AUSTRALIAN PRODUCT INFORMATION – THYMOGLOBULINE (ANTI-THYMOCYTE GLOBULIN [RABBIT]) POWDER FOR SOLUTION FOR INFUSION

1 NAME OF THE MEDICINE

Anti-thymocyte globulin [rabbit], rATG).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains rabbit antithymocyte immunoglobulin (rATG) 25 mg.

Solution reconstituted with 5 mL water for injection contains a nominal rabbit anti-human thymocyte immunoglobulin (rATG) concentration of 5 mg/mL. The reconstituted solution must be diluted with 0.9% sodium chloride injection (USP/EP) or 5% glucose solution prior to intravenous administration.

For the full list of excipients, see section 6.1. LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

Thymoglobuline is a sterile creamy white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Thymoglobuline (rabbit anti-human thymocyte immunoglobulin) is indicated for the prophylaxis of graft rejection in renal transplantation; treatment of steroid-resistant or moderate to severe renal transplant rejection; and treatment of refractory or relapsing aplastic anaemia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Preparation and Administration Instructions: Use Aseptic Techniques

Thymoglobuline must always be used under strict medical supervision and prescribed by physicians with experience in using immunosuppressive agents. The dosage depends on the indication, the administration regimen and the combination with other immunosuppressive agents. The following dosage may be used as a reference. Treatment can be discontinued without gradual tapering of the dose.

The recommended route of administration is intravenous infusion using a high-flow vein; however, it may be administered through a peripheral vein. When Thymoglobuline is administered through a peripheral vein, concomitant use of heparin and hydrocortisone in an infusion solution of 0.9% sodium chloride may minimise the potential for superficial

thrombophlebitis and deep vein thrombosis. The combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES).

Administration of antiviral prophylactic therapy is recommended. Premedication with corticosteroids, antipyretic agents, and/or antihistamine 1 hour prior to the infusion is recommended and may reduce the incidence and intensity of side effects during the infusion. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: 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.

Renal Transplantation

Prophylaxis of Graft Rejection in Renal Transplantation: 1 to 1.5 mg/kg/day for 3 to 9 days after transplantation corresponding to a cumulative dose of 3 to 13.5 mg/kg.

Treatment of Steroid-Resistant or Moderate to Severe Renal Transplant Rejection: 1.5 mg/kg/day for 7 to 14 days after transplantation of a kidney, corresponding to a cumulative dose of 10.5 to 21 mg/kg.

Dose Modifications

Obese Patients: For obese patients dosing should be based on ideal weight rather than actual weight.

Paediatric and Elderly Patients: The dosage recommendations in the paediatric population (infants, children and adolescents) and elderly patients are the same as for adults.

Renal and Hepatic Impairment: In view of the PK and metabolism no dose adjustment is necessary in patients with hepatic and/or renal impairment.

Aplastic Anaemia

Treatment of Relapsing or Refractory Aplastic Anaemia: 2.5 to 3.75 mg/kg/day for 5 consecutive days, corresponding to a cumulative dose of 12.5 to 18.75mg/kg.

Dose Modifications

Paediatric and Elderly Patients: The dosage recommendations in the paediatric population (infants, children and adolescents) and elderly patients are the same as for adults.

Renal and Hepatic Impairment: In view of the PK and metabolism no dose adjustment is necessary in patients with hepatic and/or renal impairment.

Preparation and Administration Instructions: Use Aseptic Technique

Thymoglobuline is usually administered in the context of a therapeutic regimen combining multiple immunosuppressive agents. It is recommended to administer pre-medication with intravenous corticosteroids and antihistamines prior to infusion of rabbit anti-human thymocyte immunoglobulin. Anti-pyretic agents (e.g. paracetamol) may also increase the tolerability of the initial infusion.

Thymoglobuline is for intravenous infusion, is supplied as a sterile lyophilised powder for injection. Each Thymoglobuline vial is intended for single use administration only. The nominal content of the 10mL vial is 25mg of the active substance rabbit anti-human thymocyte immunoglobulin.

A volume of 5mL water for injection is required to reconstitute the finalised product in the 10mL vial to give a nominal rabbit anti-human thymocyte immunoglobulin concentration of 5mg/mL. The reconstituted Thymoglobuline solution is further diluted with 0.9% sodium chloride injection (USP/EP) or 5% glucose solution prior to intravenous administration.

1. Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose.

   Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

2. Reconstitute each vial by slowly injecting 5mL of sterile water for injection to the inside wall of each vial. Each reconstituted vial will yield 5mg/mL or 25mg of Thymoglobuline. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilised cake. Tilt and roll each vial gently. Do not invert, swirl, or shake.

3. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discolouration. The solution is clear or slightly opalescent. Inspect solution for particulate matter after reconstitution. Should some particulate matter remain, continue to gently rotate the vial until no particulate matter remains. If upon inspection particulate matter remains or if the solution is discoloured do not use.

4. Withdraw the calculated volume of Thymoglobuline from the appropriate number of vials and transfer the contents of the calculated number of Thymoglobuline vials into the bag of infusion solution (0.9% sodium chloride or 5% glucose solution). Recommended volume: per 1 vial of Thymoglobuline use 50mL of infusion solution (total volume usually between 50 to 500mL).

5. Gently invert or massage the infusion bag to mix. Do not shake. To reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C-8°C for no more than 24 hours. Protect from light.

6. 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.

To minimise inadvertent administration of particulate matter from reconstitution it is recommended that Thymoglobuline is administrated through a 0.22 µm in-line filter. Thymoglobuline should not be infused in the same intravenous line with other products.

Infuse slowly into a high-flow vein; Thymoglobuline may also be administered through a peripheral vein (refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Preparation and Administration Instructions: Use Aseptic Techniques). Adjust the infusion rate so that the total duration of infusion is not less than 4 hours. Refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS sections for advice about the management of any adverse events associated with infusion.

4.3 CONTRAINDICATIONS

Thymoglobuline is contraindicated in patients with hypersensitivity to rabbit proteins or to any of the excipients listed in Section 6.1.

Thymoglobuline is also contraindicated for patients with acute or chronic infections, which would contraindicate any additional immunosuppression.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Appropriate dosing for Thymoglobuline is different from dosing for other anti-thymocyte globulin (ATG) products, as protein composition and concentrations vary depending on the source of ATG used. Physicians should therefore exercise care to ensure that the dose prescribed is appropriate for the ATG product being administered.

Thymoglobuline should be used under strict medical supervision in a hospital setting. Patients should be carefully monitored during the infusion. Infusion-Associated Reactions (IARs) may occur following administration of Thymoglobuline and may occur as soon as the first or second infusion during a single course of Thymoglobuline treatment. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of IARs. Additionally, reducing the infusion rate may minimise many of these IARs. Premedication with antipyretics, corticosteroids and/or antihistamines may decrease both the incidence and severity of these adverse reactions. Rapid infusion rates have been associated with case reports consistent with cytokine release syndrome. In rare instances, severe cytokine release syndrome can be fatal.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobuline and consist of anaphylaxis or severe cytokine release syndrome. Very rarely, fatal anaphylaxis has been reported (See Section 4.8 ADVERSE EFFECTS). If an anaphylactic reaction occurs, the infusion should be terminated immediately and appropriate emergency treatment should be initiated. Any further administration of Thymoglobuline to a patient who has had a history of anaphylaxis to Thymoglobuline is not recommended.

Severe, acute IARs are consistent with cytokine release syndrome, which is attributed to the release of cytokines by activated monocytes and lymphocytes. In rare instances, these reported reactions are associated with serious cardio-respiratory events and/or death (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS).

Infection

Thymoglobuline is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral and protozoal), reactivation of infection (particularly CMV) and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases these infections have been fatal. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

Haematological Effects

Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments. When thrombocytopenia and/or leukopenia are not part of the underlying disease or associated with the condition for which Thymoglobuline is being administered, the following dose reductions are suggested:

- A reduction in dosage must be considered if the platelet count is between 50,000 and 75,000 cells/mm^3 or if the white cell count is between 2,000 and 3,000 cells/mm^3,
- Stopping Thymoglobuline 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 Thymoglobuline therapy.

Malignancy

Use of immunosuppressive agents, including Thymoglobuline, may increase the incidence of malignancies including lymphoma or lymphoproliferative disorders (which may be virally mediated). These events have sometimes been associated with fatal outcome, lymphoma or post-transplant lymphoproliferative disease (PTLD) (See Section 4.8 ADVERSE EFFECTS).

Thrombotic Microangiopathy

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.

