AUSTRALIAN PRODUCT INFORMATION – ATGAM® (EQUINE ANTITHYMOCYTE IMMUNOGLOBULIN)

1. NAME OF THE MEDICINE

Equine antithymocyte immunoglobulin.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL ampoule of ATGAM contains 250 mg of horse gamma globulin (equine antithymocyte immunoglobulin) stabilised in 0.3 molar glycine to a pH of approximately 6.8 (pH range 6.4 – 7.2).

ATGAM is the purified, concentrated and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunised with human thymus lymphocytes.

Before release for clinical use, each ATGAM lot is tested for its ability to inhibit rosette formation between human peripheral lymphocytes and sheep red blood cells *in vitro*. The potency of lots may vary over a twelve-fold range. The clinical significance of this is unknown.

ATGAM is not solely anti-human thymocyte globulin.

ATGAM is likely to contain low levels of antibodies against other formed elements of the blood and also other antibodies raised by the horse in response to prior antigenic exposure. These may include pertussis, tetanus, influenza, mycobacterium, equine encephalomyelitis or strangles.

During processing, the drug is adsorbed with human erythrocyte stroma and with IgG-free human plasma proteins to reduce or remove antibodies against human red blood cells and human plasma proteins. Each lot is tested before release to assure that antibody activity against platelets is within acceptable limits. Each lot of ATGAM must also test negative for anti-human serum protein antibody and anti-glomerular basement membrane before release.

No preservative or antimicrobial agent added.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection. To be diluted prior to intravenous infusion.

ATGAM is a transparent to slightly opalescent, colourless to light brown solution. It may develop a slight granular or flaky deposit during storage.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ATGAM is indicated for renal transplant patients in whom reduction of peripheral T-lymphocyte function as measured by rosette-forming cell assay could be desirable.

During controlled clinical trials, this immunosuppression has been demonstrated in renal allograft recipients treated with ATGAM. When it was administered prophylactically with conventional immunosuppressive therapy, ATGAM delayed the onset of the first rejection episode, and when it was administered at the time of the first rejection, ATGAM resolved the acute rejection episode more frequently than did conventional therapy alone.

4.2 Dose and method of administration

Dosage

Renal-allograft recipients

Delaying the onset of allograft rejection

The recommended dose is 15 mg/kg daily for 14 days, then on alternate days for 14 days for a total of 21 doses in 28 days. The first dose should be administered within 24 hours before or after the transplant.

Treatment of rejection

The first ATGAM dose can be delayed until the diagnosis of the first rejection episode. The recommended dose is 10 to 15 mg/kg daily for 14 days. Additional alternate-day therapy up to a total of 21 doses may be given.

Usually, ATGAM is used concomitantly with azathioprine and corticosteroids, which are commonly used to suppress the immune response. Exercise caution during repeat courses of ATGAM; carefully observe patients for signs of allergic reactions.

Adult renal allograft patients have received ATGAM 10 to 30 mg/kg of body weight daily. The few children studied received 5 to 25 mg/kg daily. ATGAM has been used to delay the onset of the first rejection episode and at the time of the first rejection episode. Most patients who received ATGAM for the treatment of acute rejection had not received it starting at the time of transplantation.

Method of administration

For intravenous infusion.

Skin testing

To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients before commencing treatment **is strongly recommended**. A conservative, conventional approach would first employ epicutaneous (prick) testing with undiluted ATGAM. If the subject does not show a wheal ten minutes after pricking, proceed to intradermal testing with 0.02 mL of a 1:1000 v/v (volume/volume) saline dilution of ATGAM with a separate saline control injection of similar volume. Read the result at 10 minutes: a wheal at the ATGAM site 3 mm or larger in diameter than that at the saline control site (or a positive prick test) suggests clinical sensitivity and an increased possibility of a systemic allergic reaction should the drug be used intravenously.

In the presence of a locally positive skin test to ATGAM, serious consideration to alternative forms of therapy should be given. The risk to benefit ratio must be carefully weighed. If therapy with ATGAM is deemed appropriate following a locally positive skin test, treatment should be administered in a setting where intensive life support facilities are immediately available and a physician familiar with the treatment of potentially life threatening allergic reactions is in attendance.

