activate B cells. This lack of effect on B cell activation and subsequent differentiation into antibody-secreting cells, together with its antiproliferative activity toward lymphoblastoid and some lymphomatous B cell lines, may be responsible for a low incidence of B cell lymphomas in THYMOGLOBULIN-treated patients.

THYMOGLOBULIN has been shown to interfere with adhesion pathways in an assay measuring the binding of activated lymphocytes to renal tubular epithelial cells. THYMOGLOBULIN is, in fact, more active than a mixture of monoclonal antibodies directed at these adhesion molecules.

In Vivo Pharmacology

A number of studies, including the US Phase II Prophylaxis and the US Phase III Acute Renal Graft Rejection studies, have addressed the in vivo pharmacology of THYMOGLOBULIN. This was also examined in the study THP 01291, an open-label, prospective study conducted in 20 patients undergoing first cadaveric renal transplantation in one center. Patients were to have received THYMOGLOBULIN 1.5 mg/kg/day through a central vein for 11 consecutive days via a four-hour infusion as prophylaxis for renal graft rejection. The actual mean daily dosage was 1.27±0.23 mg/kg, which was at the lower limit of the recommended dose for that indication in France (1.25 mg/kg/day). Day 1 of the study was the day of renal transplantation; the initial THYMOGLOBULIN infusion was given just before renal transplantation. The dose was to have been reduced if the previous day's lymphocyte count was <3,000 cells/mm^3; or if the platelet count was <100,000 cells/mm^3. Concomitant therapy included corticosteroids (methylprednisone and prednisolone), cyclosporine A, and azathioprine.

Evaluations included physical examination, complete blood count (with differential), determination of lymphocyte subsets, clinical chemistry profile, determination of serum THYMOGLOBULIN (rabbit IgG) concentrations, and assessment of anti-THYMOGLOBULIN antibodies.

Table 6: Mean (±SD) Pretreatment Lymphocyte Subset Counts

and Mean (±SD) Percentage Reductions in Lymphocyte Subsets Over Time (Study THP01291)

Subset	Pretreatment Counts	Percent Reduction compared to Pretreatment Value											
		Week 1			Week 2		Week 3			Days			
		M	W	F	M	W	F	M	W	30	60	90	180
Total	1480±345	91±5	87±5	87±7	88±5	89±6	81±16	85±6	86±13	72±20	41±42	47±25	57±18
CD2	1313±313	96 ±3	95±5	97±4	98 ±2	97±3	91 ±13	92 ±4	89 ±13	78 ±21	43 ±45	51 ±26	60 ±18
CD3	1160±322	96 ±3	96±4	97±5	99 ±1	98±2	91 ±12	92 ±5	89 ±13	76 ±26	38 ±49	47 ±27	57 ±19
CD4	722±260	96 ±3	95±5	97±4	98 ±2	98±2	93±7	94 ±4	91 ±9	83 ±20	66 ±26	67 ±16	71 ±20
CD8	485±170	96 ±4	95±4	96±5	96 ±4	96±4	87 ±21	90 ±6	88 ±14	69 ±25	8 ±100	22 ±58	43 ±20
CD14	69±57	32 ±69	35 ±61	66 ±29	43 ±86	52±65	62 ±13	56 ±32	32 ±90	70 ±21	80 ±10	76 ±21	68 ±23
CD19	66±81	34 ±78	+53±109	+72±104	+66 ±81	+117±12	+58±103	+24±71	+66 ±81	+38±79	+29±95	+30±112	26 ±50

CD25	**22±15**	**75±25**	**87±8**	**74 ±20**	**73 ±20**	**78 ±17**	**70 ±28**	**37 ±47**	**87 ±1**	**78±5**	**66 ±11**	**66±5**	**--**
CD56	**202±93**	**94 ±6**	**91 ±10**	**94±5**	**93 ±8**	**93±6**	**82 ±35**	**91 ±6**	**78 ±41**	**73 ±35**	**61 ±43**	**63 ±42**	**68 ±30**
CD57	**184±132**	**90 ±20**	**86 ±21**	**94±6**	**87 ±27**	**94±5**	**82 ±37**	**92 ±5**	**89 ±14**	**52 ±101**	**+119±423**	**+84±239**	**+36±158**
M=Monday, W=Wednesday, F=Friday: Day of week samples were obtained; --=no data													

In addition to the lymphopenia noted in all patients, other hematological changes in neutrophil and platelet counts were possibly related to THYMOGLOBULIN treatment. During the first 15 days after transplantation, neutropenia (<2,500 cells/mm^3) was reported in nine patients, lasting for two consecutive days in six patients. Severe neutropenia (lowest value was 1,394 cells/mm^3) was reported in two patients; neither lasted for more than one day. In general, the effect of THYMOGLOBULIN therapy on neutrophil counts was moderate; end of treatment values were about 4,000 cells/mm^3 and remained stable over the six-month follow-up.