Immunisations

The safety of immunisation with attenuated live vaccines following Thymoglobuline therapy has not been studied; therefore, immunisation with attenuated live vaccines is not recommended for patients who have recently received Thymoglobuline.

Use in the elderly

For renal transplantation, studies obtained from the literature did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

In the treatment of aplastic anaemia, a retrospective analysis by the European Bone Marrow Transplant demonstrated that ATG treatment in older patients was effective and maintains a positive benefit/risk balance, though greater care should be taken in its administration and in the monitoring of the patients. The response rate was not significantly different in 664 patients <60 and 127 patients >60.

Paediatric use

The safety and effectiveness of Thymoglobuline in paediatric 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 clinical trials.

Effects on laboratory tests

In the French post marketing study (00PTF01) 240 patients were followed up daily for 2 weeks, on day 30 and at 1 year for routine biological tests, to make clinical assessment of patient and graft functioning and note any adverse events. Table 1 below details the percentage of patients with haematological events.

Table 1 - Haematological Events (n = 240)

Events	Patients n (%)	Discontinuations as a result (n)
Thrombocytopenia < 80 x 10^9/L	34 (14%)	-
(severe) Thrombocytopenia < 50 x 10^9/L	7 (3%)	4
Neutropenia < 2.5 x 10^9/L	121 (50%)	-

Events	Patients n (%)	Discontinuations as a result (n)
(moderate) Neutropenia < 1.5 x 10^9/L	32 (13%)	-
(severe) Neutropenia < 0.8 x 10^9/L	6 (2%)	6

The incidence of severe neutropenia was 2%, and that of severe thrombocytopenia was 3%. These haematological events led to reduction of Thymoglobuline dosage, discontinuation of Thymoglobuline or/and switch to Lymphoglobuline. Thymoglobuline dosage adaptation was carried out by monitoring of lymphocyte counts with consequent dosage adjustment. There were 12 patients (0.5%) who switched from Thymoglobuline to Lymphoglobuline. In half the cases, the reason for the switch was known and was mostly rash and/or fever. In most of the remaining 6 patients, there was either a neutropenia (<1.5 x 10^9/l) or a thrombocytopenia (<80 x 10^9/l) noted on the switch day or preceding day, which was likely to be the cause of the switch. Thymoglobuline has shown to have potential risk of transient alterations in various coagulation analyses.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed. Interactions with food and drink are unlikely.

Thymoglobuline has not been shown to interfere with any routine clinical laboratory tests which use immunoglobulins. Thymoglobuline may interfere with rabbit antibody-based immunoassays and with cross - match or panel - reactive antibody cytotoxicity assays. Thymoglobuline may interfere with ELISA tests.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies to assess the effect on fertility of Thymoglobuline have not been conducted.

Use in pregnancy (Category C)

Thymoglobuline should not be used during pregnancy. It is not known whether Thymoglobuline can cause fetal harm or affect reproduction capacity.

Thymoglobuline has not been studied in labour or delivery.

Animal reproduction studies have not been conducted with Thymoglobuline. Drugs of this class are known to cross the feto-placental barrier, and Thymoglobuline may cause immunosuppressive effects in the fetus, or other unknown effects.

Use in lactation

Thymoglobuline 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, breast feeding should be discontinued during Thymoglobuline therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In the French post marketing study (00PTF01) the number of patients suffering from adverse events associated with Thymoglobuline administration is thought to be related to its use. All such adverse reactions were transient, resolved spontaneously and had no clinical consequences. These IARs given in Table 2 below were assumed to be temporally related to the infusion or due to Thymoglobuline administration unless another cause was given by the investigator.

Table 2 - Infusion - Associated Reactions

Infusion Associated Reactions (occurring during the period of infusion)	**Adverse Event Patients** n=240 (%)
Fever (> 38.5°C)	131 (55)
Fever 2 consecutive days	39 (16)
Rash	28 (12)
Arthralgia	18 (11)
Shivering	21 (9)
Diarrhoea	18 (8)
Vomiting	20 (8)
Nausea	19 (8)
Myalgia	14 (6)
Pruritus	12 (5)
Dyspnoea	6 (3)
Dysphagia	8 (3)
Hypotension	4 (2)
Trismus (temporo-mandibular pain and stiffness)	3 (1)

From the Phase III US study (n = 163) there were no clinical significant differences between the safety profiles of Thymoglobuline compared to Atgam for the treatment of acute rejection episodes after kidney transplantation. Thymoglobuline adverse events were in general more manageable or reversible compared to Atgam. During the 1 year follow - up both groups reported 3 malignancies each and included two PTLDs for each treatment group. The results are summarised in Table 3 below.