A systemic reaction such as generalised rash, tachycardia, dyspnoea, hypotension, or anaphylaxis precludes an additional administration of ATGAM.

Note: The predictive value of this test has not been clinically proven. Allergic reactions to ATGAM can occur in the presence of a negative skin test. Also, skin testing done as described above will not predict for later development of serum sickness. See Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects).

Preparation of solution for infusion

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. As ATGAM is a gamma globulin product, undiluted and diluted ATGAM are transparent to slightly opalescent, colourless to light brown, which may develop a slight granular of flaky deposit during storage.

ATGAM should be diluted for intravenous infusion in an inverted bottle or bag of sterile vehicle, so that the undiluted ATGAM does not contact the air inside.

Undiluted and diluted ATGAM should not be shaken. Excessive foaming and/or denaturation of the protein may occur. Diluted solutions should be gently rotated or swirled prior to use.

Add the total daily dose of ATGAM to an inverted bottle or bag of one of the following sterile intravenous diluents.

- 0.9% sodium chloride solution
- 5% glucose and 0.225% sodium chloride solution
- 5% glucose and 0.45% sodium chloride solution.

The recommended concentration of the diluted ATGAM is 1 mg/mL in the sterile vehicle. The concentration should not exceed 4 mg of ATGAM per mL.

Adding ATGAM to glucose-only solutions is not recommended as low salt concentrations can cause precipitation. Highly acidic infusion solutions can also contribute to physical instability over time.

ATGAM should not be kept in a diluted form for more than 24 hours (including actual infusion time). To reduce microbiological hazard use should be as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C. Total time in dilution should not exceed 24 hours.

Diluted ATGAM should be at room temperature before infusion. ATGAM is appropriately administered into a vascular shunt, arterial venous fistula or a high-flow central vein using an in-line filter with a pore size of 0.2 to 1.0 micron. The inline filter should be used with all intravenous infusions to prevent the inadvertent administration of any insoluble material that may develop in the undiluted product during storage. The infusion volume of the diluted solution should take into consideration factors such as patient's haemodynamic status, age, and weight. Following administration, it is recommended to flush the intravenous line.

Following dilution, ATGAM is intended for intravenous use and administration via a high-flow central vein is preferred. The use of high-flow veins will minimise the occurrence of phlebitis and thrombosis.

Do not infuse a dose of ATGAM in less than 4 hours.

Always keep a tray containing adrenaline, antihistamines, corticosteroids, syringes and an airway at the patient's bedside while ATGAM is being administered. Always keep appropriate resuscitation equipment at the patient's bedside while ATGAM is being administered.

Monitor the patient continuously for possible allergic reactions throughout the infusion (see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects)).

Dosage adjustment

Elderly (≥65 years of age)

In general, the dose for an elderly patient should be selected with caution, usually starting at the low end of the dosage range (see Section 4.4 Special warnings and precautions for use, Use in the elderly (≥65 years of age)).

4.3 Contraindications

Do not administer ATGAM to a patient who has had a severe systemic reaction (e.g., anaphylactic reaction) during prior administration of ATGAM or any other equine gamma globulin preparation.

4.4 Special warnings and precautions for use

Anaphylaxis/skin testing

Treatment with ATGAM should be discontinued if anaphylaxis occurs.

To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients before commencing treatment is strongly recommended (see Section 4.2 Dose and method of administration, Method of administration, Skin testing and See Section 4.8 Adverse effects (undesirable effects), Management of adverse effects for further information on the treatment of these adverse effects.

Transmission of infectious diseases

In common with products derived from, or purified with equine and human blood components, the possibility of transmission of infectious diseases, including viral hepatitis, human immunodeficiency virus (HIV - the causative agent for AIDS or acquired immuno-deficiency syndrome), and theoretically, the Creutzfeldt-Jakob disease (CJD) agent must always be considered, and should be conveyed to patients who may receive the product.

All infections suspected to have been transmitted by this product should be reported by healthcare professionals. See Section 4.8 Adverse effects (undesirable effects), Reporting of suspected adverse effects.

The patients should be monitored for concurrent infection. Also see subsection heading, Infections, later in this section.

Specialised administration and medical facilities

Only physicians experienced in immunosuppressive therapy should use ATGAM.