Only a transient relative thrombocytopenia was observed during THYMOGLOBULIN therapy. During the first 15 days post-transplantation, no patient experienced thrombocytopenia (<80,000 cells/mm^3). On average, platelets returned to baseline values by day 20.

Viral Inactivation

Human blood components (formaldehyde treated red blood cells), and thymus cells are used in the manufacturing process for THYMOGLOBULIN. Standard measures are in place to prevent infections resulting from the use of biological products prepared using human components. These include the screening of donors and individual donations for specific markers of infection and the inclusion of effective manufacturing steps for inactivation/removal of viruses. Virus removal steps (nanofiltration and purification) and a viral inactivation step (pasteurization, i.e., heat treatment of active ingredient) are performed for each lot.

Despite this, when biological 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.

14. Clinical Trials

14.1. Clinical Trials by Indication

US Phase III Study: Acute Renal Graft Rejection

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.

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 5). In Table 5, 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 the therapy.

Table 5: Response to study treatment by rejection severity and study half

Success/n	Total		First Half		Second Half	
Risk Factor: Baseline Rejection Severity:	THYMOGLOBULIN	Atgam®	THYMOGLOBULIN	Atgam®	THYMOGLOBULIN	Atgam®
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 75.5%)
Weighted estimate of difference		11.1%[a]		19.3%		-3.2%
(THYMOGLOBULIN-Atgam)						
Lower one-sided 95% confidence bound		0.07%		4.6%		-19.7%
p-value[b]		0.061[1]		0.008[2]		0.625[2]

1. one-sided stratified on rejection severity and study half

1. one-sided stratified on rejection severity

a. across rejection severity and study half

b. under null hypothesis of equivalence (Cochran-Mantel-Haenszel test)

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).

There was, however, a significant difference (p=0.05) in recurrent rejection rate between the two treatment groups. In patients treated with THYMOGLOBULIN there were six biopsy proven recurrent rejections versus 12 biopsy proven rejections in the Atgam® group.

US Phase II Study: Prophylaxis

The safety and efficacy of THYMOGLOBULIN for the prophylaxis of acute organ rejection in adult patients receiving their first kidney transplant was assessed in a randomized, prospective, controlled single center trial. The comparator was an approved lymphocyte immune globulin anti-thymocyte globulin (equine). Seventy-two consecutive patients were enrolled in the trial and randomized 2:1 to receive, in addition to standard maintenance immunosuppressive therapy (with cyclosporine, azathioprine or mycophenolate mofetil, and steroids), THYMOGLOBULIN (n=48) 1.5 mg/kg or Atgam® (n=24) 15 mg/kg. Patient demographics and concomitant immunosuppressive use were not statistically significant between the two groups. The first dose of THYMOGLOBULIN was administered intravenously (IV) during the transplant surgery and then once daily IV during the following six days for a total of 7 days of therapy. Patients were observed for at least 1 year of follow-up with a mean follow-up of 17.2 months (range 12-23 months). Endpoints were the incidence and severity of rejection, cytomegalovirus (CMV) disease, serious adverse events, graft and patient survival, delayed graft function and length of stay of the initial hospitalization. Based on intent-to-treat analysis of the data, the overall incidence of biopsy- proven acute rejection in the THYMOGLOBULIN group was 4.2% versus 25% in the Atgam® group (p=0.014). Event-free survival at one year, defined as no rejection, no death and no graft loss, was achieved by 94% of THYMOGLOBULIN patients as compared to 63% of Atgam® patients (p=0.0005).