Table 3 - Frequently Reported and Significant Adverse Events

Preferred Term	Thymoglobuline N=82		ATGAM N=81		p-value†
Frequently Reported Events	No. of Patients (%)		No. of Patients (%)		
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
Diarrhoea	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 oedema	28	(34.1)	28	(34.6)	1.0
Dyspnoea	23	(28.0)	16	(19.8)	0.271
Asthenia	22	(26.8)	26	(32.1)	0.495
Hyperkalaemia	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 AEs are those reported by more than 25% of patients in a treatment group regardless of causality; significant AEs are those where the incidence rate differed between treatment groups by a significant level of 0.05.
† p-value comparing treatment groups using Fisher's exact test
§ Statistically significant differences in AEs incidence between treatment groups

Infections occurring in both treatment groups during the 3 month follow - up are summarised in Table 4 below. No significant differences were seen between the Thymoglobuline and Atgam treatment groups for all types of infections and the incidence of CMV infection was also equivalent in both groups. (Viral prophylaxis was by the centre's discretion during antibody treatment, but all centres used gancyclovir infusion during treatment).

Table 4 - Infections in Patients Receiving Thymoglobuline or Atgam for Treatment of Acute Rejection

Body System Preferred Term	Thymoglobuline N=82 No. of Patients (%) Total Reports	ATGAM N=81 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

Body System Preferred Term	Thymoglobuline N=82 No. of Patients (%) Total Reports	ATGAM N=81 No. of Patients (%) Total Reports	P value†
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	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 infection incidences between treatment groups using Fisher's exact test

Immunogenicity

It is expected that the introduction of a xeno - protein, such as Thymoglobuline will induce an immune response, even in the immunosuppressed patient. A study was conducted by Regan to quantify the degree of sensitisation following Thymoglobuline therapy. Serum samples were obtained from 163 patients participating in a multicentre double - blind randomised phase III trial comparing Thymoglobuline and Atgam where 80 of the patients received Thymoglobuline in the treatment of biopsy proven acute rejection of a first or second renal allograft. Antibodies were detected in 68% of the patients treated with Thymoglobuline. It is reported that of the 9 patients for whom full - time course serum samples were available and developed a specific antibody response, seven developed a response by day 7 and the remaining 2 at the next time point.

Adverse events due to immunosuppression

Infections, reactivation of infection, febrile neutropenia and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In rare instances, malignancies including but not limited to lymphoproliferative and other lymphomas (which may be virally mediated) as well as solid tumours have been reported. These events have sometimes been associated with fatal outcome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). These adverse events were always associated with a combination of multiple immunosuppressive agents.

Post-Marketing Experience

Infections and infestations

Infections (including reactivation of infections)

Sepsis

Neoplasms benign, malignant and unspecified

Lymphomas (which may be virally mediated)

Lymphoproliferative disorder, neoplasms malignant (solid tumours)

Blood and lymphatic system disorders

Coagulopathy

Febrile neutropenia, Disseminated intravascular coagulopathy, Anaemia

Immune System Disorder

- Cytokine release syndrome (CRS)–post-marketing reports of severe CRS have been associated with cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome, pulmonary oedema, myocardial infarction, tachycardia and/or death)
- Anaphylactic reactions (including very rare instances of fatal anaphylactic reactions)
- Serum sickness–including reactions such as fever, rash, urticaria, arthralgia and/or myalgia. Serum sickness tends to occur 5-15 days after onset of Thymoglobuline 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 Thymoglobuline administration.

Hepatocellular injury, hepatotoxicity, hepatic failure, Hyperbilirubinaemia

General disorders and administration site conditions

Infusion associated reactions (IARs)–clinical manifestations of IARs have included some of the following signs and symptoms: fever, chills/rigors, dyspnoea, nausea/vomiting, diarrhoea, hypotension or hypertension, malaise, rash, urticarial, decreased oxygen saturation and/or headache.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Inadvertent overdoses of Thymoglobuline may induce leucopoenia (including lymphopenia and neutropenia) and thrombocytopenia.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmaco-therapeutic group: Immunosuppressive agents, ATC code: L04AA04.