Patients who receive ATGAM should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. Patients should be carefully monitored during and after therapy with ATGAM for adverse events. Treatment of the adverse events should be instituted in accordance with local guidelines.

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of ATGAM. Clinical signs associated with anaphylaxis, other infusion associated reactions and serum sickness and associated symptoms such as rash, arthralgia, pyrexia, chills, and pain have been reported (see Section 4.8 Adverse effects (undesirable effects)).

Based on the mechanism of action of ATGAM, there is a potential risk of cytokine release syndrome, which can be fatal.

A systemic reaction such as a generalised rash, tachycardia, dyspnoea, hypotension or anaphylaxis precludes any additional administration of ATGAM (see Section 4.2 Dose and method of administration, Method of administration, Skin testing).

Thrombocytopenia and neutropenia

Because ATGAM is an immunosuppressive agent ordinarily given with corticosteroids and anti-metabolites, patients should be monitored carefully for signs of leucopenia, thrombocytopenia or concurrent infection.

Treatment with ATGAM may exacerbate thrombocytopenia and neutropenia. Consider discontinuing therapy if severe and unremitting thrombocytopenia or leucopenia occurs.

See Section 4.8 Adverse effects (undesirable effects), Management of adverse effects for further information on the treatment of these adverse effects.

Traceability

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

Infections

Monitor patients carefully for concurrent infection as in rare cases these can be fatal. Due to the nature of the immunosuppressive effects of ATGAM, opportunistic infections (bacterial and fungal) are very common. Sepsis has also been reported. There is an increased risk of viral reactivation (e.g., cytomegalovirus (CMV) infection, Epstein-Barr virus (EBV) infection, herpes simplex virus (HSV)). If infection occurs, appropriate adjunctive therapy should be instituted promptly. The physician should decide whether or not to continue therapy with ATGAM depending on clinical circumstances.

Antibodies to horse globulin

Despite concurrent immunosuppressive agents, a number of ATGAM-treated patients have developed antibodies to horse globulin. There is inadequate experience to determine the

efficacy and safety of repeated courses of ATGAM for rejection crises, and its use in these circumstances should be undertaken only with great care.

Concomitant use of vaccines

The safety and effectiveness of immunisation with vaccines and treatment with ATGAM have not been studied. Vaccination is not recommended in conjunction with ATGAM therapy as the effectiveness of the vaccines could be reduced. The prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to immunosuppressive therapy. Additionally, patients on immunosuppressive therapy should be carefully assessed to determine suitability to receive live vaccines.

Use in renal and hepatic impairment

Specific clinical studies have not been performed to assess the effect of renal or hepatic impairment on the pharmacokinetics of ATGAM.

Use in the elderly (≥65 years of age)

Clinical experience in a limited number of elderly patients (≥65 years of age) has not identified differences in responses between the elderly and younger patients. In general, the dose for an elderly patient should be selected with caution, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group (refer to Section 4.2 Dose and method of administration, Dosage adjustment, Elderly (≥ 65 years old).

Paediatric use

Experience in children is limited. ATGAM has been administered safely to a small number of paediatric renal, liver and bone marrow allograft recipients and aplastic anaemia patients at dosage levels comparable to those in adults.

Effects on laboratory tests

In patients with aplastic anaemia and other haematologic abnormalities who have received ATGAM, abnormal test results of liver function and renal function have been observed.

4.5 Interactions with other medicines and other forms of interactions

Corticosteroids and other immunosuppressants

When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to ATGAM may appear. Under these circumstances, monitor patients especially closely during and after therapy with ATGAM.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Administration of ATGAM to cynomolgus monkeys (*Macaca fascicularis*) at doses comparable to those used in clinical studies was not associated with impairment of male or female fertility.

Use in pregnancy – Pregnancy Category C

ATGAM was not teratogenic in rats or monkeys.

ATGAM was not embryotoxic, fetotoxic, or teratogenic in rats, at doses up to 50 mg/kg/day. However, an increase in hypoplastic cervical vertebrae was observed in rat fetuses at ATGAM doses of 100 mg/kg/day administered during organogenesis.