Other Published Studies

In another published randomized, prospective controlled study, THYMOGLOBULIN prophylaxis of acute organ rejection in sensitized renal allograft recipients was compared to standard triple therapy immunosuppression (cyclosporine, azathioprine and steroids). This study, as with others in the literature, was not placebo controlled as constitutional symptoms or laboratory values related to the lymphocyte depletion of THYMOGLOBULIN prevents adequate placebo blinding of the patient or clinician respectively. All patients were sensitized, as defined as a panel reactive antibody (PRA) level of >5%. Stratification of quintiles of PRA % was performed. Demographics were not statistically different between groups. In this study, of randomized patients, 47 patients received THYMOGLOBULIN (1.25mg/kg/day over 10 days, but doses adjusted based on thrice weekly CD2 and CD3 counts) and 42 received standard triple immunosuppression. Overall, THYMOGLOBULIN-treated patients experienced a decrease in the incidence of biopsy-proven rejection episodes (38% versus 64% in control group [p=0.02]). Although all PRA% stratified groups had lower rejection rates with THYMOGLOBULIN therapy versus controls, statistical significance was reached only in the lower PRA groups (>5% to >40%). Twelve-month graft survival was also increased in the THYMOGLOBULIN group (89% versus 76%, Mantel-Cox p=0.04). THYMOGLOBULIN induced more leukopenia (43% versus 17% p=0.007), and thrombocytopenia (32 versus 17%, p=0.008). Infections were not different between groups.

A number of uncontrolled trials have also reported an evaluation of THYMOGLOBULIN therapy for the prophylaxis of acute organ rejection. Guttmann reported the use of THYMOGLOBULIN for induction therapy in 108 patients receiving cadaveric and living donor renal allografts. THYMOGLOBULIN 1.5 to 2.5 mg/kg/day for 10 days was administered as part of a quadruple sequential immunosuppression regimen with azathioprine, corticosteroids and cyclosporine. On average, patients received 6.1 days of THYMOGLOBULIN at a dose of 2 mg/kg/day. Average serum creatinine level at baseline was 877 ± 263

mmol/L, compared to 146 ± 44 mmol/L at 3 months and 136 ± 40 mmol/L at 1 year post. Graft survival at 2 and 4 years were 88.6% and 83.6%, respectively. Patient survival at 1, 2, 3, and 4 years was 96.6% for each year at risk. The incidence of acute rejection episodes was 32%. Fever was the most common adverse event, noted in 75% of patients. Other common associated side effects were mild or moderate chills (27%) and leukopenia (22%). Fever and chills typically occurred on the day of THYMOGLOBULIN administration. Leukopenia occurred during and following THYMOGLOBULIN administration and was treated with reduction in the azathioprine dose. There were 5 cases of CMV infection, of which 4 were moderate in severity and one was associated with retreatment anti-rejection therapy.

The benefits of the use of THYMOGLOBULIN outside kidney transplantation are not well studied.

16. Non-Clinical Toxicology

General toxicology

Investigational studies in animals included acute toxicology in mice and rats and subacute toxicity in monkeys. In the rodent studies, no toxicity or unscheduled deaths occurred and no gross pathology at necropsy was observed in 10 male and 10 female mice injected with 25 mg/kg iv THYMOGLOBULIN, (Anti-thymocyte Globulin [Rabbit]) and in 10 male and 10 female rats injected with 15 mg/kg IV THYMOGLOBULIN. These doses correspond to approximately 10-20 times the maximum human daily dose.

In the multi-dose subacute studies in cynomologous monkeys, 6 animals were injected with non-pasteurized THYMOGLOBULIN, 6 with pasteurized THYMOGLOBULIN, and 4 with saline control. They were infused with 20 mg/kg/day IV for 14 days which corresponds to 8 times the maximum human daily dose, and 5.3 times the maximum cumulative human dose. Toxicity was assessed by observation and by necropsy. At these high doses severe morbidity including anemia and symptoms suggestive of septicemia, and mortality (five unexpected deaths in 12 animals) were found. Since four of the animals were sacrificed early, the mortality rate may be underestimated. Immune-depressive changes which were observed were reversed after a 4-week treatment-free period. The pasteurized and non-pasteurized THYMOGLOBULIN showed equivalent immune-suppressive activity.

In addition to the acute and subacute studies in rodents, routine release tests for general safety in mice and guinea pigs and pyrogen tests in rabbits on 10 consecutive lots of THYMOGLOBULIN have all passed specifications.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTHYMOGLOBULIN®

Anti-thymocyte Globulin [Rabbit]

This Patient Medication Information is written for the person who will be taking **THYMOGLOBULIN**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **THYMOGLOBULIN**, talk to a healthcare professional.