Mechanism of action

Rabbit anti-human thymocyte immunoglobulin is an immunosuppressive agent (mostly acting on T lymphocytes). Lymphocyte depletion probably constitutes the primary mechanism of the immunosuppression induced by rabbit anti-human thymocyte immunoglobulin. This depletion is both peripheral and central; peripheral lymphocyte depletion can be detected as early as 24 hours after the first infusion. Lymphocyte counts generally start to rise as soon as Thymoglobuline is discontinued.

Lymphocyte depletion was shown to occur *in vitro* by a number of different mechanisms (e.g. apoptosis, complement dependent lysis and antibody dependent cytotoxicity). *In vivo* apoptosis of lymph node lymphocytes was observed in monkeys treated with Thymoglobuline.

In addition to the T cell depletion, Thymoglobuline also has effects on dendritic cells (causing apoptosis) and on B and NK cells. Anti-proliferative activity against B-cells and certain lymphoblastoid cell lines has also been demonstrated *in vitro*. This effect may be partially protective against the development of post-transplant lymphoproliferative disease (PTLD).

Thymoglobuline also has activity against a number of cell surface epitopes (e.g. CD3, CD7, CD8, CD20, CD32 and CD28), binding to them and causing down modulation. The epitopes targeted include those involved in the immune response, in apoptosis, and in signal transduction, and include epitopes for many haematopoietic cell types. In particular, Thymoglobuline has activity against both leucocyte and endothelial cell adhesion molecules (e.g. CD11a, CD18, CD44, CD54 and LPAM 1) which in animal studies has shown to reduce tethering of leucocytes to the endothelium.

Effector cells are thus unable to migrate through the endothelium to the graft. This effect may also, in theory, reduce ischaemia-reperfusion injury by allowing better flow through the microcirculation. The combination of T depletion and down modulation of adhesion molecules results in interference with multiple pathways by which rejection occurs.

The exact mechanism of action of ATGs in the treatment of aplastic anaemia is unknown. Aplastic anaemia is caused by an autoimmune process resulting in destruction of trilineage

cells in the bone marrow, but sparing some CD34+ stem cells. If the autoimmune process can be halted, the stem cells can regenerate all three blood lineages. The mechanism of action of Thymoglobuline may be through depleting T cells and by preventing their activation as well as by eliminating clonal expansion of cytotoxic T cells in patients with Aplastic anaemia.

Clinical trials

Renal Transplantation

Prophylaxis of Graft Rejection in Renal Transplantation

US Phase II Study: Prophylaxis

The safety and efficacy of Thymoglobuline for the prophylaxis of acute organ rejection in adult patients receiving their first kidney transplant was assessed in a randomised, prospective, controlled single centre trial. The comparator was an approved lymphocyte immune globulin anti-thymocyte globulin (equine). 72 consecutive patients were enrolled in the trial and randomised 2:1 to receive, in addition to standard maintenance immunosuppressive therapy (with cyclosporine, azathioprine or mycophenolate mofetil, and steroids), Thymoglobuline (n = 48) 1.5 mg/kg/day or Atgam (n = 24) 15 mg/kg/day.

Patient demographics and concomitant immunosuppressive use were not statistically significant between the two groups. The first dose of Thymoglobuline was administered intravenously (IV) during the transplant surgery and then once daily IV during the following 6 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 hospitalisation. Based on intent-to-treat analysis of the data, the overall incidence of biopsy proven acute rejection in the Thymoglobuline group was 4% versus 25% in the Atgam group ($p = 0.014$) at 1 year. Event-free survival at one year, defined as no rejection, no death and no graft loss, was achieved by 94% of Thymoglobuline patients as compared to 63% of Atgam patients ($p = 0.0005$).

The summary efficacy results from the comparator trials between Thymoglobuline and Atgam was found to be statistically significant with respect to the number of rejections, the number of steroid-resistant rejections, and graft survival. A higher graft survival and lower rejection rate was seen in the Thymoglobuline treatment arm compared to patients treated with Atgam. The patient survival of 85% at 5 years in the Hardinger analysis is comparable to the data published for the EU population of 83.1-84.4% [European Renal Association Annual Report 2002]. When combined with equivalent triple immunosuppression therapies, no statistically significant difference was seen in the primary endpoints between Thymoglobuline and the other 3 study drugs investigated: Basiliximab, ATG-Fresenius and OKT3.