In cynomolgus monkey (Macaca fascicularis) reproduction studies, ATGAM was embryotoxic and fetotoxic. Maternal toxicity was observed with anti-thymocyte globulin (equine) ATGAM doses of 20 mg/kg/day after 14 days of dosing with maternal deaths occurring at doses of 40 mg/kg/day. Fetal deaths occurred in dams treated with 20 mg/kg/day during the first part of organogenesis, but not in dams treated during the latter part of organogenesis. The maternal and fetal deaths were attributed to maternal anaemia due to red blood cell antigen that humans do not share. Therefore, this toxicity is not considered relevant to human fetal development.

ATGAM has not been evaluated in pregnant women. There is a limited amount of data from the use of ATGAM in pregnant women. The outcome of pregnancies cannot be determined. It is also not known whether ATGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ATGAM should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during and up to 10 weeks after cessation of therapy.

Use in lactation

ATGAM has not been evaluated in lactating women. It is not known whether ATGAM is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse effects in breastfed neonates and infants from ATGAM, a decision should be made whether to discontinue breastfeeding or to discontinue the drug taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed. Given the potential adverse reactions that may be experienced (e.g., dizziness, convulsion, confusional state, syncope), caution should be taken when driving or using machinery while on this medication (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The primary clinical experience with ATGAM has been in renal allograft patients who were also receiving concurrent standard immunosuppressive therapy (azathioprine, corticosteroids).

Clinical trials

In controlled trials, the very commonly reported adverse events (occurring in greater than 10% of patients) are pyrexia (45 - 60%), chills (15 - 30%), leucopenia (30 - 50%), thrombocytopenia (44 - 52%), dermatological reactions such as rash, pruritis, urticaria, wheal and flare (15 - 25%).

Adverse events reported in patients treated with ATGAM during clinical trials are presented below. Adverse events are listed by MedDRA System Organ Class and Preferred Term.

System Organ Class	Frequency of >10%	Frequency of >1% to <10%	Frequency of <1%
Infections and infestations			Localised infection Herpes simplex Encephalitis Systemic infection
Blood and lymphatic system disorders	Leucopenia Thrombocytopenia		Lymphadenopathy
Immune system disorders			Anaphylactic reaction Serum sickness
Metabolism and nutrition disorders			Hyperglycaemia
Psychiatric disorders			Agitation
Nervous system disorders		Headache	Dizziness Syncope Seizure Paraesthesia
Eye disorders			Periorbital oedema
Cardiac disorders			Tachycardia
Vascular disorders		Thrombophlebitis Hypotension	Hypertension Iliac vein occlusion
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Hiccups Laryngospasm Pulmonary oedema Pleural effusion
Gastrointestinal disorders		Diarrhoea Nausea Vomiting Stomatitis	Abdominal pain upper
Skin and subcutaneous tissue disorders	Rash Urticaria Pruritus Wheal and flares	Night sweats	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		Arthralgia Back pain	Myalgia
Renal and urinary disorders			Renal artery thrombosis Proteinuria
General disorders and administration site conditions	Pyrexia Chills	Chest pain Infusion site pain	Asthenia Oedema Malaise
Injury, poisoning and procedural complications		Arteriovenous fistula thrombosis	Wound dehiscence

Medical events similar to those listed above have been reported in patients receiving ATGAM for reasons other than prevention of renal allograft rejection.

Post-marketing experience

Adverse events reported in patients receiving ATGAM and not listed above by MedDRA System Organ Class and Preferred Term are listed below. Because events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Infections and infestations: Hepatitis viral, sepsis, Epstein-Barr virus infection, cytomegalovirus infection.

Blood and lymphatic system disorders: Neutropenia, granulocytopenia, eosinophilia, anaemia, pancytopenia, haemolysis, haemolytic anaemia.

Psychiatric disorders: Confusional state, disorientation.

Nervous system disorders: Dyskinesia, tremor.

Cardiac disorders: Bradycardia, congestive heart failure.

Vascular disorders: Deep vein thrombosis, vasculitis.

Respiratory, thoracic and mediastinal disorders: Cough, epistaxis, apnoea, oropharyngeal pain.

Gastrointestinal disorders: Abdominal pain, gastrointestinal haemorrhage, gastrointestinal perforation, oral pain.

Skin and subcutaneous tissue disorders: Hyperhidrosis.

Musculoskeletal and connective tissue disorders: Rigidity, pain in extremity, flank pain.

Renal and urinary disorders: Acute kidney injury, kidney enlargement.

