NEW ZEALAND DATA SHEET

1. PRODUCT NAME

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ATGAM is available in 5 mL ampoules containing 250 mg/5 mL equine antithymocyte immunoglobulin (antithymocyte immunoglobulin 50 mg/mL (equine)).

Each ampoule of ATGAM contains 250 mg of horse gamma globulin stabilised in 0.3 molar glycine to a pH of approximately 6.8. The product contains no preservatives.

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated injection. For intravenous use only.

ATGAM is a transparent to slightly opalescent aqueous protein solution, colourless to faintly pink or brown and nearly odourless. It may develop a slight granular or flaky deposit during storage. For information about inline filters, see section 4.2 Dose and method of administration, Preparation of infusion solution.

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).

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 sections 4.4 and 4.8).

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, it can be transparent to slightly opalescent, colourless to light brown, and may develop a slight granular of flaky deposit during storage.

Dilute ATGAM in saline solution before intravenous infusion. Invert the IV bottle of saline so the undiluted ATGAM does not contact the air inside. Ideally the concentration should not exceed 4 mg of ATGAM per mL of saline.

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

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

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

During clinical trials, most investigators chose to infuse ATGAM into a vascular shunt, arteriovenous fistula or a high-flow central vein through 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 product during storage.

Using 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.

Observe the patient continuously for possible allergic reactions throughout the infusion (see section 4.8).

Diluted or undiluted 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.

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

Treatment with ATGAM should be discontinued if any of the following occurs:

- Anaphylaxis
- Severe or unremitting thrombocytopenia
- Severe or unremitting leucopenia.

See section 4.8, Management of Adverse Effects for further information on the treatment of these adverse effects.

Skin testing

To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients before commencing treatment is **strongly** recommended (see section 4.2, Method of administration, Skin testing).

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. Some studies have suggested an increase in the incidence of cytomegalovirus infection in patients receiving ATGAM.

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.

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 have been reported (see section 4.8). Based on the mechanism of action of ATGAM, there is a potential risk of cytokine release syndrome.

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

Immunosuppression

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.

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. Some studies have suggested an increase in the incidence of cytomegalovirus infection in patients receiving ATGAM. 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.

Live-virus vaccines

Live-virus vaccines may not replicate successfully and antibody response could be reduced when the vaccine is administered after immune globulin administration. Live-virus vaccines should ideally be administered six months after therapy with intravenous immune globulin.

Effects on liver and renal function tests

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

Use in the elderly

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.

Paediatric population

Experience with children has been 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.

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, observe patients especially carefully during therapy with ATGAM.

4.6 Fertility, pregnancy and lactation

Fertility

In monkey reproduction studies, maternal toxicity was observed with ATGAM. While the aetiology of this toxicity is uncertain, it may be attributed to haemolytic anaemia due to cross-reactivity of ATGAM to a monkey red blood antigen.

Pregnancy

Australian Pregnancy Category C.

ATGAM has not been evaluated in pregnant women. It is also not known whether ATGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ATGAM administration to pregnant women is not recommended and should be considered only under exceptional circumstances.

An increase in hypoplastic cervical vertebrae was observed in rat foetuses administered ATGAM during organogenesis.

In monkey reproduction studies, maternal toxicity was observed with ATGAM, including maternal deaths. Fetal deaths occurred in dams treated during the first part of organogenesis, but not in dams treated during the latter part of organogenesis. The aetiology of this maternal and fetal toxicity is uncertain, and it may be attributed to haemolytic anemia due to cross-reactivity of ATGAM to a monkey red blood antigen not present in humans.

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 nursing neonates and infants from ATGAM, a decision should be made whether to discontinue nursing 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).

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.

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).

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 a 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.

5.2 Pharmacokinetic properties

Distribution

During infusion of 10mg/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 12 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/Carcinogenicity

Mutagenicity and carcinogenicity studies have not been conducted with ATGAM.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium hydroxide
Hydrochloric acid
Water for Injections.

6.2 Incompatibilities

Adding antithymocite globulin (equine) to dextrose injections is not recommended as low salt concentrations can cause precipitation. Highly acidic infusion solutions can also contribute to physical instability over time.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Before diliution

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 packs of 5 ampoules.

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.

9. DATE OF FIRST APPROVAL

23 May 1985.

10. DATE OF REVISION OF THE TEXT

09 April 2021.

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Summary table of changes

Section changed	Summary of new information
6.4	Instructions to keep ampoule in carton until use to protect from light.