Patient survival at 12 months reported by Mourad and Lebranchu was comparable to levels reported for the EU population [European Renal Association Annual Report 2002]. Patient survival at 5 years was reported by Hardinger et al. (2004) and again is comparable to the EU population and lower.

Treatment of Steroid-Resistant or Moderate to Severe Renal Transplant Rejection

A review of the published literature demonstrates the efficacy of Thymoglobuline for the treatment of rejection in renal transplantation.

4 pivotal studies were identified (Midtvedt 2003, Mariat 1998, Gaber 1998 and Alamartine 1994) all of which were comparator controlled. No controlled studies without a comparator were identified. Treatment for renal rejection endpoints included graft function (drop in serum creatinine levels), acute rejection episodes, graft survival and finally patient survival. Efficacy results from the 4 comparator controlled clinical trials are discussed. The most recent study from 1996 to 1999 (Midtvedt 2003) involved sensitised patients treated where no difference in efficacy was seen between Thymoglobuline and OKT3 on the basis of serum creatinine levels, graft failure, graft function and total deaths. The study included an analysis of T cell levels in patients before and after therapy and it is noted that the number of serum T cells was lower in the Thymoglobuline patients after treatment than in the OKT3 patients ($p<0.05$). The format of the Mariat study (1998) was similar, although patients were treated at an early period (1992-1995).

US Phase III Study: Acute Renal Graft Rejection

A controlled, double-blind, multicentre, randomised clinical trial comparing Thymoglobuline and Atgam was conducted at 25 US transplant centres in renal transplant patients (n = 163) with steroid-resistant Grade I (mild), with biopsy-proven Banff Grade II (moderate) or Grade III (severe). This clinical trial rejected the null hypothesis that Thymoglobuline was more than 20% less effective in reversing acute rejection than Atgam. The overall weighted estimate of the treatment difference (Thymoglobuline-Atgam success rate) was 11.1% with a lower 95% confidence bound of 0.07%. Therefore, Thymoglobuline was at least as effective as Atgam in reversing acute rejection episodes. In the study, patients were randomised to receive 7 to 14 days of Thymoglobuline (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 (Thymoglobuline 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 the therapy.

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

Success/n	Total		First Half		Second Half	
	Thymoglobuline	Atgam	Thymoglobuline	Atgam	Thymoglobuline	Atgam
Risk Factor: Baseline Rejection Severity:						
Mild	9/10	5/8	5/5	1/3	4/5	4/5
Moderate	44/58	41/58	22/26	22/32	22/32	19/26
Severe	11/14	8/14	6/8	3/8	5/6	5/6
Overall	64/82	54/80	33/39	26/43	31/43	28/37
Weighted estimate of difference (Thymoglobuline – Atgam)	11.1%[a]		19.3%		-3.2%	
Lower one-sided 95%	0.07%		4.6%		-19.7%	
Confidence bound 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 (Thymoglobuline 93%, n = 82 and Atgam 96%, n = 80), (iv) day 30 and (v) one year post-rejection graft survival (Thymoglobuline 83%, n = 82; Atgam 75%, n = 80).

There was however, a significant difference (p = 0.039) in recurrent rejection rate between the two treatment groups. In patients treated with Thymoglobuline there were 6 biopsy proven recurrent rejections versus 12 biopsy proven rejections in the Atgam group.

Thymoglobuline was reported by Alamartine (1994) as providing inferior graft survival than OKT3 (p = 0.05). Graft survival rates in the Thymoglobuline treatment arm in the study were poorer than those seen in the more recent study by Mariat (1998).

Treatment of Refractory or Relapsing Aplastic Anaemia

The patient population studied in the Di Bona (1999) study was a group of patients with severe disease and a poor prognosis. Thirty adults and children (17 males, 13 females, median age 21 years, range 2-67 years), suffering from severe or very severe aplastic anaemia, who did not respond to a first course of equine ALG and remained transfusion dependent were studied. All the patients had been given the same initial therapy that consisted of Lymphoglobuline (same dose, for all patients), cyclosporine and G-CSF, given over 90 days.