Congenital, familial and genetic disorders: Aplasia.

General disorders and administration site conditions: Infusion site swelling, infusion site erythema.

Investigations: Renal function test abnormal, liver function test abnormal.

Injury, poisoning and procedural complications: Kidney rupture.

Management of adverse effects

The recommended management for some of the adverse effects that could occur during treatment with ATGAM are outlined below.

Anaphylaxis

Anaphylaxis is uncommon but serious and may occur during therapy with ATGAM. If this condition does occur, infusion of ATGAM should be discontinued immediately; 0.3 mL aqueous adrenaline (1:1000 dilution) should be administered intramuscularly along with steroids, respiration should be assisted and other resuscitative measures provided. DO NOT resume therapy with ATGAM.

Haemolysis

Haemolysis can usually be detected only in the laboratory. Fulminant haemolysis has been reported rarely. Appropriate treatment of haemolysis often includes transfusion of erythrocytes; if necessary, administer intravenous mannitol, frusemide, sodium bicarbonate, and fluids. Severe and unremitting haemolysis may necessitate discontinuation of therapy with ATGAM.

Thrombocytopenia and leucopenia

Thrombocytopenia and leucopenia are usually transient. Platelet and white cell counts generally return to adequate levels without interrupting therapy and with transfusions. If thrombocytopenia and leucopenia become severe, it may be helpful to decrease the dose of concomitant immunosuppressant (particularly azathioprine). If after one or two days the situation does not improve, the dose of ATGAM may also be reduced (see Section 4.4 Special warnings and precautions for use).

Respiratory distress

Respiratory distress may indicate an anaphylactoid reaction. Infusion of ATGAM should be discontinued. If distress persists, antihistamine, adrenaline, methylprednisolone, or some combination of the three should be administered.

Pain in chest, flank or back

Pain in the chest, flank or back may indicate anaphylaxis or haemolysis. Treatment is the same as for respiratory distress or, if haemolysis has occurred, the see Haemolysis as listed in this section above.

Hypotension

Hypotension may indicate anaphylaxis. Infusion of ATGAM should be discontinued and blood pressure stabilised with pressors if necessary.

Chills and pyrexia

Chills and pyrexia occur in most patients receiving ATGAM. ATGAM may release endogenous leucocyte pyrogens. Prophylactic and/or therapeutic administration of antihistamines or corticosteroids generally controls this reaction.

Chemical phlebitis

Chemical phlebitis can be caused by infusion of ATGAM through peripheral veins. This often can be avoided by administering the infusion solution into a high-flow vein. A subcutaneous arterialised vein produced by a Brescia fistula is also a useful administration site.

Itching and erythema

Itching and erythema probably result from the effect of ATGAM on blood elements. Antihistamines generally control the symptoms.

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

Because of its mode of action and because it is a biological substance, the maximum tolerated dose of ATGAM would be expected to vary from patient to patient. To date, the largest single daily dose administered to one patient (renal transplant recipient) was 7,000 mg administered at a concentration of approximately 10 mg/mL of saline, seven times the recommended total dose and infusion concentration. In this patient, administration of ATGAM was not associated with any signs of acute intoxication or late sequelae.

The greatest number of doses (10 to 20 mg/kg/dose) that can be administered to a single patient has not yet been determined. Some renal transplant patients have received up to 50 doses in 4 months, and others have received 28-day courses of 21 doses followed by as many as 3 more courses for the treatment of acute rejection. The incidence of toxicological manifestations did not increase with any of these regimens, however close monitoring of the patient is recommended.

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

Caution: ATGAM is available only to hospital units which are equipped and staffed for transplant surgery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

ATGAM is a lymphocyte-selective immunosuppressant as demonstrated by its reduction in the peripheral circulation of thymus-dependent T-lymphocytes that form rosettes with sheep erythrocytes. This anti-lymphocyte effect is believed to reflect an alteration of the function of the T-lymphocytes, which are responsible in part for cell-mediated immunity and are involved in humoral immunity. In addition to its anti-lymphocyte activity, ATGAM contains low concentrations of antibodies against other formed elements of blood. In rhesus and cynomolgus monkeys, ATGAM reduces lymphocytes in the thymus-dependent areas of the spleen and lymph nodes. It also decreases the circulating sheep-erythrocyte rosetting lymphocytes that can be detected, but ATGAM does not cause severe lymphopenia.