Serious warnings and precautions box

- **THYMOGLOBULIN** should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients.
  In rare instances, serious immune-mediated reactions have been reported with the use of **THYMOGLOBULIN** and consist of anaphylaxis or severe cytokine release syndrome (CRS). CRS is a condition where the immune system releases too many substances called cytokines into the blood, which can cause serious symptoms requiring immediate medical attention.

What THYMOGLOBULIN is used for:

- treating acute kidney transplant rejection in conjunction with other medicines used to suppress the immune system.
- in the prevention of acute rejection in adult kidney transplant recipients.

How THYMOGLOBULIN works:

THYMOGLOBULIN is an immune globulin and works by suppressing the body's immune system.

The ingredients in THYMOGLOBULIN are:
Medicinal ingredient(s): Anti-thymocyte Globulin [Rabbit]

Non-medicinal ingredients: D-Mannitol, Glycine, Sodium Chloride

THYMOGLOBULIN comes in the following dosage form(s):

THYMOGLOBULIN is supplied in a powder format that is mixed by a health care professional with Sterile Water for Injection prior to administration.

Do not use THYMOGLOBULIN if:

- you ever had an allergic reaction (for example rash, itchiness, or difficulty breathing) to rabbit products.
- you ever had an allergic reaction to any ingredient in THYMOGLOBULIN.

- you have an active acute or chronic infection, which would contraindicate any additional immunosuppression.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take THYMOGLOBULIN. Talk about any health conditions or problems you may have, including if you:

- plan to drive or operate machinery
- have an acute viral illness
- had severe or acute infections in the past
- are pregnant or plan to become pregnant or are breast feeding
- plan to be vaccinated or have recently been vaccinated
- are taking other medications

Other warnings you should know about:

Medical surveillance is required during **THYMOGLOBULIN** infusion.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with THYMOGLOBULIN®:

- Live vaccines should not be administered when you are about to receive, receiving, or after treatment with THYMOGLOBULIN.
- The combination of THYMOGLOBULIN, heparin, and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended.

How to take THYMOGLOBULIN:

THYMOGLOBULIN will normally be administered by a health care professional in hospital.

Usual dose:
The recommended dosage of **THYMOGLOBULIN** (Anti-thymocyte Globulin [Rabbit]) for treatment of acute renal graft rejection is 1.5 mg/kg of body weight administered daily for 7 to 14 days. For prophylaxis in adult renal transplant recipients the recommended dose is 1.5 mg/kg/day intravenously for at least seven days beginning intraoperatively, through a high-flow vein.

Overdose:

If you think you, or a person you are caring for, have taken too much **THYMOGLOBULIN**, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you missed a **THYMOGLOBULIN** dose, contact your doctor.

Possible side effects from using THYMOGLOBULIN:

These are not all the possible side effects you may have when taking **THYMOGLOBULIN**. If you experience any side effects not listed here, tell your healthcare professional.

These side effects may include:

- Fever
- Chills
- Low white blood cells
- Pain
- Headache
- Abdominal pain
- Diarrhea
- High blood pressure
- Nausea
- Bleeding
- Bruising
- Fatigue
- Tiredness
- Low platelets
- Swelling of your hands, ankles, feet, or legs
- Shortness of breath
- Unusual weakness
- High potassium levels in the blood
- Rapid heartbeat
- Infection

Other possible side effects include:

- Anemia (low red blood cells or hemoglobin)
- Hyperbilirubinemia (increased bilirubin levels in the blood).
- Damage to the smallest blood vessels known as thrombotic microangiopathy (TMA).

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		[Stop taking this drug and get immediate medical help] OR [Get immediate medical help]
	Only if severe	In all cases	
Common			
Fever		✓	
Shivering		✓	
Shortness of breath, difficulty breathing, wheezing or coughing		✓	
Feeling or being sick		✓	
Dizzy or feeling faint		✓	
Tiredness		✓	
Muscle or joint pain		✓	
Rash		✓	
Headache		✓	
Bleeding or bruising more easily		✓	
Irregular or fast heartbeat		✓	
Symptoms of infection such as fever, chills, sore throat, mouth ulcers		✓	
Diarrhea		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

You will not be asked to store your medicine. THYMOGLOBULIN will be stored in a refrigerator between +2°C and +8°C (36°F to 46°F). Protect from light. Do not freeze.

If you want more information about THYMOGLOBULIN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sanofi.com/en/canada, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

Date of Authorization: 2026-01-22