Thymoglobuline (3.5 mg/kg/day from day 1 to day 5) was combined with a standard dose of cyclosporine (5 mg/kg/day), and 24 / 30 patients received G-CSF (5 µg/kg/day for 3 months). The response defined as transfusion independence, was achieved in 77%

(23/30) patients, after a median time of 95 days. This response rate is quite remarkable, considering that these patients failed to respond to the first course of Lymphoglobuline. The response rate of patients to re-treatment with Thymoglobuline was similar to the response rate of patients initially treated by Lymphoglobuline. The range of response time (14-377 days) was wide. Transfusion independence was observed in 90% of the patients in the first year after treatment. However, the blood cell count often remained subnormal. Only 30% of the patients (9/30) achieved a complete response after a median time of 61 days (range 14-196) defined by a neutrophil count $\geq 2.0 \times 10^9$/l, haemoglobin ≥ 11 g/dl and platelets $\geq 100 \times 10^9$/l. Fourteen other patients (47%) achieved a partial remission, and their response was significantly delayed, in comparison with complete responders occurring after a median period of 150 days (range 23-377 days, $p = 0.04$). Response was sustained in these patients. No relapses have been reported. However, at the last observation, only 30% (7/23) of the responders were not receiving any drug, after a mean period of 27 months (range 9-34 months) since the last transfusion. Most patients continued cyclosporine with or without tailored dosage of G-CSF. This long lasting treatment may explain the absence of relapses. The actuarial survival was 93%: 100% for responders and 71% for non-responders, based on the median follow-up time of 2.5 years. This survival rate compares well with figures reported by Frickhofen (2003); the actuarial survival of all patients treated with Lymphoglobuline at 41 months was 64% when combined with cyclosporine.

5.2 PHARMACOKINETIC PROPERTIES

Following the first infusion of 1.25 mg/kg of Thymoglobuline (in kidney transplant recipients), total serum rabbit IgG levels of between 10 and 40 µg/ml are obtained. The serum levels decline steadily until the following infusion with an estimated elimination half-life of 2-3 days. There has been shown to be a relationship between dose given and total Thymoglobuline levels.

The trough rabbit IgG levels increase progressively reaching 23 to 170 µg/ml at the end of an 11-day course of treatment. A gradual decline is subsequently observed following discontinuation of treatment with rabbit anti-human thymocyte immunoglobulin. However, total rabbit IgG remains detectable in 81% of patients at 2 months. Active Thymoglobuline (that is IgG which is available to bind to human lymphocytes and which causes the desired immunological effects) has a less noticeable relationship with dose given, and disappears from the circulation faster, with only 12% of patients having detectable active Thymoglobuline levels at day 90.

The incidence of sensitisation to rabbit IgG peaked in approximately 70% of subjects, at days 21-30. However, in most cases, immunisation develops within the first 15 days of treatment initiation. Patients presenting with immunisation show a faster decline in total but not active rabbit IgG levels.

However, since there are many idiotypic specificities in the polyclonal antibody (pAb) preparation, the clinical relevance of these data is uncertain.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies to assess the mutagenic potential of Thymoglobuline have not been conducted.

Carcinogenicity

Studies to assess the carcinogenic potential of Thymoglobuline have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glycine 50mg
Mannitol 50mg
Sodium chloride 10mg.

6.2 INCOMPATIBILITIES

Based on a single compatibility study, the combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended. In the absence of additional pharmaceutical incompatibility data, Thymoglobuline should not be mixed with other medicinal products in the same infusion.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store Thymoglobuline under refrigeration at 2°C–8°C. Do not freeze or shake. Do not use Thymoglobuline after the expiration date on the vial.

This product contains no preservatives. The diluted solution should be used immediately in order to prevent microbial contamination. If not used immediately, the diluted solution should be stored refrigerated at 2°C–8°C. Storage after dilution should not exceed 24 hours from the time of preparation to the completion of administration unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in a 10mL Type 1 glass vial. The vials are closed with a siliconised stopper with Teflon coating on the non-product contact side and an aluminium seal with plastic flip off cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Thymoglobuline is a purified, pasteurised, gamma immune globulin obtained by immunisation of rabbits with human thymocyte suspensions derived from human paediatric thymus fragments that are surgical waste during cardiac surgery. The manufacture of Thymoglobuline involves a series of intricate processes. 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 variable region. In the SDS-polyacrylamide gel electrophoresis, under non-reducing condition the molecular weight of the bands obtained from Thymoglobuline were calculated to be about 155,000 Daltons. 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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

18 July 2008

10 DATE OF REVISION

02 February 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of Anti-Thymocyte Globulin and Thrombotic Microangiopathy in special warnings and precautions

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