In general, when ATGAM is given with other immunosuppressive therapy, such as anti-metabolites and corticosteroids, the patient's own antibody response to horse gamma globulin is minimal.

Immunogenicity

Antibody against horse IgG was assessed in two clinical studies performed in renal transplant patients treated with ATGAM; 2 out of 22 patients (9%) and 10 out of 27 patients (37%) showed detectable levels of anti-horse IgG antibodies. The potential of neutralising antibodies in renal transplant patients is unknown and its clinical significance has not been established.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Distribution

During infusion of 10 to 15 mg/kg/day, the mean peak value (n=27 renal transplant patients) was found to be 727±310 micrograms/mL.

Biotransformation/Elimination

In a small clinical study, ATGAM administered with other immunosuppressive therapy and measured as horse IgG had a serum half-life of 5.7 $\pm$ 3 days. The range for half-life was 1.5 to 13 days.

5.3 Preclinical safety data

In the routine development of ATGAM, aliquots of the various clinical lots have been infused intravenously to either Macaca rhesus or Macaca irus monkeys. Two dosage regimens have been used: 100 mg/kg on day 0, 200 mg/kg on day 2 and 400 mg/kg on day 4 or, currently, 50 mg/kg on days 0, 2, 4 and 7. A three week observation period has followed the last infusion in either dosage regimen. These studies do not fully explore the toxicological potential of ATGAM.

The observed changes could have been anticipated on the basis of the anti-lymphocyte activity with ATGAM. Within 24 hours after infusion, decreased peripheral blood lymphocytes and increased total leukocyte and neutrophil counts occurred. Decreased thymus size with involution or atrophy or both and decreased lymphocyte populations in the thymus-dependent areas of the spleen and lymph nodes were noted. The atrophy was most prevalent in animals that received the higher doses.

In animals receiving either dosage regimen, packed cell volume, total erythrocyte counts, and haemoglobin concentrations have decreased, and reticulocytes and nucleated erythrocytes have increased enough to be classified as anaemia. An occasional death believed to have resulted from anaemia has occurred.

Transient decreases in blood platelet counts have also occurred. Thrombus formation occurred frequently along the routes of infusion, i.e., the saphenous and femoral veins. However, the incidence of thrombi has decreased since inline filters have been used during infusion. In these animals no evidence of DIC (disseminated intravascular coagulation) has appeared.

Genotoxicity

Non-clinical data reveal no special hazard identified for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Carcinogenicity

Carcinogenicity and pre-/post-natal development studies have not been conducted on ATGAM.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Hydrochloric acid
Sodium hydroxide

Water for injections.

6.2 Incompatibilities

Adding ATGAM to glucose-only solutions is not recommended as low salt concentrations can cause precipitation. Highly acidic infusion solutions can also contribute to physical instability over time.

ATGAM must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and method of administration, Method of administration, Infusion instructions.

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

Before dilution

Store at 2°C to 8°C. Refrigerate. Do not freeze. To protect from light, keep the ampoule in the carton until use.

After dilution

To reduce microbiological hazard, use should be as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C. Total time in dilution should not exceed 24 hours, including infusion time.

6.5 Nature and contents of container

ATGAM is available in 5 mL type 1 glass ampoules in packs of 1 or 5 ampoules.

Not all pack sizes are supplied.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

No data available.

CAS number

No data available.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000.

Toll Free Number: 1800 675 229.
www.pfizermedicalinformation.com.au.

9. DATE OF FIRST APPROVAL

2 August 1991.

10. DATE OF REVISION

17 January 2024.

® Registered trademark.

Summary table of changes

Section changed	Summary of new information
4.2	Addition of recommendations for concentration and infusion volumes
4.4	Updated information regarding concomitant use of Atgam with vaccines
4.6	Updated preclinical data for fertility, pregnancy Warning to use effective contraception during and up to 10 weeks after stopping therapy.
4.8	Adverse events listed by MedRA SOC and preferred term
5.1	Potential of neutralising antibodies and clinical significance in renal transplant patients.
5.2	Peak plasma level of horse immunoglobulin and mean peak value and half life range
5.3	Updated preclinical data for genotoxicity
All	Minor editorial changes throughout the document