

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ATGAM[®] 250 mg/5 mL concentrate injection for infusion.

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 of 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.

ATGAM contains no preservatives or antimicrobial agents.

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

3. PHARMACEUTICAL FORM

Concentrate 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 the management of allograft rejection, including delay of onset of first rejection episode, in patients who have undergone renal transplantation.

4.2 Dose and method of administration

Dose

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.

Dosage adjustments

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)).

Method of administration

Concentrate injection. To be diluted prior to 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 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. Because ATGAM is a gamma globulin product, undiluted and diluted ATGAM are transparent to slightly opalescent, colourless to light brown, and may develop a slight granular or 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.

ATGAM (diluted and undiluted) 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 to effect thorough mixing.

Add the total daily dose of ATGAM to one of the following sterile intravenous diluents.

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

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.

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

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 (including infusion time) should not exceed 24 hours.**

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.

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 (not supplied) with a pore size of 0.2 to 1.0 micron. The in-line filter should be used with all intravenous infusions to prevent the inadvertent administration of any insoluble

material that may develop in the product during storage. Infusion volumes of 250 mL to 500 mL may be used. 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.

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.

Monitor the patient continuously throughout the infusion for possible allergic reactions (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). Always keep appropriate resuscitation equipment at the patient's bedside while ATGAM is being administered.

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 section 4.8 Undesirable effects), Management of adverse effects for further information on the treatment of the adverse effect).

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.

No cases of transmission of viral diseases or CJD have been associated with the use of ATGAM.

All infections suspected to have been transmitted by this product should be reported by healthcare professionals. See section 4.8 Undesirable effects, Reporting of suspected adverse reactions.

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 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 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.

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 (also refer to section 4.2 Dose and method of administration, Dosage adjustments, Elderly (≥65 years of age)).

Paediatric population

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 Interaction with other medicines and other forms of interaction

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

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 (see section 5.3 Preclinical safety data).

Pregnancy

Australian Pregnancy Category C.

ATGAM was not teratogenic in rats or monkeys. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). These effects are not considered relevant to humans.

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.

Lactation

In animal studies, ATGAM was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys (*Macaca fascicularis*). 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 breast-fed neonates and infants from ATGAM, a decision should be made whether to discontinue breast-feeding 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 Undesirable effects).

4.8 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 following adverse effects were reported:

Frequency of >5%

Fever (45 - 60%), chills (15 - 30%), leucopenia (30 - 50%), thrombocytopenia (44 - 52%), dermatological reactions such as rash, pruritis, urticaria, wheal and flare (15 - 25%).

Frequency of >1% to <5%

Arthralgia, chest or back pain or both, clotted A/V fistula, diarrhoea, dyspnoea, headache, hypotension, nausea or vomiting or both, night sweats, pain at the infusion site, peripheral thrombophlebitis, stomatitis.

Frequency of <1%

Anaphylaxis, dizziness, agitation, weakness or faintness, oedema, herpes simplex reactivation, hiccoughs or epigastric pain, hyperglycaemia, hypertension, iliac vein obstruction, laryngospasm, localised infection, lymphadenopathy, malaise, myalgia, paraesthesia, possible serum sickness, possible encephalitis, pleural effusions, pulmonary oedema, periorbital oedema, renal artery thrombosis, proteinuria, seizures, systemic infection, tachycardia, toxic epidermal necrosis, 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

In post-marketing experience, the frequency of adverse effects in voluntary reported cases is as follows:

Frequency of >10%

Fever (51%), chills (16%), thrombocytopenia (30%), leucopenia (14%), rashes (27%), systemic infection (13%).

Frequency of >5 to <10%

Abnormal renal function tests, serum sickness-like symptoms, dyspnoea/apnoea, arthralgias, chest, back and flank pain, diarrhoea and nausea and/or vomiting.

Frequency of <5%

Hypertension, herpes simplex infection, pain, swelling or redness at infusion site, eosinophilia, headache, myalgias or leg pains, hypotension, anaphylaxis, tachycardia, bradycardia, oedema, localised infection, malaise, seizures, GI bleeding or perforation, deep vein thrombosis, sore mouth-throat, hyperglycaemia, acute renal failure, abnormal liver function tests, confusion or disorientation, cough, neutropenia or granulocytopenia, anaemia, thrombophlebitis, dizziness, epigastric or stomach pain, lymphadenopathy, pulmonary oedema or congestive heart failure, abdominal pain, nosebleed, vasculitis, aplasia or pancytopenia, abnormal involuntary movement or tremor, rigidity, sweating laryngospasm/oedema, haemolysis or haemolytic anaemia, viral hepatitis, faintness, enlarged or ruptured kidney, paraesthesias, renal artery thrombosis, syncope.

Frequency not known (cannot be estimated from the available data)

Sepsis, Epstein-Barr virus infection, cytomegalovirus infection.

Management of adverse effects

The recommended management for some of the adverse effects that could occur during treatment with ATGAM follows:

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, see Haemolysis 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 fever

Chills and fever 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Because of its mode of action and because it is a biological substance, the maximal tolerated dose of ATGAM sterile solution 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 Sodium Chloride Injection, USP, approximately 7 times the recommended total dose and infusion concentration. In this patient, administration of ATGAM was not associated with any signs of acute intoxication.

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.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressive agents, ATC Code L04AA03.

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; 9% to 37% of treated patients show 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.

5.2 Pharmacokinetic properties

Distribution

During infusion of 10 to 15 mg/kg/day, the peak plasma level of horse immunoglobulin was seen after 5 days of treatment. The mean peak value (n=27 patients) was found to be 727 ± 310 micrograms/mL.

Biotransformation/Elimination

The half-life of horse immunoglobulin after ATGAM infusion was found to be 5.7 ± 3.0 days in one group of recipients. 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.

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.

Pregnancy

ATGAM was not embryotoxic, fetotoxic, or teratogenic in rats, after doses similar to doses used in humans. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium hydroxide
Hydrochloric acid
Water for Injections.

6.2 Incompatibilities

Adding ATGAM to dextrose only injections 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, Preparation of solution for infusion.

6.3 Shelf life

36 months.

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. for a maximum of 24 hours (including infusion time).

6.5 Nature and contents of container

Glass ampoules. 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

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.

Toll Free Number: 0800 736 363.
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

23 May 1985.

10. DATE OF REVISION OF THE TEXT

11 November 2022.

® Registered trademark.

Summary table of changes

Section changed	Summary of new information
2	pH range for Atgam
4.2	Instruction to keep resuscitation equipment handy. Update to infusion volumes and concentration of diluted solution for infusion.
4.4	Patients monitoring for AE during and after therapy. Symptoms for anaphylaxis, other infusion associated reactions and serum sickness. Cytokine release syndrome can be fatal. Opportunistic bacterial and fungal infections and increased risk of viral reactivations extending to EBV infection and HSV. Concomitant use of Atgam with vaccines not recommended
4.6	Warning to use effective contraception during and up to 10 weeks after stopping therapy.
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, fertility, pregnancy
4.8	New AE - sepsis, Epstein-Barr virus infection, cytomegalovirus infection.
All	Minor editorial changes