

ATGAM[®]

Lymphocyte Immune Globulin, Antithymocyte Globulin (Equine)

For intravenous use only

DESCRIPTION

ATGAM is a transparent to slightly opalescent aqueous protein solution, colourless to faintly pink or brown and nearly odourless, containing 50mg per ml antithymocyte globulin. ATGAM is the purified, concentrated and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunised with human thymus lymphocytes. . It may develop a slight granular or flaky deposit during storage. (For information about inline filters, see Infusion Instructions).

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 absorbed 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 antihuman serum protein antibody and antiglomerular basement membrane before release.

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.

CLINICAL AND ANIMAL PHARMACOLOGY

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 antilymphocyte 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 antilymphocyte 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 antimetabolites and corticosteroids, the patient's own antibody response to horse gamma globulin is minimal. In a small clinical study, ATGAM administered with other immunosuppressive therapy and measured as horse IgG had a serum half-life of 5.7 ± 3 days.

Pharmacokinetics

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. 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.

ANIMAL TOXICOLOGY

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 antilymphocyte 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.

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.

CONTRAINDICATIONS

ATGAM should not be administered to a patient who has previously had a severe systemic reaction to it or any other equine gamma globulin preparation.

WARNINGS

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

1. Anaphylaxis
2. Severe and unremitting thrombocytopenia
3. Severe and unremitting leukopenia.

<p>In common with products derived from, or purified with, human blood components, the possibility of transmission of infectious diseases including viral hepatitis and human immunodeficiency virus (HIV - the causative agent for AIDS or acquired immunodeficiency syndrome) must always be considered, and should be conveyed to patients who may receive the product.</p>
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PRECAUTIONS

Only physicians experienced in immunosuppressive therapy should use ATGAM.

Patients who receive ATGAM should be managed in facilities equipped with adequate laboratory and supportive medical resources.

Because ATGAM is an immunosuppressive agent ordinarily given with corticosteroids and antimetabolites, patients should be monitored carefully for signs of leucopenia, thrombocytopenia or concurrent infection. In common with products derived from, or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind.

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.

Dilution of ATGAM in glucose infusion solutions is not recommended, as low salt concentrations may result in precipitation. The use of highly acidic infusion solutions is also not recommended because of possible physical instability over time.

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.

Use in children

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.

Use in pregnancy and lactation

ATGAM has not been evaluated in pregnant or lactating women. Animal reproduction studies have not been conducted with ATGAM. It is also not known whether ATGAM can cause foetal 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. 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 reactions in nursing infants from ATGAM Sterile Solution caution should be exercised when ATGAM is administered to a nursing woman.

ADVERSE EFFECTS

The primary clinical experience with ATGAM has been in renal allograft patients who were also receiving concurrent standard immunosuppressive therapy (azathioprine, corticosteroids). In controlled trials, investigators frequently reported the following adverse reactions: fever in 45 - 60% of patients; chills in 15 - 30%; leukopenia in 30 - 50%; thrombocytopenia in 44 - 52%; and dermatological reactions, such as rash, pruritis, urticaria, wheal, and flare in 15 - 25% of patients. The following reactions were reported in more than 1% but less than 5% of the patients: 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 and stomatitis.

Reactions reported in less than 1% of the patients in the controlled trials were 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, and wound dehiscence.

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

In five years of Postmarketing Voluntary Reporting, adverse reactions have been seen in the following percentages of reported patients: fever 51%; chills 16%; thrombocytopenia 30%; leukopenia 14%; rashes 27%; systemic infection 13%.

The following have been seen in 5 to 10% of reported patients: abnormal renal function tests, serum sickness-like symptoms, dyspnoea/apnoea, arthralgias, chest, back and flank pain, diarrhoea and nausea and/or vomiting.

Reported with a frequency of less than 5% include: hypertension, Herpes Simplex infection, pain, swelling or redness at infusion site, eosinophilia, headache, myalgias or leg pains, hypotension, anaphylaxis, tachycardia, oedema, localized infection, malaise, seizures, GI bleeding or perforation, deep vein thrombosis, sore mouth-throat, hyperglycemia, 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, paresthesias and renal artery thrombosis.

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

1. **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.
2. **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.
3. **Thrombocytopenia and Leukopenia** are usually transient. Platelet and white cell counts generally return to adequate levels without interrupting therapy and with transfusions. If thrombocytopenia and leukopenia 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 WARNINGS).
4. **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.
5. **Pain in chest, flank, or back** may indicate anaphylaxis or haemolysis. Treatment is the same as for respiratory distress or, if haemolysis has occurred, the same as listed in (2) above.
6. **Hypotension** may indicate anaphylaxis. Infusion of ATGAM should be discontinued and blood pressure stabilised with pressors if necessary.
7. **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.
8. **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.

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

INTERACTIONS

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.

DOSAGE RECOMMENDATIONS

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.

PREPARATION AND ADMINISTRATION

1. 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 or more mm 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, dyspnea, 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 WARNINGS, PRECAUTIONS, and ADVERSE EFFECTS.

2. Infusion Instructions

- a) Parenteral drug products should be inspected visually for particulate matter and discoloration 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 or flaky deposit during storage.
- b) Dilute ATGAM in saline solution before intravenous infusion. Invert the IV bottle of saline so the undiluted ATGAM does not contact the air inside.
- c) Add the total daily dose of ATGAM to a sterile 0.9% sodium chloride injection; 5% glucose and 0.225% sodium chloride injection; and, 5% glucose and 0.45% sodium chloride injection. Ideally the concentration should not exceed 4 mg of ATGAM per mL of saline. Adding ATGAM to glucose 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.**
- d) During clinical trials, most investigators chose to infuse ATGAM into a vascular shunt, arterial venous 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.
- e) Using high-flow veins will minimise the occurrence of phlebitis and thrombosis.
- f) Do not infuse a dose of ATGAM in less than 4 hours.

- g) Always keep a tray containing adrenaline, antihistamines, corticosteroids, syringes and an airway at the patient's bedside while ATGAM is being administered.
- h) Observe the patient continuously for possible allergic reactions throughout the infusion (see ADVERSE REACTIONS)
- i) 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.

OVERDOSAGE

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, a renal transplant recipient, was 7000mg administered at a concentration of approximately 10mg/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 20mg/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 toxicologic manifestations did not increase with any of these regimes.

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

PHARMACEUTICAL PRECAUTIONS

Store in refrigerator at 2 to 8 degrees C.
Do not freeze.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

ATGAM Sterile Solution is packaged in 5mL ampoules.

FURTHER INFORMATION

Nil.

NAME AND ADDRESS OF SPONSOR

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